Special Article

Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Pediatric Critically Ill Patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition

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The American College of Critical Care Medicine (ACCM), which honors individuals for their achievements and contributions to multidisciplinary critical care medicine, is the consultative body of the Society of Critical Care Medicine (SCCM) that possesses recognized expertise in the practice of critical care. The College has developed administrative guidelines and clinical practice parameters for the critical care practitioner. New guidelines and practice parameters are continually developed, and current ones are systematically reviewed and revised.

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This document represents the first collaboration between two organizations, American Society of Parenteral and Enteral Nutrition and the Society of Critical Care Medicine, to describe best practices in nutrition therapy in critically ill children. The target of these guidelines is intended to be the pediatric (> 1 mo and < 18 yr) critically ill patient expected to require a length of stay greater than 2 or 3 days in a PICU admitting medical, surgical, and cardiac patients. In total, 2,032 citations were scanned for relevance. The PubMed/Medline search resulted in 960 citations for clinical trials and 925 citations for cohort studies. The EMBASE search for clinical trials culled 1,661 citations. In total, the search for clinical trials yielded 1,107 citations, whereas the cohort search yielded 925. After careful review, 16 randomized controlled trials and 37 cohort studies appeared to answer one of the eight preidentified question groups for this guideline. We used the Grading of Recommendations, Assessment, Development and Evaluation criteria to adjust the evidence grade based on assessment of the quality of study design and execution. These guidelines are not intended for neonates or adult patients. The guidelines reiterate the importance of nutritional assessment, particularly the detection of malnourished patients who are most vulnerable and therefore potentially may benefit from timely intervention. There is a need for renewed focus on accurate estimation of energy needs and attention to optimizing protein intake. Indirect calo-

rimetry, where feasible, and cautious use of estimating equations and increased surveillance for unintended caloric underfeeding and overfeeding are recommended. Optimal protein intake and its correlation with clinical outcomes are areas of great interest. The optimal route and timing of nutrient delivery is an area of intense debate and investigations. Enteral nutrition remains the preferred route for nutrient delivery. Several strategies to optimize enteral nutrition during critical illness have emerged. The role of supplemental parenteral nutrition has been highlighted, and a delayed approach appears to be beneficial. Immunonutrition cannot be currently recommended. Overall, the pediatric critical care population is heterogeneous, and a nuanced approach to individualizing nutrition support with the aim of improving clinical outcomes is necessary. (*Pediatr Crit Care Med* 2017; 18:675–715)

Key Words: adolescent; algorithm; child; critical illness; energy; enteral nutrition; guidelines; immunonutrition; indirect calorimetry; infant; intensive care unit; malnutrition; nutrition team; obesity; parenteral nutrition; pediatric; pediatric nutrition assessment; protein; protein balance; resting energy expenditure

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This document represents the first collaboration between two organizations, American Society of Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM), to describe best practices in nutrition therapy in critically ill children.

Guideline Limitations. These SCCM-ASPEN Clinical Guidelines are based on general consensus among a group of professionals who, in developing such guidelines, have examined the available literature on the subject and balanced potential benefits of nutrition practices against risks inherent with such therapy. A task force of multidisciplinary experts in clinical nutrition composed of physicians, nurses, pharmacists, dietitians, and statisticians was jointly convened by the two societies. These individuals participated in the development of the guidelines and authored this document. These practice guidelines are not intended as absolute policy statements. Use of these practice guidelines does not in any way guarantee any specific benefit in outcome or survival. The professional judgment of the attending health professionals is the primary component of quality medical care delivery. Since guidelines cannot account for every variation in circumstances, practitioners must always exercise professional judgment when applying these recommendations to individual patients. These Clinical Guidelines are intended to supplement, but not replace, professional training and judgment.

The current guidelines represent an expanded body of literature since the publication of the first guidelines in 2009 (1). The guidelines offer basic recommendations that are supported by review and analysis of the current literature and a blend of expert opinion and clinical practicality. Current literature has limitations that include variability in study design, small sample size, patient heterogeneity, variability in disease severity, lack of information on baseline nutritional status, and insufficient statistical power for analysis. The authors of these guidelines acknowledge the scarcity of high-level evidence for nutrition practices in the PICU environment. Most questions addressed in this guideline do not have enough homogeneous, high-quality trials and therefore do not lend themselves to any statistical analyses. A combination of cohort studies and trials, where available, has been summarized and used to develop practical recommendations by consensus. Where randomized controlled trials (RCTs) were not available, observational studies formed the main evidence. Their quality was critically reviewed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology and guided the consensus-derived recommendations (2).

Definitions. Nutrition support therapy refers specifically to the provision of either enteral nutrition (EN) by enteral access device and/or parenteral nutrition (PN). Standard therapy refers to provision of IV fluids, no EN or PN, and advancement to oral diet as tolerated.

Target Patient Population for Guideline. The target of these guidelines is intended to be the pediatric (> 1 mo and < 18 yr) critically ill patient expected to require a length of stay (LOS) greater than 2 or 3 days in a PICU admitting medical, surgical, and cardiac patients. These guidelines are not intended for neonates or adult patients. We believe that neonates are different physiologically from older children, and therefore, these guidelines specifically do not include them. These guidelines are not intended for patients with specific diagnoses such as burn injuries. These guidelines are directed toward generalized patient populations but, like any other management strategy in the PICU, nutrition therapy should be tailored to the individual patient.

Target Audience. These guidelines are intended for use by all healthcare providers involved in nutrition therapy of the critically ill child, primarily physicians, nurses, dietitians, and pharmacists.

METHODS

The GRADE process was used to develop the key questions and to plan data acquisition and conflation for these guidelines (2). The task force of experts defined keywords to be used for the literature search, developed key questions that address major practice themes at the bedside, and determined the time frame for the literature search, target population, and the specific outcomes to be addressed. Ultimately, questions related to eight major practice areas were developed, which were reviewed and approved by the ASPEN and SCCM boards. These questions and the recommendations are summarized in **Table 1**. Due to a dearth of well-designed RCTs, many studies addressing these questions and relevant outcomes are either prospective or retrospective observational reports of clinical outcomes associated with a strategy. In some cases, these interventions were protocolized. The evidence provided by these observational studies was strengthened, however, when the effects shown were strong, when the sample size was large, or when there was a dose-response relationship. We used the GRADE criteria to adjust the evidence grade based on assessment of the quality of study design and execution. The GRADE process distinctly separates the body of evidence from the recommendation statements. This separation enables

TABLE 1. Nutrition Support Clinical Guideline Recommendations for the Critically Ill Child

Questions and Recommendations	Evidence/GRADE
Q1A. What is the impact of nutritional status on outcomes in critically ill children?	
R1A. Based on observational studies, malnutrition, including obesity, is associated with adverse clinical outcomes including longer periods of ventilation, higher risk of hospital-acquired infection, longer PICU and hospital stay, and increased mortality. We recommend that patients in the PICU undergo detailed nutritional assessment within 48 hr of admission.	Quality of evidence: very low
Furthermore, as patients are at risk of nutritional deterioration during hospitalization, which can adversely affect clinical outcomes, we suggest that the nutritional status of patients be re-evaluated at least weekly throughout hospitalization.	GRADE recommendation: strong
Q1B. What are the best practices to screen and identify patients with malnutrition or those at risk of nutritional deterioration in the PICU?	
R1B. Based on observational studies and expert consensus, we recommend that weight and height/length be measured on admission to the PICU, and z scores for body mass index-for-age (weight-for-length < 2 yr), or weight-for-age (if accurate, height is not available), be used to screen for patients at extremes of these values. In children under 36 mo old, head circumference must be documented.	Quality of evidence: very low
Validated screening methods for the PICU population to identify patients at risk of malnutrition must be developed. Screening methods might allow limited resources to be directed to high-risk patients who are most likely to benefit from early nutritional assessment and interventions.	GRADE recommendation: strong
Q2A. What is the recommended energy requirement for critically ill children?	Quality of evidence: low
R2A. Based on observational cohort studies, we suggest that measured energy expenditure by indirect calorimetry (IC) be used to determine energy requirements and guide prescription of the daily energy goal.	GRADE recommendation: weak
Q2B. How should energy requirement be determined in the absence of IC?	Quality of evidence: very low
R2B. If IC measurement of resting energy expenditure (REE) is not feasible, we suggest that the Schofield or Food Agriculture Organization/World Health Organization/United Nations University equations may be used "without" the addition of stress factors to estimate energy expenditure. Multiple cohort studies have demonstrated that most published predictive equations are inaccurate and lead to unintended overfeeding or underfeeding. The Harris-Benedict equations and the RDAs, which are suggested by the Dietary Reference Intakes, should not be used to determine energy requirements in critically ill children.	GRADE recommendation: weak
Q2C. What is the target energy intake in critically ill children?	Quality of evidence: low
R2C. Based on observational cohort studies, we suggest achieving delivery of at least two thirds of the prescribed daily energy requirement by the end of the first week in the PICU. Cumulative energy deficits during the first week of critical illness may be associated with poor clinical and nutritional outcomes. Based on expert consensus, we suggest attentiveness to individualized energy requirements, timely initiation and attainment of energy targets, and energy balance to prevent unintended cumulative caloric deficit or excesses.	GRADE recommendation: weak
Q3A. What is the minimum recommended protein requirement for critically ill children?	Quality of evidence: moderate
R3A. Based on evidence from RCTs and supported by observational cohort studies, we recommend a minimum protein intake of 1.5 g/kg/d. Protein intake higher than this threshold has been shown to prevent cumulative negative protein balance in RCTs. In critically ill infants and young children, the optimal protein intake required to attain a positive protein balance may be much higher than this minimum threshold. Negative protein balance may result in loss of lean muscle mass, which has been associated with poor outcomes in critically ill patients. Based on a large observational study, higher protein intake may be associated with lower 60-d mortality in mechanically ventilated children.	GRADE recommendation: strong
Q3B. What is the optimal protein delivery strategy in the PICU?	Quality of evidence: moderate
R3B. Based on results of randomized trials, we suggest provision of protein early in the course of critical illness to attain protein delivery goals and promote positive nitrogen balance. Delivery of a higher proportion of the protein goal has been associated with positive clinical outcomes in observational studies.	GRADE recommendation: weak

(*Continued*)

TABLE 1. (*Continued*). Nutrition Support Clinical Guideline Recommendations for the Critically Ill Child

Questions and Recommendations	Evidence/GRADE
Q3C. How should protein delivery goals be determined in critically ill children?	Quality of evidence: moderate
R3C. The optimal protein dose associated with improved clinical outcomes is not known. We do not recommend the use of RDA values to guide protein prescription in critically ill children. These values were developed for healthy children and often underestimate the protein needs during critical illness.	GRADE recommendation: strong
Q4A. Is EN feasible in critically ill children?	Quality of evidence: low
R4A. Based on observational studies, we recommend EN as the preferred mode of nutrient delivery to the critically ill child. Observational studies support the feasibility of EN, which can be safely delivered to critically ill children with medical and surgical diagnoses, and to those receiving vasoactive medications. Common barriers to EN in the PICU include delayed initiation, interruptions due to perceived intolerance, and prolonged fasting around procedures. Based on observational studies, we suggest that interruptions to EN be minimized in an effort to achieve nutrient delivery goals by the enteral route.	GRADE recommendation: strong
Q4B. What is the benefit of EN in this group?	Quality of evidence: low
R4B. Although the optimal dose of macronutrients is unclear, some amount of nutrient delivered as EN has been beneficial for gastrointestinal mucosal integrity and motility. Based on large cohort studies, early initiation of EN (within 24–48 hr of PICU admission) and achievement of up to two thirds of the nutrient goal in the first week of critical illness have been associated with improved clinical outcomes.	GRADE recommendation: weak
Q5A. What is the optimum method for advancing EN in the PICU population?	Quality of evidence: low
R5A. Based on observational studies, we suggest the use of a stepwise algorithmic approach to advance EN in children admitted to the PICU. The stepwise algorithm must include bedside support to guide the detection and management of EN intolerance and the optimal rate of increase in EN delivery.	GRADE recommendation: weak
Q5B. What is the role of a nutrition support team or a dedicated dietitian in optimizing nutrition therapy?	Quality of evidence: low
5B. Based on observational studies, we suggest a nutrition support team, including a dedicated dietitian, be available on the PICU team, to facilitate timely nutritional assessment, and optimal nutrient delivery and adjustment to the patients.	GRADE recommendation: weak
Q6A. What is the best site for EN delivery - gastric or small bowel?	Quality of evidence: low
R6A. Existing data are insufficient to make universal recommendations regarding the optimal site to deliver EN to critically ill children. Based on observational studies, we suggest the gastric route be the preferred site for EN in patients in the PICU. The postpyloric or small intestinal site for EN may be used in patients unable to tolerate gastric feeding or those at high risk for aspiration. Existing data are insufficient to make recommendations regarding the use of continuous vs intermittent gastric feeding.	GRADE recommendation: weak
Q6B. When should EN be initiated?	Quality of evidence: low
R6B. Based on expert opinion, we suggest that EN be initiated in all critically ill children, unless it is contraindicated. Based on observational studies, we suggest early initiation of EN, within the first 24–48 hr after admission to the PICU, in eligible patients. We suggest the use of institutional EN guidelines and stepwise algorithms that include criteria for eligibility for EN, timing of initiation, and rate of increase as well as a guide to detecting and managing EN intolerance.	GRADE recommendation: weak
Q7A. What is the indication for and optimal timing of PN in critically ill children?	Quality of evidence: moderate
R7A. Based on a single RCT, we do not recommend the initiation of PN within 24 hr of PICU admission.	GRADE recommendation: strong

(*Continued*)

TABLE 1. (*Continued*). Nutrition Support Clinical Guideline Recommendations for the Critically Ill Child

Questions and Recommendations	Evidence/GRADE
Q7B. What is the role of PN as a supplement to inadequate EN?	Quality of evidence: low
R7B. In children tolerating EN, we suggest stepwise advancement of nutrient delivery via the enteral route and delaying commencement of PN. Based on current evidence, the role of supplemental PN to reach a specific goal for energy delivery is not known. The time when PN should be initiated to supplement insufficient EN is also unknown. The threshold for and timing of PN initiation should be individualized.	GRADE recommendation: weak
Based on a single RCT, supplemental PN should be delayed until 1 wk after PICU admission in patients with normal baseline nutritional state and low risk of nutritional deterioration. Based on expert consensus, we suggest PN supplementation in children who are unable to receive any EN during the first week in the PICU. In patients who are severely malnourished or at risk of nutritional deterioration, PN may be supplemented in the first week if they are unable to advance past low volumes of EN.	
Q8. What is the role of immunonutrition in critically ill children?	Quality of evidence: moderate
R8. Based on available evidence, we do not recommend the use of immunonutrition in critically ill children.	GRADE recommendation: strong

EN = enteral nutrition, GRADE = Grading of Recommendations, Assessment, Development and Evaluation, IC = indirect calorimetry, PN = parenteral nutrition, RCT = randomized controlled trial, RDA = Recommended Daily Allowance.

incorporation of the weight of the risks versus the benefits that occur from adopting the recommendation. Thus, a recommendation may be "strong" despite comparatively weak published evidence if the net benefits outweigh the harms from its adoption. Recommendations based mainly on expert opinion were deemed weak. **Table 2** describes the standard language and rationale for the grade assigned to a recommendation.

A rigorous search of the Medline/PubMed and EMBASE databases was performed spanning January 1995 through March 2016 for citations relevant to nutrition support in the critically ill pediatric population using the techniques outlined in a recent publication (3). For the Medline portion of the search, Medical Subject Heading (MeSH) folders for "Critical Illness," "Intensive Care," and "Critical Care" were searched for relevant citations. To meet our search criteria, these citations had to also be indexed in MeSH folders for "Nutritional Support," "Malnutrition," "Nutrition Assessment," "Energy Intake," "Energy Metabolism," or "Dietary Proteins." To further restrict citations to our chosen population, the terms were cross-referenced in the MeSH folders for "Pediatrics," "Infant," "Child," "Adolescent," or "Young Adult." Alternatively, we also accepted citations that had the terms pediatric*, paediatric*, infan*, adolescen*, or child* in at least one of their PubMed/Medline subject fields. Finally, all citations had to be cross-referenced in the "Humans" MeSH folder. The PubMed (non-Medline) database was then searched using text-based terms (**Fig. 1**). As an added protection against MeSH miscategorization of citations, this text-based search was then used to search the Medline database restricting the search to only yield citations carrying those terms in their title or abstract. For the clinical trials search, the Medline portion was restricted to those citations categorized according to the publication type "Clinical Trials." For the cohort search, the Medline portion was restricted to those studies cross-referenced in the "Cohort" MeSH folder, whereas the text-based portion was restricted to only those citations that were not indexed according to the publication types "Clinical Trial," "Review," "Case Reports," or "Commentary." An analogous search strategy focusing only on EMBASE-indexed non-Medline clinical trials was created and implemented for the EMBASE database.

TABLE 2. Language for Guidelines Recommendations

Quality of Evidence	Weighing Risks vs Benefits	Grading of Recommendations, Assessment, Development and Evaluation Recommendations	Clinical Guideline Statement
High to very low	Net benefits outweigh harms	Strong	We recommend
High to very low	Tradeoffs for patient are important	Weak	We suggest
High to very low	Uncertain tradeoffs	Further research needed	We cannot make a recommendation at this time

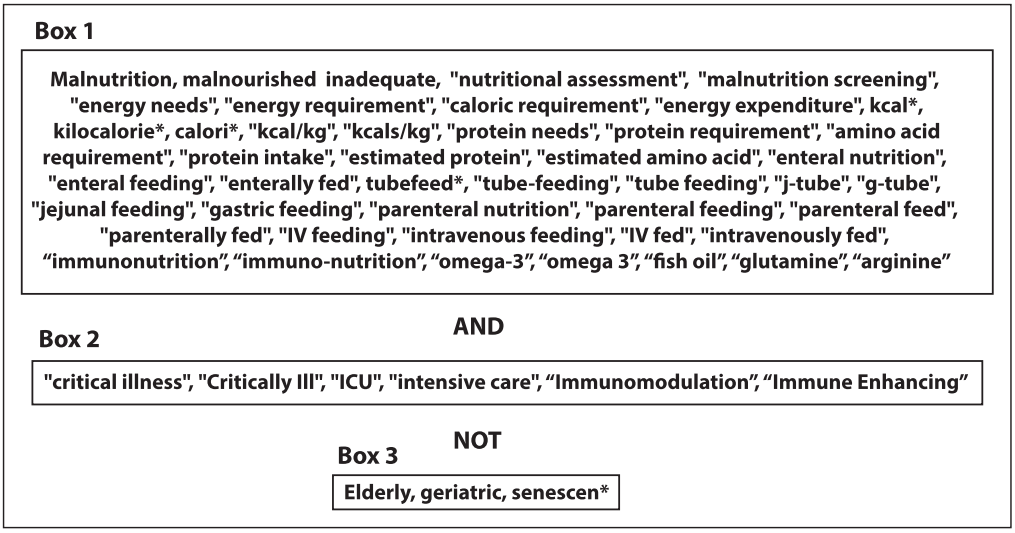

Figure 1. Overview of the literature search strategy.

RESULTS

In total, 2,032 citations were scanned for relevance. The PubMed/Medline search resulted in 960 citations for clinical trials and 925 citations for cohort studies. The EMBASE search for clinical trials culled 1,661 citations. In total, the search for clinical trials yielded 1,107 citations, whereas the cohort search yielded 925. Each citation was reviewed by at least two reviewers to examine eligibility for inclusion in guideline development. After careful review, 16 RCTs and 37 cohort studies appeared to answer one of the eight preidentified question groups for this guideline. These studies were then reviewed, and the relevant data were abstracted by the authors using a standardized form. After review of the abstracted data, evidence tables were generated for each question. Based on the evidence tables, the authors used an iterative process to develop practical recommendations for each question using the GRADE methodology where applicable and by consensus. The recommendations for questions are summarized in Table 1. The rationale for the GRADE and the language for the recommendations are described in Table 2. **Tables 3–10** summarize the evidence in the form of trials and cohort studies related to each of the guideline questions. Each table is followed by a discussion on the rationale for the recommendation(s) and suggested areas for future investigation for the question(s).

Introduction

The role of nutrition in contributing to the outcomes of patients with critical illness is being increasingly recognized. Since the first pediatric critical care nutrition guidelines (ASPEN) published in 2009, there has been a substantial increase in research and publications related to this subject. The impact of nutritional status and nutrient delivery during critical illness has been demonstrated on clinical outcomes such as mortality, infectious complications, and LOS (4–10). Thus, careful planning and monitoring of nutrient delivery at the bedside is attempted in most ICUs. As more information becomes available from higher quality studies, the field will eventually move toward uniform evidence-based strategies for most nutrition practices in the PICU. However, at present, many questions remain unanswered, and practices are widely variable between institutions and among providers. RCTs, while providing definitive evidence, require tremendous time and resources to complete. Hence, there is a scarcity of RCTs in the pediatric critical care nutrition literature. Furthermore, results of single RCTs in the adult population have often not been replicated in subsequent studies (10–13). Despite these limitations, there have been a number of both small and large studies published over the past decade. Observational cohort and case-controlled studies have provided meaningful information and helped develop hypotheses that can be tested by clinical trials with more robust study designs. Prospective or retrospective cohorts allow measurement of disease occurrence and its association with an exposure by offering a temporal dimension. These studies are described in more detail in relevant sections of this article.

The PICU is unique in terms of the heterogeneity of patients in relation to age, disease type, interventions, comorbid conditions, and presenting nutritional status. It is therefore overly simplistic to expect that one strategy will be applicable to all patients. Nutritional support must be individualized based on the baseline nutritional status and vulnerabilities of patients, anticipated time to volitional feeding, and the risk-to-benefit ratio of intended nutritional therapies. Therefore, the recommendations provided here are useful starting points on which to build customized nutritional therapy for individual patients.

Question 1A. What Is the Impact of Nutritional Status on Outcomes in Critically Ill Children?

Recommendation 1A. Based on observational studies, malnutrition, including obesity, is associated with adverse clinical outcomes including longer periods of ventilation, higher risk of hospital-acquired infection, longer PICU and hospital stay, and increased mortality. We recommend that patients in the PICU undergo detailed nutritional assessment within 48 hours of admission.

Furthermore, as patients are at risk of nutritional deterioration during hospitalization, which can adversely affect clinical outcomes, we suggest that the nutritional status of patients be re-evaluated at least weekly throughout hospitalization.

Quality of Evidence. Very low.

GRADE Recommendation. Strong.

TABLE 3. The Impact of Nutritional Status on Outcomes and the Best Practices to Detect Malnutrition or Risk of Nutritional Deterioration

Reference	Study Design, No. of Sites	Study Aim(s)	Population (n), Eligibility	Results/Outcome	Comments
Bechard et al (4)	Prospective, observational cohort (combined dataset from two studies), multicenter (90 PICUs from 16 countries)	To determine the influence of admission BMI z score on clinical outcomes in mechanically ventilated children in the PICU	$n = 1{,}622$ Mechanically ventilated, critically ill children, age 1 mo to 18 yr old, with an expected PICU stay of at least 3 d, and dependent on enteral or parenteral nutrition support Mean age (SD): 4.5 yr (5.1 yr)	54.2%, normal weight; 17.9%, underweight; 14.5%, overweight; and 13.4%, obese Outcomes (compared with normal nutritional status) 60-d mortality: Higher in underweight: OR, 1.53 (CI 1.24–1.89; $p < 0.001$) Likelihood of discharge alive: for each additional day in the hospital, underweight had 29% (HR, 0.71; CI, 0.60–0.84; $p < 0.001$); and obese had 18% (HR, 0.82; CI, 0.68–0.99; $p = 0.04$) lower chance of being discharged. Hospital-acquired infection: higher in underweight: OR, 1.88 (CI, 1.18–3.01; $p = 0.008$) Higher in obese: OR, 1.64 (CI, 1.33–2.03; $p < 0.001$) VFD: Underweight associated with 1.3 fewer VFD vs normal weight (CI, −2.1 to −0.6; $p = 0.001$; 1.6 fewer VFD vs overweight (CI, −2.4 to −0.9; $p < 0.001$); 1.2 fewer VFD vs obese (95% CI, −1.9 to −0.6; $p < 0.001$). No significant differences in VFD among overweight and obese	45% of the cohort was malnourished (obese, overweight, or underweight) on admission Both underweight and obese status associated with poor outcomes compared with normal nutritional status on admission Limitations: centers from the developing world, where malnutrition may be more prevalent, were excluded due to smaller PICU size Potential for inaccuracy of weight and height/length measurements, especially when influenced by fluid shifts Cross-sectional study (no interventions)
Castillo et al (5)	Prospective, observational, single center	To assess the association between mortality and nutritional status of children receiving CRRT	$n = 174$ PICU patients receiving CRRT Malnutrition: less than third percentile for body weight for age Median age (IQR): 18.5 mo (4.0–81.8 mo)	35% of the cohort was malnourished Majority of malnourished patients were < 1 yr old Low incidence of obesity Hypoalbuminemia in 28% Mortality was higher (42.6%) in malnourished children	A third of the cohort was malnourished Malnutrition was associated with higher mortality Limitations: body weight was used to determine nutritional status, and albumin was used to determine protein status
De Souza Menezes et al (6)	Prospective, observational, single center	To determine the nutritional status of children admitted to a PICU and to assess the effect of malnutrition as an independent risk factor affecting outcome (the outcome variables were 30-d mortality, length of ICU stay, and duration of mechanical ventilation)	$n = 385$ Malnutrition (z score, < −2) based on weight for age (< 2 yr) or BMI (≥ 2 yr) and height for age (if chronic disease) Median age (IQR): 18.3 mo (3.9–63.3 mo)	45.5% were malnourished on admission. 9.14% of the malnourished group and 11.9% of the nonmalnourished group died Malnutrition was associated with longer duration of MV and PICU LOS, but not with mortality on univariate analysis Malnutrition was associated with longer duration of mechanical ventilation on multiple logistic regression modeling (OR, 1.76; 95% CI, 1.08–2.88; $p = 0.024$)	Center with high prevalence of malnutrition showing independent impact on duration of MV Limitations: single-center study; methodologic issues with sample size calculation

(*Continued*)

TABLE 3. (*Continued*). The Impact of Nutritional Status on Outcomes and the Best Practices to Detect Malnutrition or Risk of Nutritional Deterioration

Reference	Study Design, No. of Sites	Study Aim(s)	Population (n), Eligibility	Results/Outcome	Comments
Delgado et al (7)	Retrospective, observational, single center	To evaluate the incidence of malnutrition in the first 72 hr after PICU admission Examine differences in IL-6, CRP, LOS, sepsis, and mortality between the malnourished and well-nourished groups	$n = 1{,}077$ Malnutrition based on weight-for-age z score: moderate, −1 to −2; severe, < −2 Median age: malnourished, 25.6 mo; well nourished, 10.7 mo	No significant differences between well nourished and malnourished for CRP, PICU LOS, hospital mortality, or incidence of sepsis IL-6 was significantly different between well-nourished and malnourished over time ($p = 0.043$)	Over 50% of patients admitted to this Brazilian PICU were malnourished Malnourished patients had higher inflammatory markers compared with well-nourished patients

BMI = body mass index, CRP = *C*-reactive protein, CRRT = continuous renal replacement therapy, HR = hazard ratio, IL = interleukin, IQR = interquartile range, LOS = length of stay, MV = mechanical ventilation, OR = odds ratio, VFD = ventilator-free days.

Question 1B. What Are the Best Practices to Screen and Identify Patients With Malnutrition or Those at Risk of Nutritional Deterioration in the PICU?

Recommendation 1B. Based on observational studies and expert consensus, we recommend that weight and height/length be measured at admission to the PICU, and z scores for body mass index (BMI)-for-age (weight-for-length, < 2 yr) or weight-for-age (if accurate, height is not available) be used to screen for patients at extremes of these values. In children under 36 months old, head circumference must be documented.

Validated screening methods for the PICU population to identify patients at risk of malnutrition must be developed. Screening methods might allow limited resources to be directed to high-risk patients who are most likely to benefit from early nutritional interventions.

Quality of Evidence. Very low.

GRADE Recommendation. Strong.

Rationale A. Malnutrition is prevalent in children admitted to the PICU (6, 7, 14, 15). Although variables used to define malnutrition are inconsistent across reports, both underweight and overweight status have been associated with worse morbidity and mortality (4–6, 10). More recently, guidelines to define pediatric malnutrition have become available to facilitate early identification of individuals at risk (16). A uniform approach to define pediatric malnutrition may allow determination of thresholds for interventions aimed at ameliorating nutritional deterioration (17). A large portion of children admitted to PICU is at risk for nutritional deterioration; therefore, periodic nutritional re-evaluation is essential (15, 18). Nutritional assessment must include a dietary history, detection of changes in anthropometry, functional status, and nutrition-focused physical examination. A nutrition-focused physical examination in this cohort allows for determination of individualized nutrient needs, interventions, and monitoring to optimize nutrient intake during illness. The subjective global nutrition assessment is correlated with anthropometric variables in one study but has not been shown to predict outcomes in critically ill children (19).

Rationale B. In a limited resource setting, timely and detailed nutritional assessment of every patient in the PICU may not be feasible. A validated method to screen critically ill children for malnutrition risk may help allocate resources to high-risk patients. However, such a screening method is not currently available. The Pediatric Yorkhill Malnutrition Score, the Screening Tool for the Assessment of Malnutrition in Pediatrics, and the Screening Tool for Risk of Impaired Nutritional Status and Growth (STRONGKids) were recently evaluated in 2,567 patients from multiple centers in Europe (20). These screens varied significantly in their ability to identify and classify malnutrition risk and were unable to detect a significant proportion of children with abnormal anthropometrics. The authors concluded that none of these screens could be recommended for use in clinical practice. Admission weight-for-age and BMI-for-age (or weight-for-length in children, < 2 yr) *z* scores of individual patients in relation to population reference standards have been used to classify patients as undernourished or obese. Admission BMI *z* scores predicted mortality in a large multicenter cohort of mechanically ventilated children (4). Due to their consistent associations with LOS, duration of mechanical ventilation, and mortality, BMI *z* scores may be useful to screen for patients at risk of poor outcomes in the PICU (17). Despite the inherent challenges of obtaining accurate anthropometric measurements at admission to PICU, the routine evaluation of weight-for-age and BMI-for-age or weight-for-length *z* scores must be prioritized. Indeed, in a majority of tertiary centers, documentation of anthropometric measurements at admission is seen as the standard of care.

Future Direction. A validated nutrition screen for timely and accurate identification of malnourished PICU patients is needed. This tool will facilitate allocation of resources, early interventions, and close monitoring of nutritional status in high-risk patients. A uniform definition of malnutrition must be employed, and validated methods for nutritional assessment must be developed and implemented in the PICU. Subsequently, the impact of malnutrition on clinical outcomes in the PICU population should be examined.

TABLE 4. The Recommended Energy Requirement for Critically Ill Children

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility	Results/Outcome	Comments
Jotterand Chaparro et al (36)	Prospective cohort, single center	To assess protein and energy requirements to achieve nitrogen and energy balance and to compare MREE with the DRIs	*n* = 76 Mechanically ventilated, critically ill children Median age (IQR): 21 mo (4–35 mo)	402 IC measurements Mean MREE 55 kcal/kg/d (95% CI, 54–57) MREE was stable for first 10 d MREE decreased 6% with neuromuscular blockade ($p = 0.031$) and increased by 8% per degree centigrade body temperature ($p = 0.003$) DRI strongly overestimated MREE Protein intake ≥ 1.5 g/kg/d and energy intake ≥ 58 kcal/kg/d needed for nitrogen and energy balance	Study suggests a threshold for optimal energy intake and a relationship between energy intake and protein balance Limitations: protein balance was determined via nitrogen balance measurements
Wong et al (44)	Retrospective cohort, single center	To describe nutrition support and identify adequate caloric intake by children with ARDS and to determine whether provision of adequate nutrition is associated with improved clinical outcomes	*n* = 107 Children with ARDS Median age (IQR): 5.2 yr (1.0–10.4 yr)	Inadequate vs adequate caloric intake and outcomes Adequate calories defined as ≥ 80% Schofield equation by third day of ARDS PICU mortality: 60.5% vs 34.6%; $p = 0.003$ PICU-free days: 0 (0–15) vs 0 (0–17); $p = 0.687$ Ventilator-free days: 0 (0–4) vs 3 (0–12); $p = 0.068$ Multiple organ dysfunction: 72.5% vs 53.8%; $p = 0.093$	Study suggests that inadequate energy intake is associated with poorer clinical outcomes Limitations: outcomes based on estimated energy requirements
Dokken et al (21)	Observational cohort with repeated measures, single center	To describe the agreement of the delivered energy with MREE and to explore the role of RQ in the delivery of nutrition support	*n* = 30 Mechanically ventilated children Median age (range): 15.5 mo (3 mo to 14 yr)	104 IC measurements Underfeeding: 22 d (21.2%) Adequate feeding: 19 d (18.3%) Overfeeding: 63 d (60.5%) RQ < 0.85: sensitivity 27%, specificity 87% for underfeeding RQ > 1.0: sensitivity 21%, specificity 98% for overfeeding Significant variability in MREE between patients: median, 37.2 kcal/kg/d, range, 16.8–66.4 kcal/kg/d Small variability in MREE within patients	The study describes the variability in metabolic state and inability of RQ to detect under/overfeeding Limitations: small sample size; heterogeneous sample for age, weight, and diagnosis; IC measurements performed at different times during the illness course; and no outcomes reported

(*Continued*)

TABLE 4. (*Continued*). The Recommended Energy Requirement for Critically Ill Children

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility	Results/Outcome	Comments
Mtaweh et al (24)	Prospective cohort, single center	To compare MREE to estimated BMR (Harris-Benedict and Schofield equations)	$n = 13$ Mechanically ventilated children with severe traumatic brain injury (Glasgow Coma Scale, < 9) Mean age (SD): 9.8 yr (1.4 yr)	32 IC measurements MREE vs Harris-Benedict: five of 32 IC measurements greater than estimation Mean MREE: 70.2% ± 3.8% of Harris-Benedict MREE vs Schofield: Three of 32 IC measurements greater than estimation Mean MREE: 69% ± 4.5% of Schofield	The study demonstrates a prevalence of hypometabolism in critically ill children with severe traumatic brain injury Limitations: small sample size; energy intake not reported; and no outcomes reported
Meyer et al (32)	Prospective, observational cohort, multicenter Three PICUs	To develop equations to estimate energy requirements and to compare three new equations with MREE and current equations used to estimate resting energy expenditure (Schofield, FAO/WHO/UNU, White)	$n = 175$ Mechanically ventilated children Median age (range): 54 mo (1–91 mo)	369 IC measurements Three equations developed, $R^2 > 0.8$ for each equation Inotropes, neuromuscular blockade, temperature, C-reactive protein, and organ dysfunction scores did not impact MREE Three new equations vs current equations vs MREE ($n = 30$): 25% of estimates, including three new equations, within 10% of MREE; 75% of estimations, including three new equations, varied 26–29% from MREE White: differed up to 82% from MREE	The research demonstrates that new and existing equations are not accurate within 10% of MREE in a majority of critically ill children Limitations: larger sample size necessary to develop and test new equations; did not include all ages; constraints of MREE, i.e., exclusion of patients that cannot have MREE measured; and no outcomes reported
Mehta et al (8)	Prospective, cohort with consecutive patients enrolled, multicenter 31 PICUs in eight countries	To examine variables associated with achieving optimal EN, explore relationship between energy intake adequacy and clinical outcomes; primary outcome: 60-d mortality	$n = 500$ Children requiring mechanical ventilation for > 48 hr Mean age (SD): 4.5 yr (5.1 yr)	Mortality lower with energy intake 33.3–66.6% vs $< 33.3\%$ prescribed goal (OR, 0.27 [0.11–0.67]), with $> 66.7\%$ vs $< 33.3\%$ (OR, 0.14 [0.03–0.61]); $p = 0.002$	Study suggests that adequate energy intake is associated with lower mortality Limitations: limited use of indirect calorimetry and reliance on equations to estimate energy requirements Severity of illness scores missing in 31%—although all patients were mechanically ventilated for more than 48 hr

(*Continued*)

TABLE 4. (*Continued*). The Recommended Energy Requirement for Critically Ill Children

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility	Results/Outcome	Comments
Mehta et al (22)	Prospective cohort, single center	To examine the role of IC in detecting the adequacy of energy intake and the risk of cumulative energy imbalance in a subgroup of critically ill children with suspected alterations in energy expenditure	*n* = 33 Children in the PICU Median age (range): 2 yr (0.1–28 yr)	High incidence (72%) of alterations in energy expenditure Predominance of hypometabolism in those admitted to the medical service PICU length of stay was significantly higher for patients with hypermetabolism (median, 142 d; $p = 0.04$) vs normal (median, 33 d) or hypometabolism (median, 50 d)	The study described the risk of cumulative energy imbalance when using equations to estimate energy requirements and proposed the concept of targeted IC with selection criteria for patients at risk of altered metabolism Limitations: small sample size Note: majority were long stay patients
Teixeira-Cintra et al (23)	Prospective, observational cohort, single center	To establish the amount of protein and energy intake needed to minimize catabolism following cardiac surgery	*n* = 11 Mechanically ventilated infants in the PICU following cardiac surgery Median age (range): 54 d (6–163 d)	Positive vs negative protein balance was associated with increased energy intake (54 vs 17 kcal/kg/d), $p < 0.0001$; positive correlation between protein balance and energy intake ($r = 0.77$; $p < 0.0001$)	The study suggests a threshold for energy intake and a relationship between energy and protein intake to positively impact protein balance Limitations: small sample size and three subjects were < 30 d old Urinary urea nitrogen excretion may underestimate total nitrogen excretion
Mehta et al (41)	Prospective cohort, single center	To examine if a model for targeting IC measurements to a select group of PICU patients by a dedicated nutrition team could prevent unintended excesses or deficits in energy balance	*n* = 14 Critically ill children 50% postoperative Mean age (range): 11.2 yr (1.6 mo to 32 yr)	Altered metabolism: 13 of 14 subjects, 15 of 16 measurements (94%) Average daily energy balance: 200 kcal/d (range, −518 to +859 kcal/d) Poor agreement between MREE and estimated energy expenditure: mean bias 72.3±446 kcal/d (limits of agreement: 801.9 to +946.5 kcal/d) No correlation between subjects' metabolic status and severity of illness scores, initial diagnosis, age, and body mass index Energy intake: 132% (± 68) of MREE Mean RQ: 0.94 No correlation between RQ and energy balance	The study shows a disparity between estimated energy expenditure, energy intake, and MREE. The metabolic state did not correlate with standard clinical characteristics and therefore could not be accurately predicted Limitations: small sample size

(*Continued*)

TABLE 4. (*Continued*). The Recommended Energy Requirement for Critically Ill Children

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility	Results/Outcome	Comments
Sy et al (25)	Prospective cohort, single center	To estimate MREE using bicarbonate kinetics and to compare bicarbonate kinetics with MREE estimated via FAO/WHO/UNU and Schofield equations in three groups: one receiving PN, one receiving EN, and another receiving glucose-electrolytes	*n* = 31 Critically ill children Mean age (SD), PN group (*n* = 12): 7.8 yr (7.4 yr) EN group (*n* = 7): 3.3 yr (4.1 yr) Glucose-electrolytes group (*n* = 12): 6.3 yr (5.0 yr)	PN group FAO/WHO/UNU 2001: 155% of bicarbonate kinetics, 195% of Schofield Bicarbonate kinetics: 120% of Schofield Enteral nutrition group and glucose-electrolytes group FAO/WHO/UNU 2001: 142% of bicarbonate kinetics, 167% of Schofield Bicarbonate kinetics: not significantly different from Schofield	The study demonstrates equations, especially those developed for growth in healthy infants and children are not accurate within 10% of MREE in a majority of critically ill children Limitations: small sample size and no outcomes reported
Zappitelli et al (26)	Retrospective cohort, single center	To describe protein and energy intake during CRRT	*n* = 195 Children requiring CRRT Mean age (SD): 8.8 yr (6.8 yr)	Maximum protein: 2 ± 1.5 g/kg/d Maximum energy: 48.2 ± 31.5 kcal/kg/d Predictors of higher energy and protein intake: younger age, higher protein or calorie intake at CRRT initiation, longer CRRT duration	Descriptive report of energy and protein intake during CRRT Large variation between centers in protein and energy delivery Limitations: no outcomes reported
Framson et al (28)	Prospective cohort with repeated measures, single center	To describe the variation in energy expenditure during PICU course and evaluate the accuracy of White equation for estimating energy expenditure	*n* = 44 Children in the PICU Mean age (SD): 5.16 yr (5.87 yr)	20% of MREE measurements were > 110% estimated, 32% were < 90% estimated, 45% were 90–110% estimated Mean MREE did not vary in the same patient over time The White equation estimate was within 10% of MREE for only 30% of measurements	The study demonstrates the variability in metabolic state and the inaccuracy of estimated energy expenditure by White equation in a majority of this cohort Limitations: small sample size and no outcomes reported
van der Kuip et al (34)	Prospective cohort, single center	To obtain MREE (via IC), TEE (via doubly labeled water technique), PAL during the week following PICU admission	*n* = 20 Children with severe sepsis or septic shock, or following major abdominal, thoracic, or trauma surgery Mean age (SD): 5 yr (6 yr)	TEE was approximately 122% of MREE No differences in TEE, MREE, activity related energy expenditure, PAL between sepsis and surgery group	Children with sepsis and surgery have no difference in TEE or MREE, and physical activity contributes to TEE Limitations: small sample size; potential for fluid status changes, especially in septic shock patients, affecting TEE assessment; and no outcomes reported

(*Continued*)

TABLE 4. (*Continued*). The Recommended Energy Requirement for Critically Ill Children

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility	Results/Outcome	Comments
Havalad et al (30)	Retrospective cohort, single center	To compare MREE to BMR estimated by Harris-Benedict, FAO/WHO/UNU, Schofield, and White equations in mechanically ventilated children with severe traumatic brain injury (Glasgow Coma Scale, ≤ 8)	*n* = 30 Median age (range): 10.9 yr (6.1–16.2 yr)	40% of estimates within 10% of MREE 43% patients had MREE greater than the estimate Bland Altman: poor agreement between MREE and all four equations No correlation between MREE and severity of illness scores, weight-for-age z score	The study shows a prevalence of hypometabolism and hypermetabolism in critically ill children with severe traumatic brain injury Limitations: small sample size; MREE obtained once in the first 24 hr of admission; energy intake not reported; and actual MREE values not reported
Hardy et al (29)	Prospective cohort, single center	To compare MREE to BMR estimated by various methods	*n* = 52 35 ventilated 17 spontaneously breathing Median age (range): 4.5 yr (0–22 yr)	Difference between all equations and individual IC measurements was large and highly variable 4–10% of estimates were within 10% of MREE Strong relationship between severity of illness scores and MREE: r = 0.72, $p < 0.01$ Equations both overestimated and underestimated MREE	The study demonstrates the variability in metabolic state, and the inaccuracy of several equations to estimate energy expenditure Limitations: single IC measurement during the PICU course; and no outcomes reported

ARDS = acute respiratory distress syndrome, BMR = basal metabolic rate, CRRT = continuous renal replacement therapy, DRI = Dietary Reference Intake, EN = enteral nutrition, FAO/WHO/UNU = Food Agriculture Organization/World Health Organization/United Nations University, IC = indirect calorimetry, IQR = interquartile range, MREE = measured resting energy expenditure, OR = odds ratio, PAL = physical activity level, PN = parenteral nutrition, RQ = respiratory quotient, TEE = total energy expenditure.

Question 2A. What Is the Recommended Energy Requirement for Critically Ill Children?

Recommendation 2A. Based on observational cohort studies, we suggest that measured energy expenditure by indirect calorimetry (IC) be used to determine energy requirements and guide prescription of the daily energy goal.

Quality of Evidence. Low.

GRADE Recommendation. Weak.

Question 2B. How Should Energy Requirement Be Determined in the Absence of IC?

Recommendation 2B. If IC measurement of resting energy expenditure (REE) is not feasible, we suggest that the Schofield or Food Agriculture Organization/World Health Organization (WHO)/United Nations University equations may be used "without" the addition of stress factors to estimate energy expenditure. Multiple cohort studies have demonstrated that most published predictive equations are inaccurate and lead to unintended overfeeding or underfeeding. The Harris-Benedict equations and the Recommended Daily Allowances (RDAs), which are suggested by the Dietary Reference Intakes, should not be used to determine energy requirements in critically ill children.

Quality of Evidence. Very low.

GRADE Recommendation. Weak.

Question 2C. What Is the Target Energy Intake in Critically Ill Children?

Recommendation 2C. Based on observational cohort studies, we suggest achieving delivery of at least two thirds of the prescribed daily energy requirement by the end of the first week in the PICU. Cumulative energy deficits during the first week of critical illness may be associated with poor clinical and nutritional outcomes. Based on expert consensus, we suggest attentiveness to individualized energy requirements, timely initiation and attainment of energy targets, and energy

TABLE 5. The Recommended Protein Requirement for Critically Ill Children

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
Randomized Controlled Trials			
Geukers et al (49)	RCT (double blinded), single center	To investigate the short-term (< 48 hr) effects of high protein dietary intake on whole body protein synthesis and balance, whole body valine kinetics, and rate of albumin synthesis on endocrine response	*n* = 28 (*n* = 20 analyzed) Postcardiac surgery Median age (range): experimental group, 7 mo (3–14 mo); control group, 12 mo (3–15 mo)
[1]de Betue et al (50) and [2]de Betue et al (48)	RCT, two centers	[1]Hypothesized that protein-enriched formula would stimulate amino acid (arginine) appearance and nitric oxide synthesis [2]To study the efficacy of increased protein and energy intake to promote protein synthesis	*n* = 18 Infants with RSV bronchiolitis requiring mechanical ventilation Mean age (SD): experimental, 2.7 mo (1.4 mo); control, 2.9 mo (1.8 mo)
Verbruggen et al (52)	RCT (crossover trial), single center	To investigate the effects of insulin infusion and increased PN AA intakes on whole body protein balance, glucose kinetics, and lipolysis	*n* = 9 Critically ill, insulin-resistant, septic adolescents receiving PN Mean age (SD): 15.0 yr (1.2 yr)
Botran et al (46)	RCT, single center	To determine if increased protein delivery improves protein metabolism with measurements of serum and urine markers and to evaluate safety and efficacy of increased protein dose	*n* = 51 children (41 analyzed) All required mechanical ventilation > 72 hr Median age (IQR): 7 mo (3–13 mo)
van Waardenburg et al (51)	RCT (double blind), two centers	To compare nutrient delivery, energy and nitrogen balance, and plasma amino acids with a protein-energy–enriched formula vs a standard formula and also to assess tolerance and safety of the protein-energy–enriched formula	*n* = 20 (*n* = 18 for analysis) Infants with RSV bronchiolitis requiring mechanical ventilation with expected length of stay > 96 hr Mean age (SD): experimental, 2.7 mo (0.5 mo); control, 3.0 mo (0.6 mo)

Intervention	Results/Outcome	Comments
EN initiated within 24 hr following PICU admission. Schofield equation used to determine energy needs Experimental group: high protein, 5 g/kg/d Control group: normal protein, 2 g/kg/d	Experimental vs control group Valine synthesis rate: 2.73 vs 2.26 μmol/kg/min Net valine balance: 0.54 vs 0.24 μmol/kg/min No differences between groups regarding cardiac intraoperative times	Unable to demonstrate improvement in protein balance (using stable isotopes and valine as an indicator) or a difference between the groups in fractional synthesis rate Limitations: not powered to test the primary outcome
EN started within 24 hr PICU admission; advanced by 25% of target volume every 12 hr Experimental group: Protein-energy–enriched formula: 2.6 g protein/100 mL, 100 kcal/100 mL Control group: Standard formula: 1.4 g protein/100 mL, 67 kcal/100 mL	Experimental vs control group Day 5 nutritional intake: 119 ± 25 vs 84 ± 15 kcal/kg/d; 3.1 ± 0.3 g/kg/d vs 1.7 ± 0.2 g/kg/d protein Whole body protein balance: 0.73 ± 0.5 vs 0.02 ± 0.6 g/kg/hr ($p = 0.026$) Protein synthesis: 9.6 ± 4.4 vs 5.2 ± 2.3 g/kg/d ($p = 0.019$) Protein breakdown: 8.9 ± 4.3 vs 5.2 ± 2.6 g/kg/d ($p = 0.046$) Nitrogen balance: 274 ± 127 vs 137 ± 53 mg/kg/d ($p < 0.05$) No significant differences in duration of mechanical ventilation or PICU length of stay; no intolerance or complications from the feeding regimens	Both studies demonstrated that protein-energy–enriched formula improved protein synthesis, protein metabolism, protein anabolism, and nitrogen balance vs standard formula Limitations: cointerventions were not described and small sample size
Experimental group: high (3.0 g/kg/d) PN AA Control group: standard (1.5 g/kg/d) PN AA Primed stable isotope tracer infusion with hyperinsulinemic euglycemic clamp	High AA intake improved protein balance ($p < 0.05$), insulin did not have an additive effect At high AA intake, endogenous glucose production was not suppressed by insulin and lipolysis rates increased	Standard PN AA was insufficient and high AA was needed to support positive protein balance Limitations: no discussion of impact of findings on PICU mortality or length of stay and small sample size
Unit feeding protocol: Continuous EN started within 24 hr of PICU admission to reach approximately 60 kcal/kg/d within first 24 hr IC, nitrogen balance, serum urea, albumin, total proteins, prealbumin, transferrin, retinol binding Study measurement times: baseline, 24 hr, 72 hr, 5 d Control diet: breast milk (1.1 g protein/100 mL) or cow milk–based formula (1.6 g protein/100 mL), or pediatric formula (2.6 g protein/100 mL) Experimental diet: same as control with supplementation of 1.1 g protein/100 mL	Intervention diet well tolerated No difference in IC measurements between groups Experimental vs control nutritional intake Mean 71.9 vs 65.9 kcal/kg/d (NS) Mean 3.1 vs 1.7 g/kg/d ($p = 0.004$) protein Positive nitrogen balance achieved by day 5 in experimental group	Protein supplementation resulted in positive nitrogen balance Limitations: 10 patients did not complete the study (six control, four experimental); no discussion on association(s) with mortality, duration of mechanical ventilation, or length of stay; and small sample size analyzed
Continuous EN target = 130 mL/kg/d; started at 25% of target, advanced 25% every 12 hr Study period: 5 d Experimental group Protein-energy–enriched formula: 100 kcal/100 mL, 2.6 g/100 mL Control group Standard formula: 1.4 g protein/100 mL, 67 kcal/100 mL	Experimental vs control groups Day 5 nutritional intake: 112 ± 13 vs 82 ± 4 kcal/kg/d ($p < 0.01$); 2.8 ± 0.3 vs 1.5 ± 0.1 g protein/kg/d ($p < 0.01$) Cumulative nitrogen balance, days 2–5: 866 ± 113 vs 297 ± 71 mg/kg/d ($p < 0.01$) Increased gastric residual volumes in protein-enhanced formula group ($p < 0.01$) No intolerance reported No differences between the groups in mechanical ventilation duration and PICU length of stay Positive nitrogen balance achieved on day 2 in experimental group vs up to day 4 for control group	Protein-energy–enriched formula improved energy and nitrogen balance Gastric residual volumes were statistically higher in the protein-energy–enriched formula, but clinically insignificant Limitations: small sample size

(*Continued*)

TABLE 5. (*Continued*). The Recommended Protein Requirement for Critically Ill Children

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
Chaloupecky et al (47)	RCT, single center	To evaluate the effect of nutritional support on the hypercatabolic reaction within 7 d following cardiac surgery	*n* = 37 Postcardiac surgery Mean age (SD): 6.7 mo (3.4 mo)
Observational Studies			
Jotterand Chaparro et al (36)	Prospective cohort, single center	To assess amount of protein and energy necessary to achieve nitrogen and energy balance and to compare protein and energy requirements with the ASPEN recommendations and DRIs	*n* = 76 Children requiring mechanical ventilation ≥ 72 hr Median age (IQR): 21 mo (4–35 mo)
Wong et al (44)	Retrospective cohort, single center	To describe nutrition support and identify adequate amount of protein received by children with ARDS and to determine whether provision of adequate nutrition is associated with decreased PICU mortality and improved clinical outcomes Adequate protein intake defined as = 1.5 g/kg/d by third day of ARDS	*n* = 107 Children with ARDS Median age (IQR): 5.2 yr (1.0–10.4 yr)
Mehta et al (9)	Multicenter, international prospective cohort; 59 PICUs in 15 countries	To examine the association between protein intake and 60-d mortality	*n* = 1,245 Critically ill children requiring mechanical ventilation (≥ 48 hr) Median age (IQR): 1.7 yr (0.4–7.0 yr)
Carlotti et al (54)	Prospective observational cohort, single center	Determine if negative balance of intracellular constituents are markers of cell catabolism and to evaluate effectiveness of nutrition therapy on rate of creatinine excretion	*n* = 17 Children with severe traumatic brain injury (Glasgow Coma Scale, ≤ 8) requiring mechanical ventilation with sedation and analgesics ± neuromuscular blockade Median age (range): 6 yr (2–14 yr)

Intervention	Results/Outcome	Comments
EN introduced day 2 Experimental group: PN with AA 0.8±0.1 g/kg/d Control group: 10% dextrose containing IV fluids without AA Measurements: plasma AA, urine 3-methylhistidine, nitrogen balance	Experimental vs control group Nitrogen balance: −114±81 vs 244±86 mg/kg/d ($p = 0.001$) Inverse ratio between nitrogen balance and urine 3-methylhistidine excretion in both groups No mortality	Group receiving PN with AA supplementation had less negative nitrogen balance compared with control group receiving no AA Limitations: small sample size
	Minimum 1.5 g/kg/d protein and 58 kcal/kg/d required to achieve nitrogen and energy balance in children up to 4 yr old; DRIs underestimated protein needs	The study establishes a threshold for energy intake and a relationship between energy and protein intake. ASPEN guidelines were close to study results (except in older children 4–8 yr) Limitations: small number of older children studied and patients with longer PICU stays had more measurements which may influence results
	Inadequate vs adequate protein intake ICU mortality: 60.2% vs 14.3%; $p = 0.002$ PICU-free days: 0 (0–15) vs 0 (0–14); $p = 0.940$ Ventilator-free days: 0 (0–4) vs 12 (3–19); $p = 0.005$ Multiple organ dysfunction: 70.7% vs 50%; $p = 0.136$ Inadequate protein delivery, Pediatric Index of Mortality 2 score, and oxygenation index were independent predictors of increased PICU mortality	Early initiation of nutrition support with adequate protein was associated with improved outcomes in children with ARDS Limitations: nutritional status was not documented, and its impact on outcomes is not shown; measured resting energy expenditure was not used
	$n = 985$ received EN Mean % delivery of prescribed: Energy: 36% ± 35% Protein: 37% ± 38% Adequate enteral protein intake was significantly associated with 60-d mortality ($p < 0.001$) after adjustment for disease severity, site, PICU days, and energy intake Mean enteral protein intake < 20% vs ≥ 60% of prescribed goal, OR for 60-d mortality: 0.14 (95% CI, 0.04–0.52; $p = 0.003$)	Adequate protein intake was associated with lower mortality Results generalizable to children on mechanical ventilation in PICUs with more than eight beds Limitations: noninterventional, observational study
	Anabolism was associated with increased protein intake: median 1.1 (0.7–2.2) g/kg/d vs catabolism median 0.1 (0–1.8) g/kg/d ($p < 0.0001$) Positive correlation: protein intake and balance, $R = 0.63$ ($p < 0.0001$) Positive balance for phosphate and magnesium with protein intake 0.5–1 g/kg/d Negative correlation: creatinine clearance and protein balance, $R = -0.45$ ($p < 0.0001$) Negative protein balance associated with pneumonia, sepsis, increased creatinine excretion	Patients with traumatic brain injury with negative protein balance also had negative balances in other intracellular markers; together these findings suggest losses of lean body mass Minimum intake of 1 g/kg/d protein and ≥ 50% of goal energy using Holliday-Segar formula were associated with a positive protein balance, except in septic patients Limitations: small sample size

(*Continued*)

TABLE 5. (*Continued*). The Recommended Protein Requirement for Critically Ill Children

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
Zappitelli et al (26)	Retrospective collaborative registry	To evaluate protein and caloric prescription and to evaluate factors associated with over- and under-prescription of protein and calories	*n* = 195 Critically ill children and young adults with acute kidney injury receiving CRRT Mean age (SD): 8.8 yr (6.8 yr)

AA = amino acids, ARDS = acute respiratory distress syndrome, ASPEN = American Society for Parenteral and Enteral Nutrition, CRRT = continuous renal replacement therapy, DRI = Dietary Reference Intake, EN = enteral nutrition, IC = indirect calorimetry, IQR = interquartile range, OR = odds ratio, PN = parenteral nutrition, RCT = randomized controlled trial, RSV = respiratory syncytial virus.

balance to prevent unintended cumulative caloric deficit or excesses.

Quality of Evidence. Low.

GRADE Recommendation. Weak.

Rationale. Metabolic alterations are common in critical illness and patients present with a variety of metabolic states that cannot be predicted, including hypometabolism (measured resting energy expenditure [MREE], < 90% of predicted), normal metabolism (MREE, 90–110% predicted), and hypermetabolism (MREE, > 110% predicted) (21–25). Currently available equations fail to estimate energy expenditure within ± 10% of MREE in a majority of critically ill children; IC is the only available method to accurately determine energy requirements for this population (21, 28–33). Energy expenditure measured by IC in critically ill children is independent of nutritional status, initial diagnosis, or severity of the acute illness (30–32, 34). MREE may be decreased during deep sedation and neuromuscular blockade, severe hypothyroidism, or increased with temperature greater than 38°C and prolonged PICU LOS (16, 30). In cohort studies, MREE did not significantly vary within the same patient over time (21, 28, 35). After the baseline, MREE is performed (ideally during the first week of critical illness); repeat measurements may be obtained in patients with significant changes in clinical status (27, 35). Patients at high risk for metabolic alterations are appropriate candidates for targeted MREE with IC, especially if this resource is limited (**Appendix 1**).

If IC is not feasible, the Schofield weight-height or weight equations or the WHO equations may be used to estimate energy expenditure (37–39). However, stress factors must be used selectively with caution, as their routine use might result in unintended overfeeding. In recent studies, hypometabolism has been demonstrated in patients after major cardiac surgery, and following hematopoietic stem cell transplantation (25, 40, 41). When using an equation to estimate energy requirements, it is essential to vigilantly monitor for potential signs of overfeeding (hyperglycemia, hypertriglyceridemia, increased Co_2 production, increased arm circumference, and rapid or excessive weight gain) and underfeeding (weight loss, decreased arm circumference, malnutrition, prolonged dependency on mechanical ventilation, and increased length of PICU stay). In particular, equations such as the Harris-Benedict and the RDAs developed for healthy adults and growing children, respectively, over-predict energy requirements and should not be used to determine energy requirements in critically ill children. Because IC is not widely available clinically, and predictive equations are consistently inaccurate, innovative efforts must focus on discovering more accessible surrogates of MREE. A simplified equation based on measured volumetric Co_2 (VCo_2) was recently developed in mechanically ventilated children and was found to be more accurate than equation-estimated energy expenditure (42, 43). The increased use of devices that provide bedside VCo_2 measurement in the PICU may allow this equation to replace the Schofield or WHO equations for determination of energy requirement in mechanically ventilated patients.

Observational data suggest a positive association between adequacy of energy intake and improved outcomes in the PICU population (8, 36, 44). Intake of greater than two thirds of estimated energy goal in a large, multicenter, prospective cohort and greater than 80% of estimated energy goal in a smaller, single-center, retrospective cohort was significantly associated with reduced mortality in mechanically ventilated, critically ill children (8, 44). Higher energy intake of 54–58 kcal/kg/d is positively correlated with achieving protein balance and anabolism (36, 45). Based on hypometabolic states described in a variety of pediatric illnesses and reduced mortality associated with intake of greater than two thirds of energy goal, achievement of 100% of estimated energy requirement may not be necessary in all patients (8, 22, 24, 40, 41).

Future Direction. Future studies must examine the optimal energy dose that is associated with improved nutritional and clinical outcomes in critically ill children. The impact of route of nutrition delivery must be examined when discussing this dose-outcome relationship.

Question 3A. What Is the Minimum Recommended Protein Requirement for Critically Ill Children?

Recommendation 3A. Based on evidence from RCTs and supported by observational cohort studies, we recommend a

Intervention	Results/Outcome	Comments
	Maximum protein: 2 ± 1.5 g/kg/d Median protein dose by day 5: > 2 g/kg/d Maximum energy: 48.2 ± 31.5 kcal/kg/d Predictors of higher protein and calorie intake: younger age ($p = 0.04$), higher initial protein or calories at initiation of CRRT ($p < 0.0001$), longer duration of CRRT ($p < 0.003$)	Study reports feasibility of adequate protein prescription in patients on CRRT Limitations: no recommendations for protein or caloric doses and did not assess nutrition or clinical outcomes

minimum protein intake of 1.5 g/kg/d. Protein intake higher than this threshold has been shown to prevent cumulative negative protein balance in RCTs. In critically ill infants and young children, the optimal protein intake required to attain a positive protein balance may be much higher than this minimum threshold. Negative protein balance may result in loss of lean muscle mass, which has been associated with poor outcomes in critically ill children. Based on a large observational study, higher protein intake may be associated with lower 60-day mortality in mechanically ventilated children.

Quality of Evidence. Moderate.

GRADE Recommendation. Strong.

Question 3B. What Is the Optimal Protein Delivery Strategy in the PICU?

Recommendation 3B. Based on results of randomized trials, we suggest provision of protein early in the course of critical illness to attain protein delivery goals and promote positive nitrogen balance. Delivery of a higher proportion of the protein goal has been associated with positive clinical outcomes in observational studies.

Quality of Evidence. Moderate.

GRADE Recommendation. Weak.

Question 3C. How Should Protein Delivery Goals Be Determined in Critically Ill Children?

Recommendation 3C. The optimal protein dose associated with improved clinical outcomes is not known. We do not recommend the use of RDA values to guide protein prescription in critically ill children. These values were developed for healthy children and often underestimate the protein needs during critical illness.

Quality of Evidence. Moderate.

GRADE Recommendation. Strong.

Rationale. Randomized clinical trials of protein supplementation have included small sample sizes, heterogeneous patient populations, use of the enteral, parenteral, or combined routes, and varied protein doses (0.7–5 g/kg/d) in the experimental group. Higher protein doses were associated with positive nitrogen balance, a surrogate for protein balance. These studies evaluated protein turnover and balance by stable isotope-labeled amino acid methods or with urinary urea nitrogen to obtain nitrogen balance (46–53). Variation in the methods used to assess protein balance further limits the interpretation of absolute values. These studies indicate an association between higher protein dose and positive protein balance. In a systematic review of studies in mechanically ventilated PICU patients, a minimum protein intake of 1.5 g/kg/d and a minimum energy intake of 54 kcal/kg/d were associated with achievement of positive nitrogen balance (45). In another cohort study of 76 mechanically ventilated children, a minimum daily threshold delivery of 1.5 g/kg protein and 58 kcal/kg energy was required to achieve a positive nitrogen and energy balance (36). In a recent large, prospective, international, multicenter ($n = 59$), observational study of 1,245 mechanically ventilated children from 15 countries, a total of 985 subjects received EN; delivery of greater than 60% of prescribed enteral protein goal was significantly associated with decreased 60-day mortality (< 20% vs > 60%; odds ratio, 0.14 [0.04–0.52]; $p = 0.003$) after adjustment for disease severity, site, PICU days, and energy intake (9). Hence, at the very minimum, a protein intake of 1.5 g/kg/d must be ensured to avoid cumulative protein deficits in critically ill children. The optimal protein intake threshold for infants and young children is likely to be higher than this value. Specific subgroups, such as infants and young children admitted with bronchiolitis or other causes of respiratory failure requiring mechanical ventilation, require 2.5–3 g/kg protein daily to improve protein balance (46, 48, 51). Protein intake was well tolerated in the above studies. However, the safety of protein intake greater than 3 g/kg/d in children more than 1 month old has not been adequately demonstrated and may be associated with increased blood urea nitrogen. The effect of the route of protein delivery, enteral versus parenteral, on clinical outcomes is unclear. In particular, the role of early parenteral protein intake has not been shown, and most studies demonstrating the benefits of higher protein intake have utilized the enteral route.

Current evidence for increased protein dosing in critically ill children exceeds RDA recommendations and recommendations from WHO. These recommendations are calculated estimates from derived equations of protein deposition in healthy children and do not account for the increased protein breakdown that occurs during critical illness (9, 36, 39). The use of RDA recommendations to guide protein intake during critical illness may lead to unintended negative protein balance. The determination of protein requirements for obese patients in the PICU may be challenging. The

TABLE 6. Feasibility and Benefits of Enteral Nutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility	Results/Outcome	Comments
Wong et al (44)	Retrospective cohort, single center	To determine whether the provision of adequate nutrition is associated with improved clinical outcomes	*n* = 107 Critically ill children with ARDS Median age: 5.2 yr (IQR, 1.0–10.4 yr)	28 (26.2%) of patients received early EN (within 24 hr of ARDS) PICU mortality was lower in patients who received adequate calories (34.6% vs 60.5%; $p = 0.025$) and adequate protein (14.3% vs 60.2%; $p = 0.002$) compared with those who did not	The authors report an association between adequacy of energy and protein intake and survival in children with ARDS Limitations: underpowered study; nutrition prescription was dependent on the clinical practitioner preference; and energy needs were estimated using equations
Mehta et al (9)	Prospective, cohort, multicenter 59 PICUs in 15 countries	To examine the association between protein intake and 60-d mortality in mechanically ventilated children	*n* = 1,245 Critically ill children receiving mechanical ventilation for ≥ 48 hr Median age (IQR): 1.7 (0.4–7.0) yr	*n* = 985 received EN The mean delivery of enteral energy and protein was 36% ± 35% (SD) and 37% ± 38%, respectively The adequacy of enteral protein intake was significantly associated with 60-d mortality ($p < 0.001$) after adjustment for disease severity, site, PICU days, and energy intake	Large, multicenter, prospective cohort study found an association with adequacy of enteral protein intake and decreased mortality Limitations: only PICUs with more than eight beds were included; the energy intake goals were estimated by dietitians at each site; and variability of nutritional practices at the participating sites
Mikhailov et al (66)	Retrospective cohort study, multicenter database	To determine whether early EN (within 48 hr of admission) is associated with lower mortality, shorter LOS, and shorter duration of mechanical ventilation	*n* = 5,105 Critically ill children with PICU LOS ≥ 96 hr Median age (IQR): 2.4 (0.5–9.8) yr	Early EN was achieved by 27.1% of patients Children receiving early EN were less likely to die than those who did not (OR, 0.51 [0.34–0.76]; $p = 0.001$), adjusted for propensity score, Pediatric Index of Mortality 2 score, age, and center LOS and duration of mechanical ventilation were not different between the groups that received early EN vs the group that did not	The authors report an association between receiving early EN and improved survival Propensity analyses demonstrated this relationship in their large database Limitations: energy needs estimated by equations; not all sources of energy were included; patients were included only if PICU stay was ≥ 96 hr; and inaccuracies of nutritional data recorded in health records

(*Continued*)

TABLE 6. (*Continued*). Feasibility and Benefits of Enteral Nutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility	Results/Outcome	Comments
Panchal et al (65)	Retrospective cohort, single center	To evaluate the safety of enteral feeding in critically ill children receiving vasoactive medications	$n = 339$ received greater than or equal to one vasoactive drug $n = 188$ fed and $n = 155$ nonfed based on EN received the first 4 d of admission to PICU	Patients in the fed group were younger ($p < 0.001$) and had a lower mortality ($p < 0.01$) vs the nonfed group The Vasoactive-Inotropic Score in the nonfed group was higher only on day 1 ($p < 0.05$) vs the fed group. Gastrointestinal outcomes were not different between the two groups	The authors found no adverse effects with the use of vasoactive medications during EN delivery Large sample size Limitations: the effect of greater than one vasoactive drug on intolerance to EN is not known. Retrospective study with limitations of clinical and nutrition data in health records The study showed that patients with vs without AKI are more likely to be underfed
Kyle et al (67)	Retrospective cohort, single center	To describe energy and protein EN delivery in PICU patients with and without AKI	$n = 167$ Critically ill children with PICU LOS > 3 d $n = 65$ with AKI $n = 102$ without AKI	Overall (PN and EN) protein intake was 19% and energy intake was 55% of goal AKI (injury and failure) had higher likelihood of fasting days and energy provision < 90% BMR	Limitations: does not describe outcomes related to nutrient adequacy
Kyle et al (68)	Retrospective cohort, single center	To examine current nutrition practices and the adequacy of nutrition support in the PICU	$n = 240$, Critically ill children with PICU LOS > 48 hr Documented nutrient intake by all routes (PN and EN) in the first 8 d in PICU	Actual energy intake for all patient-days was 75.7% ± 56.7% of estimated BMR Actual protein intake for all patient-days was 40.4% ± 44.2% of estimated requirements	Patients in this large tertiary PICU study received less than half of recommended protein intake Limitations: results may not be applicable to other PICUs; and energy and protein needs based on reference values
Mehta et al (8)	Prospective cohort study, multicenter 31 PICUs in eight countries	To evaluate adequacy of energy and protein intake in the PICU and their relationship to clinical outcomes	$n = 500$ Children on mechanical ventilation Mean age (SD): 4.5 yr (5.1 yr)	Mean prescribed goals for energy and protein intake were 64 kcal/kg/d and 1.7 g/kg/d, respectively; EN was used in 67% of the patients and was initiated within 48 hr of admission A higher percentage of goal energy intake via enteral route was significantly associated with lower 60-d mortality Mortality at 60 d was 8.4%	Large, multicenter, prospective cohort study found an association between higher enteral energy intake and lower mortality Limitations: energy needs estimated by equations; almost one third of the patients had missing severity of illness scores; only PICUs with more than 8 beds were included; variability in staff skills, availability and adherence to protocols, and resource availability could have influenced the results

(*Continued*)

TABLE 6. (*Continued*). Feasibility and Benefits of Enteral Nutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility	Results/Outcome	Comments
Mehta et al (61)	Prospective cohort, single center	To identify risk factors associated with avoidable interruptions to EN in critically ill children. Also, to evaluate the frequency of avoidable EN interruptions and their impact on nutrient delivery	*n* = 117 PICU population with LOS ≥ 24 hr Median age (IQR): 7.2 yr (1.7–15.3 yr)	68% received EN (20% postpyloric) for a total of 381 EN days (median, 2 d) Median time to EN initiation was < 1 d EN was interrupted in 30% at an average of 3.7 ± 3.1 times per patient (range, 1–13), for a total of 88 episodes accounting for 1,483 hours of EN deprivation in this cohort 51 of 88 (58%) episodes of EN interruptions were deemed avoidable in 15 of 80 patients. Avoidable EN interruption was associated with increased reliance on PN and impaired ability and time required to reach caloric goal, and increased costs	This study highlights factors such as prolonged fasting around procedures and intolerance, which impede optimal EN delivery. EN is frequently interrupted in the PICU; > 50% of interruptions are "avoidable" Infants and those on mechanical ventilation at risk for EN interruptions Limitations: practices and challenges might be different in other centers
de Oliveira Iglesias et al (62)	Prospective cohort, single center	To compare prescribed vs delivered energy; identify EN barriers in first 5 d of PICU stay	*n* = 58 Patients admitted to PICU and received EN for > 48 hr	Daily average intake met 60% required kilocalories and 85% prescribed kilocalories Gastrointestinal complications and use of vasoactive drugs (alpha-1 adrenergic agonists) were associated with lower energy provision	This study highlighted factors that impede optimal delivery of EN Limitations: practices and challenges might be different in other centers; and no outcomes described
King et al (64)	Retrospective cohort, single center	Evaluate the tolerance of EN in children receiving cardiovascular medications	*n* = 52 Received EN and cardiovascular medications in the same 24-hr period Age: 1 mo to 20 yr	Dopamine at ≥ 6 μg/kg/min was used in 17 patients (31%) and dopamine + norepinephrine in 23 patients (42%) 71% had ≥ 1 feeding interruption with 70% of interruptions not related to gastrointestinal tolerance; vomiting was reported in 12 (23%); four patients had gastrointestinal bleeding	The study reported reasonable EN tolerance in patients receiving cardiovascular drugs in the PICU Limitations: retrospective review with limitations of clinical data in medical records

AKI = acute kidney injury, ARDS = acute respiratory distress syndrome, BMR = basal metabolic rate, EN = enteral nutrition, IQR = interquartile range, LOS = length of stay, OR = odds ratio, PN = parenteral nutrition.

recommendation of a minimum of 1.5 g/kg/d should also be applied to this population, using their ideal body weight. This population is at risk of undetected lean body mass erosion. A reliable method to monitor the body composition for the critically ill pediatric population, particularly obese children, is needed to better address their optimal macronutrient needs.

Future Direction. Future studies are needed to determine the optimal dose of protein that improves protein balance, nutritional status (e.g., muscle mass and function), and relevant clinical outcomes (e.g., duration of mechanical ventilation, PICU LOS, and mortality). Future studies must also examine the effect of specific protein sources and the route of delivery on outcomes.

Question 4A. Is EN Feasible in Critically Ill Children?

Recommendation 4A. Based on observational studies, we recommend EN as the preferred mode of nutrient delivery to the critically ill child. Observational studies support the feasibility of EN, which can be safely delivered to critically ill children with medical and surgical diagnoses, and to those receiving vasoactive medications. Common barriers to EN in the PICU include delayed initiation, interruptions due to perceived intolerance, and prolonged fasting around procedures. Based on observational studies, we suggest that interruptions to EN be minimized in an effort to achieve nutrient delivery goals by the enteral route.

Quality of Evidence. Low.

GRADE Recommendation. Strong.

Question 4B. What Is the Benefit of EN in This Group?

Recommendation 4B. Although the optimal dose of macronutrients is unclear, some amount of nutrient delivered as EN has been beneficial for gastrointestinal mucosal integrity and motility. Based on large cohort studies, early initiation of EN (within 24–48 hr of PICU admission) and achievement of up to two thirds of the nutrient goal in the first week of critical illness has been associated with improved clinical outcomes.

Quality of Evidence. Low.

GRADE Recommendation. Weak.

Rationale. The enteral route is the preferred modality to provide nutrition support to adults and children. Animal studies have demonstrated the beneficial effects of EN on gut-associated lymphoid tissue, mucosal immunity, and improved survival after *Escherichia coli*–induced peritonitis and brief intestinal ischemia (56–60). Early initiation of EN is preferred in most PICUs. However, a variety of challenges impedes early initiation and maintenance of EN in children during critical illness (61, 63). Many of these perceived barriers to EN may be avoidable (61). In large cohorts of patients on vasoactive medications in the PICU, EN was administered without any significant adverse events (64, 65). Although the physician decision to start EN in patients may have been biased by the clinical condition of the patient, gastrointestinal complications (vomiting, diarrhea, bleeding, and abdominal distension), other severe feeding-related complications, or mortality were not increased in the group who received vasoactive medications (65).

Cohort studies of children admitted to the PICU have reported improved survival with optimal nutrient intake by the enteral route. In two large international prospective cohort studies of mechanically ventilated children, enteral delivery of greater than two thirds of the energy goal and greater than 60% of the protein goal was significantly associated with lower 60-day mortality (8, 9). These benefits were not seen for nutrients delivered via the parenteral route. In a large, retrospective, multicenter study of 5,105 patients from 12 centers, the provision of one-fourth goal calories enterally over the first 48 hours of admission was associated with reduced PICU mortality (66). In another retrospective cohort of 107 children with acute respiratory distress syndrome, enteral delivery of adequate calories (≥ 80% estimated goal) and protein (≥ 1.5 g/kg/d) was associated with a reduction in ICU mortality (44). Hence, EN is feasible during acute critical illness and must be prioritized as the preferred route for nutrient delivery.

Future Direction. Future studies evaluating the feasibility of EN in critically ill children should examine its impact on well-defined outcomes. Higher quality randomized study designs should evaluate the benefits of providing adequate EN with predefined energy and protein goals.

Question 5A. What Is the Optimum Method for Advancing EN in the PICU Population?

Recommendation 5A. Based on observational studies, we suggest the use of a stepwise algorithmic approach to advance EN in children admitted to the PICU. The stepwise algorithm must include bedside support to guide the detection and management of EN intolerance and the optimal rate of increase in EN delivery.

Quality of Evidence. Low.

GRADE Recommendation. Weak.

Question 5B. What Is the Role of a Nutrition Support Team or a Dedicated Dietitian in Optimizing Nutrition Therapy?

Recommendation 5B. Based on observational studies, we suggest a multidisciplinary nutrition support team, including a dedicated dietitian, be available on the PICU team, to facilitate timely nutritional assessment, and optimal nutrient delivery and adjustment to the patients

Quality of Evidence. Low.

GRADE Recommendation. Weak.

Rationale. Despite the preference for the enteral route for nutrition delivery and benefits reported by many authors, the practice of providing EN to critically ill children is variable. There is no uniform approach to initiate and advance EN. A stepwise protocol/algorithm is expected to address barriers to EN such as prolonged interruptions due to procedures, lack of a clear definition of feeding intolerance, and management of mechanical issues with feeding tubes, among others. The

TABLE 7. Optimum Method for Advancing Enteral Nutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
Kaufman et al (69)	Before/after cohort, single center	To examine the role of a multistep intervention including a guideline in improving energy and protein delivery	*n* = 106 Preintervention *n* = 260 Postintervention Predominantly newborns < 1 mo in the cardiac ICU
Hamilton et al (70)	Before/after cohort, single center	To examine the role of a stepwise EN advancement algorithm on adequacy of EN delivery, ability to reach goal, and time to reach energy goal	*n* = 80 Preintervention *n* = 80 Postintervention Heterogeneous PICU population with length of stay > 24 hr
Yoshimura et al (72)	Prospective case series, single center	To investigate the safety and efficacy of an EN protocol after its implementation	*n* = 62 Preintervention *n* = 47 Postintervention
Meyer et al (79)	Time series, single center	To examine the impact of introducing a series of enteral feeding protocols on nutritional practice in a PICU over a 9-yr period	*n* = 400 Over a 9-yr period and spanning four studies
Petrillo-Albarano et al (71)	Before/after cohort, single center	To examine the implementation of an early, aggressive, enteral feeding protocol in the PICU, and to describe its impact on time to achieving goal feedings and complications associated with enteral feeding	*n* = 91 Preintervention *n* = 93 Postintervention Critically ill children who received NGT feeding
Briassoulis et al (78)	Prospective study, single center	To investigate the feasibility, adequacy, and efficacy of early intragastric feeding	*n* = 71 Children requiring mechanical ventilation Mean age (range): 54 mo (2–204 mo)

EAR = estimated average requirements, EN = enteral nutrition, NGT = nasogastric tube, PN = parenteral nutrition.

Intervention	Results/Outcome	Comments
The EN protocol: start with 0.5 mL/kg/hr, advance by the same rate every 4–6 hr until goal is reached Intervention also included calorie counts, screening by specialists, bedside discussion of delivery, guideline (stepwise) for nutrient delivery Goal calories for full-term intubated and nonintubated infants: 80 and 100–130 kcal/kg/d, respectively	The percentage of patient days in a month when daily caloric goals were met increased from 50.1% to 60.7% from the preintervention to intervention period. The percentage of patient days when daily protein goals were met increased from 51.6% to 72.7% from similar periods	The study involves children in the cardiac ICU—predominantly newborns and some older infants Difficult to parse the older children from neonates Overall, the use of EN algorithm resulted in increased likelihood of reaching protein delivery goals
The protocol included nutritional assessment and goals, mode of nutrition (EN vs PN), route of EN (gastric vs postpyloric), initiation of EN, and maintenance of EN. Also included a stepwise EN algorithm development and systematic implementation in the PICU	Median time to reach energy goal decreased from 4 to 1 d ($p < 0.05$), with a higher proportion of patients reaching this goal (99% vs 61%; $p = 0.01$) Decrease in avoidable EN interruptions (3 vs 51; $p < 0.0001$) and decreased use of PN in this subset	The study reports significantly decreased time to reach and increased likelihood of reaching nutrient delivery goals after instituting a step-wise EN algorithm Limitations: no difference in clinical outcomes
The EN protocol had caloric goal-based advancements: the goal on day 1 was set at 40% of target dose and advanced by 20% each day to reach 100% by day 4	The time until initiation of EN (median of 22 vs 20 hr) and the total calories provided did not differ significantly The proportion of energy provided by EN and PN in the postgroup was significantly higher and smaller, respectively, vs the preimplementation group The frequency of vomiting was significantly lower in the postgroup vs the pregroup, and the incidence of necrotizing enterocolitis was not different between the groups	The study reports higher proportion of nutrient delivery and lower incidence of EN intolerance after implementing the algorithm in children after cardiac surgery No increase in necrotizing enterocolitis Limitations: no difference in clinical outcomes
Baseline evaluation followed by NGT feeding protocols, specifying feeding rate, type of feed, and gastric residual volume management were introduced and then further protocols (including nasojejunal tube feeding algorithm) were introduced	Over the four time periods that represented the baseline and modifications of an incremental protocol, the following serial changes were noted: Median time to initiate EN: 15, 8, 5.5, and 4.5 hr Patients receiving EN: 89%, 81%, 99%, and 96% Patients receiving PN: 11%, 19%, 1%, and 4% Patients reaching 50% of EAR by day 3: 15%, 26%, 58%, and 59% Patients reaching 70% of EAR by day 3: 6%, 10%, 35%, and 21%	EN protocols shortened the time to EN initiation, increased the number of patients fed enterally, and decreased the number of patients fed parenterally Limitations: no changes in clinical outcomes
Initiation of a feeding protocol in the PICU The protocol also included guidance on EN tolerance and management/prevention of constipation	Outcome variables for postintervention vs preintervention groups: Time to achieve goal feeding (median): 14 vs 32 hr; $p < 0.001$ Reduction in percentage of patients with emesis and constipation	This study demonstrated that a stepwise nutrition protocol reduced time to achieving goal feeding and improved nutrition tolerance Limitations: no differences in clinical outcomes
Initiation of a feeding protocol in the first 12 hr of admission to PICU	Energy intake approached predicted basal metabolic rate the second day (43 ± 1 vs 43.2 ± 1.1 kcal/kg/d) and predicted energy expenditure (based on stress factors) the fifth day (66.2 ± 2.7 vs 67.7 ± 6.4 kcal/kg/d)	The study showed the utility of a protocol to advance EN increased caloric intake during the first 5 d of admission to the PICU Limitations: energy needs were based on equations and stress factors

TABLE 8. Optimal Route (Gastric or Small Bowel) and Timing of Enteral Nutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
Randomized Controlled Trials			
Meert et al (82)	RCT, single center	To evaluate the effect of gastric vs small bowel feeding tube position on: 1) Nutrient delivery 2) Feeding complications, including micro aspiration using pepsin in tracheal aspirates	*n* = 74 Mechanically ventilated, critically ill children *n* = 32 gastric *n* = 30 small bowel 12 of 42 randomized to postpyloric group were unable to have feeding tube placed and exited the study
Kamat et al (81)	RCT, single center	To evaluate the frequency of clinical and subclinical aspiration in mechanically ventilated, critically ill children fed gastric vs postpyloric and to compare methylene blue to glucose in tracheal aspirate to detect aspiration	*n* = 44 *n* = 17 postpyloric Median age (95% CI): 17 mo (6.3–62.8 mo) *n* = 27 gastric Median age (95% CI): 4.2 mo (1.5–55.9 mo) Two of 19 randomized to postpyloric group were unable to have feeding tube placed after 24 hr and four abdominal radiographs; moved to the gastric group
[1]Horn et al (77) and [2]Horn et al (83)	RCT—convenience sample, single center	[1]To examine the relationship between two gastric feeding regimens—continuous and intermittent, and tolerance as measured by the number of stools and prevalence of diarrhea (≥ 3 stools/24 hr) and vomiting [2]To examine the effect of gastric feeding regimens, either continuous or intermittent, on GRV, defined as > 5 mL/kg	*n* = 46 *n* = 22 continuous feeding Median age: 6 mo (0–146 mo) *n* = 24 intermittent feeding (one subject removed due to only 1 d of feeding; final *n* = 23) Median age: 8 mo (1–153 mo) Random assignment to feeding regimen
Observational Studies			
Canarie et al (89)	Retrospective cohort, multicenter Six PICUs	To determine the factors associated with delayed EN Patients divided into two groups: early EN (≤ 48 hr) and delayed EN (> 48 hr) from PICU admission	*n* = 444 Median age (IQR): 4.0 yr (0.5–11.9 yr)
Mikhailov et al (66)	Retrospective cohort study, multicenter 12 PICUs	To examine the association of early EN with mortality and morbidity Early EN definition: provision of 25% of cumulative goal EN calories over the first 48 hr of admission	*n* = 5,105 Critically ill children with PICU LOS ≥ 96 hr Median age (IQR): 2.4 yr (0.5–9.8 yr)

Intervention	Results/Outcome	Comments
Gastric vs postpyloric feeding	No significant differences between groups for mortality, PICU LOS, hospital LOS, pneumonia, duration of mechanical ventilation, intolerance (vomiting, diarrhea, and abdominal distension), interruption to feeds, or tracheal aspirates positive for pepsin Experimental (small bowel) group had significantly higher energy intake (mean, SD percent of goal): 47% ± 22% vs 30% ± 23%; $p = 0.01$	This randomized trial did not show a significant difference in rates of aspiration or feeding tolerance between gastric and postpyloric feeding groups Limitations: aspiration detected by a crude marker (pepsin in tracheal aspirates); a large proportion of patients in each group had significant number of EN interruptions and did not reach goal; and no difference in clinical outcomes
Gastric vs postpyloric feeding Methylene blue: 0.2 mL/100 mL formula Endotracheal specimen every 8 hr: bedside test for glucose, spectrophotometry to detect methylene blue	Experimental vs control group Time to start feeds: median (95% CI), 24 (18–24) vs 6 (6–12) hr; $p = 0.0002$ Median (95% CI) number of abdominal radiographs: 4 (3–4) vs 1 (1–1); $p = 0.001$	No benefit of postpyloric over gastric feeds. The postpyloric group experienced significant delays in EN initiation due to the time required for feeding tube placement Centers with greater proficiency with postpyloric feeding tubes may secure placement more quickly Limitations: study underpowered to show a difference in aspiration between groups; glucose in tracheal aspirates lacks specificity and is not a marker of aspiration; and methylene blue is no longer used due to safety concerns
Experimental group: continuously fed using pump Control group: feedings delivered every 2 hr over 20–30 min using gravity method (standard practice)	[1]No significant differences in mean stool volume, diarrhea, vomiting, use of prokinetic agents, or antibiotic use [2]Experimental group vs control group: no significant differences in volume of formula received, GRV values, or incidence of GRV > 5 mL/kg. Time to initiation of feeds (hr): 13.0 (1–63) vs 18.5 (3–231); $p = 0.05$	No difference in feeding tolerance or GRV between continuous and intermittent feeding groups Limitations: timing of enrollment, in relation to critical illness is unclear; accurate adequacy of feeding not available; used nonvalidated criteria (GRV > 5 mL/kg); and small sample size (convenience sample)
	EN was started at median of 20 hr 88 of 444 children (19.8%) had delayed EN Risk factors associated with delayed EN: noninvasive (OR, 3.37 [1.69–6.72]) and invasive positive-pressure ventilation (OR, 2.06 [1.15–3.69]), severity of illness (OR for every 0.1 increase in PIM2 score, 1.39 [1.14–1.71]), procedures (OR, 3.33 [1.67–6.64]), and gastrointestinal disturbances (OR, 2.05 [1.14–3.68]) within 48 hr after admission to the PICU	Large multicenter report of EN practices in critically ill children, highlighting the role of noninvasive ventilation, procedures, gastrointestinal disturbances, and high illness severity as factors that result in delayed EN delivery Limitations: accuracy of clinical and nutritional data from retrospective chart review at different sites cannot be assured and decision making was not protocolized, therefore rationale for withholding EN may be uncertain
	27.1% achieved early EN Mortality: 5.3% Difference in outcomes between early EN vs no early EN (adjusted for PIM2, age, center) Mortality: OR, 0.51 (CI 0.34–0.76); $p = 0.001$ No difference in LOS or mechanical ventilation duration	Early EN was associated with reduced mortality in this large multicenter cohort Limitations: accuracy may be limited by the retrospective nature of the study and reliance on charts and database for detailed nutrient delivery data

(*Continued*)

TABLE 8. (*Continued*). Optimal Route (Gastric or Small Bowel) and Timing of Enteral Nutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
Mehta et al (8)	Prospective cohort study, multicenter 31 PICUs in eight countries	To evaluate adequacy of energy and protein intake in the PICU and their relationship to clinical outcomes	*n* = 500 Critically ill children requiring mechanical ventilation ≥ 48 hr Mean age (sd): 4.5 yr (5.1 yr)
Taha et al (86)	Retrospective cohort, single center	To evaluate the impact of the time of initiation of nutritional support and achieving full caloric intake on PICU LOS and disposition status at discharge	*n* = 109 Median age (range): 13 yr (8–18 yr) Children severe isolated TBI Median Glasgow Coma Scale on admission to the ICU: 3
Tume et al (87)	Prospective cohort, single center	1) To compare actual calorie intake with estimated requirements 2) Determine whether feeding guideline adherence resulted in improved nutritional intake	*n* = 47 Median age (range): 10 mo (0.03–168 mo)
López-Herce et al (84)	Prospective cohort, single center	Evaluate tolerance and adverse effects of postpyloric EN in critically ill children with shock vs without shock	*n* = 526 Critically ill children admitted to PICU and received postpyloric EN *n* = 65 with shock Median age (range): 12 mo (0.7–264 mo) *n* = 461 without shock Median age (range): 5 mo (0.1–228 mo); *p* = 0.0001
Sánchez et al (88)	Prospective cohort, single center	To compare tolerance and complications associated with early vs late transpyloric EN Early EN definition: < 24 hr from PICU admission	*n* = 526 Critically ill children admitted to PICU and received transpyloric EN *n* = 202 early EN *n* = 324 late EN

Intervention	Results/Outcome	Comments
	Mean prescribed goals Energy: 64 kcal/kg/d Protein: 1.7 g/kg/d EN started in ≤ 48 hr from admission in 67% of patients 60-d mortality: 8.4% A higher percentage of goal energy intake via EN was significantly associated with lower 60-d mortality	Higher enteral energy intake was associated with lower mortality in this large multicenter prospective cohort study Limitations: energy needs were estimated by dietitians at participating sites (mostly by equations); severity of illness scores not available in a third of the cohort; only PICUs with greater than or equal to eight beds were included; and variability in nutrition practice and resources could have influenced the performance of individual sites
	19 patients died before starting nutrition and seven died before achieving full caloric intake The time to start nutritional support was correlated with PICU LOS ($r = 0.49$; $p < 0.01$) PICU LOS was shorter when patients achieved full caloric intake sooner ($r = 0.57$; $p < 0.01$)	In children with severe TBI, early and adequate energy intake was associated with shorter length of PICU stay Limitations: estimated energy goals, hence true requirement not known and results may not be extrapolated to other centers with differing nutritional and discharge policies
	EN initiation ≤ 6 hr postadmission target: 46% 55% received < 50% estimated needs Adherence to guidelines was reported in 35% of the cohort In children who were fed following the guidelines, energy intake was 75% vs 38% of estimated goal, $p = 0.004$	A majority of patients received < 50% of prescribed energy goal. Adherence to feeding guidelines improved nutritional intake Limitations: small sample size; study limited to 24 hr; and no clinical outcomes reported
	Patients with shock vs those without shock: More gastrointestinal complications: 20 (30.7%) vs 42 (9.1%), $p = 0.020$; more gastric distention/residue: 10 (15.4%) vs 23 (5%), $p = 0.004$; more diarrhea: 13 (20%) vs 21 (4.6%), $p = 0.0001$; 1 vs 0 duodenal perforation resulting in death; definite suspension of EN: 6 (9.2%) vs 5 (1%), $p = 0.0001$; higher mortality: 18 (27.7%) vs 32 (6.9%), $p = 0.0001$	This is a large cohort of children fed via the postpyloric route. Patients with shock had more gastrointestinal complications compared with those without shock Limitations: data collectors knew both exposure and outcomes at time of data collection; EN tolerance can be difficult to objectively assess; and patients with shock received significantly higher doses of dopamine, epinephrine, milrinone, midazolam, fentanyl, and vecuronium
	Early vs late EN: EN initiation: 0.7 ± 0.2 vs 5.3 ± 7.4 d, $p < 0.001$ No difference in mortality, nosocomial pneumonia, maximum calorie intake, diarrhea Supplemental parenteral nutrition: 0.2 ± 1.4 vs 0.9 ± 2.8 d Low K^+ (16.3% vs 29.9%; $p < 0.05$) Low Ca^{++} (3.5% vs 12.1%; $p < 0.05$) Abdominal distention: 3.5% vs 7.8%; $p < 0.05$	Early EN < 24 hr was achieved in more than one third of children in this large study Early EN group received less sedation vs late EN—these medications may affect abdominal distention and EN tolerance Limitations: abdominal distention, high GRV, and diarrhea are not specific or accurate measures of intolerance and illness severity not assessed

(*Continued*)

TABLE 8. (*Continued*). Optimal Route (Gastric or Small Bowel) and Timing of Enteral Nutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
López-Herce et al (85)	Prospective cohort, single center	Compare tolerance of transpyloric EN in children with ARF vs other critically ill children ARF defined as acute increase in creatinine > 2× upper normal for age, with or without change in diuresis and/or need for renal replacement therapy	*n* = 526 Critically ill children admitted to PICU and received transpyloric EN *n* = 53 (10%) with ARF Median age (range): 18 mo (0.6–264 mo) *n* = 473 without ARF Median age (range): 5 mo (0.1–216 mo); *p* = 0.001 *n* = 38 (71.6%) of patients with ARF required continuous renal replacement therapy
Petrillo-Albarano et al (71)	Retrospective, before/after, cohort, single center	To examine the implementation of an early EN protocol (≤ 6 hr from admission) and to describe its impact on time to achieve goal feedings and complications associated with EN	*n* = 91 Preintervention Median age (IQR): 29.7 mo (5.7–119.8 mo) *n* = 93 Postintervention Median age (IQR): 21.6 mo (2.9–88.8 mo)
Briassoulis et al (78)	Prospective study, single center	To investigate the feasibility, adequacy, and efficacy of early gastric feeding (≤ 12 hr from admission)	*n* = 71 Critically ill children requiring mechanical ventilation Median age (range): 54 mo (2–204 mo)

ARF = acute renal failure, BMR = basal metabolic rate, EN = enteral nutrition, GRV = gastric residual volume, IQR = interquartile range, LOS = length of stay, OR = odds ratio, PIM2 = Pediatric Index of Mortality 2, RCT = randomized controlled trial, TBI = traumatic brain injury.

use of feeding protocols is considered safe and in individual centers has been effective in optimizing nutrient delivery without increasing the risk of other complications (70–72). In an international multicenter cohort study, nine of the 31 participating PICUs reported the use of an EN algorithm (73). These algorithms defined the rate of EN advancement, recommended nutrition screening and fasting guidelines, and most centers defined intolerance by some threshold of increased gastric residual volume (GRV). Despite being commonly measured in many PICUs, the accuracy of GRV as a marker of delayed gastric emptying has been recently challenged in both adult and pediatric intensive care populations (55, 74). Measurement of GRV has not been correlated with risk of aspiration in adult studies, and it is no longer recommended in the recent adult critical care nutrition guidelines (75, 76). In a recent single-center study of children eligible for EN initiation in the PICU, measured GRV did not correlate with delayed gastric emptying or with the ability to rapidly advance EN (55). The threshold volume used to define increased GRV in the PICU is variable (73, 77). In the absence of pediatric trials, we cannot recommend discontinuing GRV measurement in the PICU, but the role of this practice is not clear and might impede EN advancement. Several studies have reported rapid advancement of EN and achievement of nutrient delivery goals by a stepwise algorithmic approach (70, 71, 78). The use of EN algorithms/protocols has been associated with decreased time to initiation of EN, increased EN delivery and decreased reliance on PN, and increased likelihood of achieving nutrient delivery goals (70, 72, 79).

Presence of a dedicated multidisciplinary nutrition team in the ICU guides the timely initiation and management of nutrition support. It is suggested that the composition of the team includes personnel knowledgeable and experienced in pediatric critical care, pediatric nutrition, and nutrition support therapy. Dedicated dietitians support sound nutritional practices such as timely assessment and documentation of nutritional status, development of an optimal nutritional prescription, serial follow-up, and monitoring for safe nutrient delivery are some of the responsibilities of a PICU dietitian (80). In a multicenter, observational cohort study of 31 PICUs, a majority of the centers (93%) reported presence of a dedicated dietitian for an average of 0.4 full time equivalents per 10 beds (8). In a subsequent larger multicenter study of 59 PICUs, presence of a dedicated dietitian was a significant and independent predictor of adequate enteral protein intake (9). Hence, dietitians are

Intervention	Results/Outcome	Comments
	ARF vs no ARF Maximum intake: 77 (26.7) vs 85 (24.9) kcal/kg/d; $p = 0.029$ Shock: 49% vs 8.2%; $p = 0.0001$ Mortality: 30.1% vs 7.1%; $p = 0.0001$ Gastrointestinal complications: 24.5% vs 9.9%; $p = 0.008$ Abdominal distention, high gastric residual volume: 17% vs 5%; $p = 0.003$ EN suspended: 1.2 vs 9.4%; $p = 0.0001$ EN initiation < 48 hr of admission was not different between groups	Patients with ARF received less energy from EN and experienced more gastrointestinal complications compared with those without ARF Limitations: data collectors not blinded to mode of feeding; EN tolerance can be difficult to objectively assess; and same population reported in two other studies
	Postintervention vs preintervention Time to goal EN, median (IQR): 14 (9–21.5) vs 32 (12–78) hr; $p < 0.0001$ Less diarrhea: $p = 0.009$ Less constipation: $p = 0.012$	This study demonstrated that a stepwise nutrition protocol reduced time to achieve goal EN and improved feeding tolerance Limitations: abdominal distention and diarrhea may not be specific or accurate measures of intolerance
	Caloric intake approached predicted BMR on day 2 and estimated needs (BMR × 1.5) on day 5 Correlation between calorie intake and severity of illness: pediatric Risk of Mortality score: $r = -0.35$; $p = 0.003$; Therapeutic Intervention Scoring System: $r = -0.37$; $p = 0.002$	This study showed that use of a gastric EN protocol increased caloric intake during the first 5 d of admission to the PICU

essential members of the multidisciplinary care team in the PICU. It is important to develop a seamless transition of nutrition care plan as patients move across the continuum of pediatric ward to the ICU and back.

Future Direction. Future studies must clarify the evidence to inform stepwise decision making in the EN algorithms. These steps include selection of gastric versus postpyloric tube feeding, clear and practical definitions of feeding intolerance (e.g., reflux, vomiting, constipation, diarrhea, and malabsorption), and the role of adjuncts such as prokinetic, antiemetic, antidiarrheal, acid suppressive, and laxative medications. In particular, the practice of measuring GRV as a marker of EN intolerance in the PICU population must be challenged. Future studies examining the role or the optimal threshold of GRV to guide EN delivery are desirable. In addition, prospective trials are needed to show the benefit of algorithmic EN advancement and dietitian interventions on important nutritional and clinical outcomes.

Question 6A. What is the Best Site for EN Delivery - Gastric or Small Bowel?

Recommendation 6A. Existing data are insufficient to make universal recommendations regarding the optimal site to deliver EN to critically ill children. Based on observational studies, we suggest the gastric route be the preferred site for EN in patients in the PICU. The postpyloric or small intestinal route for EN may be used in patients unable to tolerate gastric feeding or those at high risk for aspiration. Existing data are insufficient to make recommendations regarding the use of continuous versus intermittent gastric feeding.

Quality of Evidence. Low.

GRADE Recommendation. Weak.

Question 6B. When Should EN Be Initiated?

Recommendation 6B. Based on expert opinion, we suggest that EN be initiated in all critically ill children, unless it is contraindicated. Based on observational studies, we suggest early initiation of EN, within the first 24–48 hours after admission to the PICU, in eligible patients. We suggest the use of institutional EN guidelines and stepwise algorithms that include criteria for eligibility for EN, timing of initiation, and rate of increase.

Quality of Evidence. Low.

GRADE Recommendation. Weak.

Rationale. Gastric feeding is physiologic and is the preferred EN route for critically ill children, unless the child has

TABLE 9. Indication and Optimal Timing of Parenteral Nutrition in Critically Ill Children

Reference	Study Design Quality; Number of Sites	Population *n* (Age-Range) Setting	Study Aim(s)	Intervention	Results/Outcome	Comments
Fivez et al (90)	Randomized controlled trial, three centers	*n* = 1,440 Term newborn–17 yr > 24 hr expected PICU stay STRONGKids Nutrition score > 2 (0, low risk of malnutrition; 1–3, med risk; 4–5, high risk)	To investigate whether a late PN strategy (withholding PN up to day 8) in the PICU is clinically superior to an early PN strategy (starting PN within 24 hr of admission) Primary endpoints: new PICU-acquired infections, duration of PICU dependency	Experimental group: late PN—started on the morning of eighth PICU day if unable to reach at least 80% caloric goal by EN Control group: early PN—started within 24 hr of admission, discontinued when EN meeting at least 80% of the goal.	Outcomes in experimental vs control groups No significant differences between the groups for PICU, hospital, or 90-d mortality PICU LOS (mean ± SD): 6.5 ± 0.4 vs 9.2 ± 0.8; $p < 0.001$ Patients in PICU ≥ 8 d: 159/717 vs 216/723; $p < 0.001$ Hospital LOS: 17.2 ± 1.0 vs 21.3 ± 1.3; $p < 0.001$ Acquired infections: 77 vs 134; $p < 0.001$; Significant differences in bloodstream and airway infections Mechanical ventilation duration (d): 4.4 ± 0.3 vs 6.4 ± 0.7; $p = 0.001$ Hypoglycemia (< 40 mg/dL in first week): 65 vs 35; $p = 0.001$	PN use within 24 hr of admission in all children in PICU is not superior to late PN strategy Limitations: The external validation of this trial results is limited. Caution must be used with extrapolation to severely malnourished children, who were not adequately represented. STRONGkids is not validated in critically ill children Definition of caloric and protein goals not standardized across study—equations used to estimate energy requirements in majority of cohort Glycemic management and the composition of EN and PN were not standardized across study centers Definition of infections was not standard and presence or absence of catheters not provided

EN = enteral nutrition, LOS = length of stay, PN = parenteral nutrition, STRONGKids = Screening Tool for Risk of Impaired Nutritional Status and Growth.

perceived or demonstrated risks of aspiration of gastric contents into the tracheobronchial tree. The use of small intestinal (postpyloric) feeding in two small RCTs did not demonstrate reduced aspiration when compared with gastric feeding (81, 82). The postpyloric route was associated with higher proportion of goal nutrition delivery in one study (82), but a delay in the initiation of nutrition via the postpyloric route in a second study (81). The provision of EN into the small bowel requires the placement of a feeding tube past the pylorus. This can be accomplished by several methods but requires time and expertise and incurs higher costs. In a single-center study, mechanical problems with postpyloric tubes led to frequent EN interruptions and failure to achieve delivery of goal nutrients (61). In centers with the necessary expertise and resources to successfully place postpyloric feeding tubes, this route may be used with caution to improve nutrient delivery. Gastric feeding has been administered to critically ill children either as a continuous or intermittent modality. In two RCTs comparing continuous versus intermittent gastric feeding, authors reported no differences in EN tolerance (77, 83). Single-center, observational studies have demonstrated the feasibility of postpyloric EN in cohorts of critically ill children with a higher prevalence of EN intolerance such as those with shock and acute kidney injury (84, 85).

Wide variability in the definition of early EN in the critically ill child has been reported in the published literature. A majority of the studies have described initiation as early as 6 hours and as late as 48 hours after admission to the PICU (66, 71, 89). In a multicenter study of nutrient delivery in the PICU, early EN, defined as delivery of one quarter of cumulative goal enteral energy over the first 48 hours, was associated with a survival benefit (66). In a multicenter retrospective examination of EN initiation in the PICU, feeding was delayed more than 48 hours from admission in 20% of the patients (89). Positive-pressure invasive and noninvasive ventilation, procedures, and gastrointestinal disturbances were common risk factors associated with delayed EN. The use of stepwise protocols or guidelines for EN delivery in the PICU has been associated with significant reductions in the time to start EN (71, 78).

Future Direction. Future, large-scale RCTs should evaluate the benefits of gastric versus small bowel feeding, early compared with delayed EN (< 24 vs ≥ 48 hr), and bolus/intermittent versus continuous gastric feeding. These studies must have clear definitions of EN delivery targets and intolerance and must include important clinical outcomes including hospital-acquired complications, PICU and hospital LOS, and duration of mechanical ventilation.

Question 7A. Is There a Role for Early PN Initiation in Critically Ill Children?

Recommendation 7A. Based on a single RCT, we do not recommend the initiation of PN within 24 hours of PICU admission.

Quality of Evidence. Moderate.

GRADE Recommendation. Strong.

Question 7B. What Is the Role and Optimal Timing of PN Initiation as a Supplement to Inadequate EN?

Recommendation 7B. In children tolerating EN, we suggest stepwise advancement of nutrient delivery via the enteral route and delaying commencement of PN. Based on current evidence, the role of supplemental PN to reach a specific goal for nutrient delivery is not known. The time when PN should be initiated to supplement insufficient EN is also unknown. The threshold for and timing of PN initiation should be individualized.

Based on a single RCT, supplemental PN should be delayed until 1 week after PICU admission in patients with normal baseline nutritional state and low risk of nutritional deterioration. Based on expert consensus, we suggest PN supplementation in children who are unable to receive any EN during the first week in the PICU. In patients who are severely malnourished or at risk of nutritional deterioration, PN may be supplemented in the first week if they are unable to advance past low volumes of EN.

Quality of Evidence. Low.

GRADE Recommendation. Weak.

Rationale. As previously discussed, EN is the preferred route of nutrition support in the critically ill child; however, PN should be considered when EN is not feasible or is contraindicated. The use of PN as a supplement to EN, timing of supplemental PN initiation, and the targeted macronutrient goal are key questions that will require an evidence-based approach. Unfortunately, there is little evidence to guide these practices. In a recent three-center RCT (PEPaNIC trial) addressing timing of supplemental PN in critically ill children, the group with late initiation of PN (on day 8) demonstrated better outcomes (fewer new infections and shorter length of PICU stay) compared with the early PN group (receiving PN within 24 hr of admission) (90). Also, the late PN group was likely to have an earlier live discharge from the PICU, shorter duration of mechanical ventilation, and lower odds of renal replacement therapy.

The finding that can be strongly generalizable from this study is that PN should not be started within 24 hours of PICU admission. For reasons outlined below, we recommend caution in broadly applying the delayed PN strategy (8 d until initiation) used in the control group of this study. Children in this study received significant enteral calories: mean of 30 kcal/kg/d (300 kcal/d) by day 4. It is possible that most of these children could have been sustained enterally using a robust EN protocol (70, 71). Children in this study were discharged at rates that are standard in most PICUs: 50% left the PICU by day 4 and 74% by day 8. As only 24% of the late PN cohort was exposed to PN, the intervention arm of the trial was more representative of a "no PN" strategy. Again, this supports the conclusion that initiation of PN within the first 24 hours of admission is not advisable as a general strategy in the PICU.

Our expert consensus is that PN should not be withheld until day 8 as a universal strategy in critically ill children. Because most children were receiving significant amounts of EN, the results

TABLE 10. The Role of Immunonutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
Jordan et al (98)	RCT	To determine whether glutamine supplementation has a role modifying both the oxidative stress and the inflammatory response of critically ill children	*n* = 101 Critically ill children with severe sepsis or after major surgery requiring PN for at least 5 d
[1]Larsen et al (95) and [2]Larsen et al (97)	RCT	Examine effects of two different lipid emulsions on [1]plasma phospholipids and [2]immune biomarkers	*n* = 32 Infants with congenital heart disease scheduled for open-heart surgery with cardiopulmonary bypass Mean age (SD): 40 wk (0.6 wk) gestational age, 3.5 ± 0.5 kg, and 10.6 d at the time of surgery
Nehra et al (96)	RCT	*n* = 19 Neonates and infants < 3 mo with a direct bilirubin < 1.0 mg/dL and PN dependent	To assess the safety and efficacy of a fish oil–based IV fat emulsion in reducing the incidence of cholestasis in neonates compared with the traditional soybean oil–based IV fat emulsion
Jacobs et al (91)	RCT Pilot feasibility	To determine if continuous feeding of enteral nutrition containing EPA, GLA, and antioxidants was feasible in critically ill children with ALI or ARDS	*n* = 26 Critically ill children receiving mechanical ventilatory support with ALI or ARDS Mean age (SD): 6.2 yr (0.9 yr)

Intervention	Results/Outcome	Comments
Experimental group ($n = 49$): standard PN + glutamine Control group ($n = 49$): standard PN	At day 5, patients in the PN + glutamine group had significantly higher levels of HSP-70 when compared with controls (68.6 vs 5.4; $p = 0.014$) No significant differences in IL-10 or IL-6 (no reductions with glutamine) No significant differences between the groups for PICU LOS or hospital LOS No adverse events in either group	Glutamine supplementation in PN administered to critically ill children failed to show any differences in clinical outcomes, but helped to maintain levels of HSP-70 by day 5 Limitations: eventual sample size was not powered to demonstrate clinical outcomes
$n = 16$ Experimental group: Lipoplus: 50% MCT, 40% LCT, 10% fish oil $n = 16$ Control group: Intralipid: 100% soybean oil Subjects were randomized to receive one of two lipid emulsions with TPN, for 1–4 d preoperation and 10 d postoperation Lipids started at 0.5 g/kg, increased to maximum of 3.5 g/kg/d Enteral intake was limited to at 30 kcal/kg/d	[1]Experimental vs control groups: lower procalcitonin 1 d postoperatively ($p = 0.01$), lower ω-6-to-ω-3 ratio ($p = 0.0001$), higher ω-3 concentration ($p = 0.001$), higher plasma phospholipid EPA ($p < 0.05$); α-linolenic acid, arachidonic acid, and docosahexaenoic acid remained constant An increase in plasma phospholipid EPA was associated with a decrease in plasma phospholipid LTB4 concentration ($p < 0.05$) On postoperative day 10, those with high Pediatric Risk of Mortality III scores exhibited a 45% lower lymphocyte concentration ($p < 0.05$) [2]TNF-α concentration was lower in the experimental vs control group (5.9 vs 14.8 pg/mL; $p = 0.003$) Plasma TNF-α was positively correlated with hospital LOS in the control group ($p = 0.01$) and negatively correlated with LOS in the treatment group ($p = 0.004$), with a significant time by treatment interaction ($p = 0.02$)	An IV lipid emulsion with ω-3 fats provides a more beneficial inflammatory and immune status compared with a lipid emulsion with ω-6 fats in infants with congenital heart disease requiring open-heart surgery. It is unknown if this difference would translate to clinical outcomes
Both groups received IV fat emulsion at 1 g/kg/d and kept constant during the study period Experimental group: received fish oil–based IV fat emulsion Control group: received soybean oil–based IV fat emulsion Patients with persistently elevated direct bilirubin > 2 mg/dL were considered treatment failures and were crossed over to the other study arm Developmental assessment was conducted at 6 and 24 mo of corrected age	No significant difference in cholestasis (maximum direct bilirubin) between the groups	Interim analysis did not show differences, possibly because of a low incidence of cholestasis among the patients enrolled Underpowered study (required $n = 30$) Additionally, both groups were held at 1 g/kg/d of fat emulsion. This is less than standard fat emulsion advancement. Perhaps, limiting fat intake in patients to 1 g/kg/d should be evaluated
Experimental group ($n = 14$): received EN formula with EPA + GLA Control group ($n = 12$): received standard pediatric enteral formula Goal intake defined as ≥ 75% of Schofield BMR × 1.3 within 48 hr of initiation of EN	No significant differences between the two groups, for PICU LOS, hospital LOS, duration of MV, or energy intake Protein intake was higher in experimental group: 2.35 ± 0.2 vs 1.63 ± 0.1; $p = 0.007$	EPA and GLA supplementation in EN administered to critically ill children with ALI or ARDS failed to show any differences in clinical outcomes. However, immunonutrient delivery was feasible (tolerated and caloric goal reached) Limitations: small sample size; too many exclusion criteria

(*Continued*)

TABLE 10. (*Continued*). The Role of Immunonutrition

Reference	Study Design, No. of Sites	Study Aim(s)	Population (*n*), Eligibility
Carcillo et al (100)	RCT	To evaluate whether daily supplementation with zinc, selenium, glutamine, and metoclopramide, compared with whey protein, prolongs the time to nosocomial infection/sepsis in critically ill children	*n* = 293 Critically ill children with endotracheal tube, central venous or urinary catheter, and anticipated to have arterial or venous access for blood draws and a feeding tube enrolled within 48 hr of PICU admission
[1]Briassoulis et al (93); [2]Briassoulis et al (94); and [3]Briassoulis et al (99)	RCT	To compare outcomes in critically ill children receiving an immune-enhancing formula or standard formula [1]NB, nutritional indices, antioxidant catalysts [2,3]Cytokines, hospital-acquired infections, nutritional indices	[1]*n* = 50 critically ill children [2]*n* = 38 (30 analyzed) critically ill children with septic shock [3]*n* = 40 critically ill children with severe traumatic brain injury

ALI = acute lung injury, ARDS = acute respiratory distress syndrome, BMR = basal metabolic rate, EN = enteral nutrition, EPA = eicosapentaenoic acid, GLA = γ-linolenic acid, HSP-70 = heat shock protein 70, IL = interleukin, LOS = length of stay, MV = mechanical ventilation, NB = nitrogen balance, PN = parenteral nutrition, RCT = randomized controlled trial, TNF = tumor necrosis factor.

of the PEPaNIC trial should not be extrapolated to children receiving no EN. The proportion of severely malnourished children in the study is unclear and likely to be low. The nutritional assessment/screening tool used in the study (STRONGkids) has not been validated in critically ill children, and its accuracy in hospitalized children has been questioned (20). Also, BMI *z* scores of patients in the study suggest that most children were well nourished at PICU admission. Therefore, the results cannot be extrapolated to severely malnourished children or those at risk of malnutrition who may not tolerate a week of cumulative nutrient deficit accrued by the late PN strategy. Finally, other vulnerable groups such as children admitted to the PICU with contraindications to EN, intestinal failure, or requiring extracorporeal membrane oxygenation often rely on PN to meet nutrient needs. In these subgroups, the optimal timing of PN to supplement or replace EN as the mode of nutrient delivery will need to be determined by future trials.

The PEPaNIC investigators chose an EN energy delivery threshold of less than 80% goal, to trigger supplemental PN at the two time points. A majority of children in this study had energy expenditure estimated using equations that have been discredited in critically ill children (refer to Recommendations and Rationale for Question 2B). Hence, it is possible that a significant portion of children in the early PN arm of this study were over-fed. In addition, glycemic control protocols were different in each of the three centers. Multiple problems exist with one of the primary outcomes in this study, new infections acquired during the ICU stay. The investigators used nonstandard definitions of acquired infections such as ventilator-associated pneumonia and catheter-related blood stream infection (BSI). The presence of indwelling devices such as central venous catheters in the two groups was not reported. It is not clear how the investigators distinguished between an infection present at baseline from a new infection.

The role of PN initiated from 2 to 7 days in the PICU cannot be determined by this study, and the findings of this study need to be confirmed by future RCTs. Until then, EN should be initiated and actively advanced in eligible children in the

Intervention	Results/Outcome	Comments
Experimental group: enteral: 20 mg/d zinc; selenium: 1–3 yr, 40 μg/d; 3–5 yr, 100 μg/d; 5–12 yr, 200 μg/d; adolescent, 400 μg/d; 0.3 g/kg/d glutamine; IV: 0.2 mg/kg/d (≤ 10 mg/dose) metoclopramide every 12 hr, from ≤ 72 hr of admission until PICU discharge or ≤ 28 d Control group: not intended as a control group, intended as a comparative effectiveness trial received 0.3 g/kg/d beneprotein (whey protein)	Experimental vs control groups: 28-d mortality: 10.3% (15/145) vs 5.8% (8/139); $p = 0.16$ PICU LOS: median, 9 vs 11 d; $p = 0.16$ No significant difference in infectious complications No differences in duration of MV Mean rates of nosocomial infection/sepsis per patient per 100 study days (95% CI): immunocompromised patients—1.57 (0.53–3.73) vs 6.09 (3.33–10.32); $p = 0.011$ No difference in immune competent patients	Enrollment terminated for futility after second interim analysis indicated the conditional power to determine a beneficial effect of zinc, selenium, glutamine, metoclopramide, compared with whey protein, was < 10% There was no significant difference between groups in terms of infections or other important outcomes. However, immunocompromised patients (a very small number of patients) experienced a significant reduction in nosocomial infections/sepsis with the study intervention compared with the whey protein group
Randomized to immunonutrition formula (glutamine, L-arginine, antioxidants, and ω-3 fatty acids, fiber, vitamin E, β-carotene, zinc, copper, selenium), or standard pediatric formula Feeds were masked and delivered through an nasogastric tube starting < 12 hr of admission Energy intake was calculated to provide 0.5, 1, 1.25, 1.5, and 1.5 of predicted BMR (calculated using the Schofield equation) on days 1–5, respectively	Experimental vs control groups: [1,2,3]No significant differences for energy and protein intake, mortality, PICU LOS, pneumonia, infections, MV duration [1,2,3]Diarrhea significantly more frequent [1,3]Positive NB in significantly higher proportion of patients on day 5 [1,3]Significantly fewer positive gastric cultures [2]Significantly lower IL-6 and higher IL-8 on day 5 [3]Significantly lower IL-8 and no difference in IL-6 on day 5	Immunonutrition is feasible in critically ill children These single-center studies of immunonutrition vs standard formula were underpowered to demonstrate important outcome differences

PICU. The optimal timing of supplemental PN in children failing to meet their nutrient delivery goals enterally must be individualized based on the nutritional and clinical status of the patient, and anticipated nutrient deficits during the course of illness.

Future Direction. Future studies should focus on determining the optimal timing for PN supplementation in cases where EN is insufficient to meet the nutritional requirements during the first week of critical illness. These trials must account for the varying baseline nutritional status of patients and their individualized energy and protein goals.

Question 8. What Is the Role of Immunonutrition in Critically Ill Children?

Recommendation 8. Based on available evidence, we do not recommend the use of immunonutrition in critically ill children.

Quality of Evidence. Moderate.

GRADE Recommendation. Strong.

Rationale. Several dietary components, including glutamine, arginine, nucleotides, omega-3 fatty acids, fiber, antioxidants, selenium, copper, and zinc, have been used in various combinations to modulate dysregulated immune responses induced by critical illness, injury, and surgery. The aim is to achieve a therapeutic benefit, such as to attenuate inflammation or provide nutrients depleted by stress. Terms used to describe this therapy include immunonutrition, immunonutrients, immunonutrient-enhanced diet, immune-enhancing nutrition, immune-modulating nutrition, pharmaconutrition, pharmaconutrients, and pharmaceutical nutrients. RCTs comparing immunonutrition to standard nutrition in critically ill children have used a variety of nutrients, delivered using the enteral or parenteral route, in heterogeneous populations, and using different methods to estimate energy needs. In some studies, a combination of interventions has been studied; therefore, the impact of any single immunonutrient is difficult to interpret. In one pilot RCT and one retrospective cohort, investigators examined the use of an

enteral formula containing omega-3 fatty acids, gamma-linolenic acid, and antioxidants in critically ill children with acute respiratory distress syndrome (91, 92). Although the specialty formulae were feasible and tolerated in these studies, neither study was powered to show difference in outcomes. Other small, single-center studies randomizing critically ill children with respiratory failure, septic shock, and traumatic brain injury to an enteral formula containing glutamine, arginine, antioxidants, fiber, and omega-3 fatty acids, or a standard pediatric formula were also underpowered and unable to demonstrate outcome differences (93, 94). In two studies, infants requiring PN were randomized to receive IV lipid emulsion as omega-3 fatty acids, either alone or in combination with medium- and long-chain (omega-6) fats, or a 100% soybean oil-based lipid (omega-6) (95, 96). These studies were designed to evaluate the effects of the two lipid formulations on inflammatory biomarkers; relevant clinical outcomes for critically ill children were not evaluated. Lipids containing omega-3 versus 100% omega-6 fatty acids were associated with lower plasma pro-inflammatory cytokines and potential for reduced ICU LOS (97). Clinical outcomes of critically ill children requiring PN randomized to receive parenteral glutamine did not differ from those administered standard PN (98). In a comparative effectiveness trial, critically ill children requiring mechanical ventilation and EN were randomized to receive enteral supplementation of a combination of glutamine, zinc, selenium, and metoclopramide, or whey protein (100). The study was terminated for futility at a planned interim analysis after enrollment of 293 patients. No differences in PICU LOS, duration of mechanical ventilation, infections, or mortality were demonstrated. However, in a small subgroup of immunocompromised children, a significant reduction in nosocomial infections was seen with the study intervention compared with whey protein (1.57 vs 6.09; $p = 0.011$). No two trials of immunonutrients in children are similar, and none demonstrated superiority of immunonutrition versus standard nutrition in critically ill children in terms of clinical outcomes.

Prior studies in critically ill adults have demonstrated reduced hospital LOS and mortality with glutamine-supplemented PN (101). Based on these observations, in a recent large multicenter two-by-two factorial trial of mechanically ventilated, critically ill adults with multiple organ failure, patients were randomized to glutamine, antioxidants, both, or placebo (102). A significant increase in hospital and 6-month mortality and a trend toward increased 28-day mortality were seen in the group receiving glutamine. A subsequent multicenter trial of critically ill mechanically ventilated adults showed no infectious benefits and possibility of harm with a significantly higher 6-month mortality in medical patients randomized to a formula containing glutamine, omega-3 fatty acids, and antioxidants versus a standard high-protein formula (103). Arginine supplementation has been considered to improve immune function and wound healing in critically ill patients but has demonstrated increased mortality in septic patients (104). The 2016 critically ill adult nutrition support therapy guidelines recommend that immunonutrition not be used in critically ill septic or medical patients but may be considered in those who are perioperative, or have traumatic injuries (75). Due to the potential harm of glutamine and arginine supplementation in adults and the paucity of pediatric data, immunonutrition cannot be currently recommended in critically ill children.

Future Direction. Future trials should examine the role of immunonutrition in select populations, such as immunocompromised and malnourished critically ill children, with standardized clinical interventions and therapies to avoid confounding results. These studies need to define immunonutrition and specific populations where it might be tested. In addition, studies are needed to identify the optimal route of immunonutrient delivery.

SUMMARY

In this article, we have provided guidelines for some of the important steps in the provision of optimal nutrition to the critically ill child. We selected key questions for this version of the guidelines, but we are aware that some of these and several other questions remain unanswered and will require systematic investigation. A majority of the recommendations in these guidelines are driven by consensus or low-level evidence. We hope that our systematic search strategy, followed by meticulous data abstraction, has allowed us to capture all the relevant studies. The process of converting a broad variety of evidence levels to meaningful and practically applicable recommendations is challenging. These recommendations provide a starting point from where the nutritional strategy for individual patients can be customized. The guidelines reiterate the importance of nutritional assessment, particularly the detection of malnourished patients who are most vulnerable and therefore potentially may benefit from timely nutritional intervention. There is a need for renewed focus on accurate estimation of energy needs and attention to cumulative energy imbalance. IC must be used to guide energy prescription, where feasible, and cautious use of estimating equations and increased surveillance for unintended caloric underfeeding and overfeeding are recommended in its absence. Optimal protein dose and its correlation with clinical outcomes is an area of great interest. The optimal route and timing of nutrient delivery is an area of intense debate and investigations. EN remains the preferred route for nutrient delivery. Several strategies to optimize EN during critical illness have emerged. The role of supplemental PN has been highlighted, and a delayed approach appears to be beneficial. Immunonutrition cannot be currently recommended. Overall, the pediatric critical care population is heterogeneous, and a nuanced approach to individualize nutrition support with the aim of improving clinical outcomes is necessary. We have summarized key areas for future investigations, which will guide us in developing the next level of evidence-based nutrition therapy in the future. Until then, multidisciplinary collaborative efforts

must continue to prioritize and highlight the unique and dynamic nutritional needs of the critically ill child in the complex PICU environment.

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APPENDIX 1. Targeted Indirect Calorimetry (31)

Children who are at high risk for metabolic alterations are suggested candidates for targeted measurement of resting energy expenditure using indirect calorimetry (IC) in the PICU:

- Underweight, overweight, or obese
- Children with more than 10% weight change during ICU stay
- Failure to consistently meet prescribed energy goals
- Failure to wean or need to escalate respiratory support
- Neurologic trauma (traumatic, hypoxic, and/or ischemic)
- Oncologic diagnoses (including children with stem cell or bone marrow transplant)
- Children with thermal injuries or amputations
- Children requiring mechanical ventilatory support for more than 3 days
- Children suspected to be severely hypermetabolic (status epilepticus, hyperthermia, systemic inflammatory response syndrome, dysautonomic storms, etc.) or hypometabolic (hypothermia, hypothyroidism, pentobarbital or midazolam coma, etc.)

Any patient with ICU stay more than 4 weeks may benefit from IC to assess adequacy of energy intake.