

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

Journal of Parenteral and Enteral
Nutrition
Volume XX Number X
Month 201X 1–37
© 2017 American Society
for Parenteral and Enteral Nutrition
and the Society of Critical Care
Medicine
DOI: 10.1177/0148607117711387
journals.sagepub.com/home/pen



Nilesh M. Mehta, MD¹; Heather E. Skillman, MS, RD, CSP, CNSC²;
Sharon Y. Irving, PhD, CRNP, FCCM, FAAN³; Jorge A. Coss-Bu, MD⁴;
Sarah Vermilyea, MS, RD, CSP, LD, CNSC⁵; Elizabeth Anne Farrington, PharmD, FCCP, FCCM, FPPAG, BCPS⁶;
Liam McKeever, MS, RDN⁷; Amber M. Hall, MS⁸; Praveen S. Goday, MBBS, CNSC⁹;
and Carol Braunschweig, PhD, RD¹⁰

Abstract

This document represents the first collaboration between 2 organizations—the American Society for 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 critically ill patient (>1 month and <18 years) expected to require a length of stay >2–3 days in a PICU admitting medical, surgical, and cardiac patients. In total, 2032 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 1661 citations. In total, the search for clinical trials yielded 1107 citations, whereas the cohort search yielded 925. After careful review, 16 randomized controlled trials and 37 cohort studies appeared to answer 1 of the 8 preidentified question groups for this guideline. We used the GRADE criteria (Grading of Recommendations, Assessment, Development, and Evaluation) 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 nutrition assessment—particularly, the detection of malnourished patients who are most vulnerable and therefore 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 calorimetry, 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 are areas 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. (*JPEN J Parenter Enteral Nutr.* XXXX;xx:xx-xx)

Keywords

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

This document represents the first collaboration between 2 organizations—the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM)—to describe best practices in nutrition therapy for 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 therapies. A task force of multidisciplinary experts in clinical nutrition—representing

physicians, nurses, pharmacists, dietitians, and statisticians—was jointly convened by the 2 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 nutrition status, and insufficient statistical power for analysis. As the authors of these guidelines, we acknowledge the scarcity of high-level evidence for nutrition practices in the pediatric intensive care unit (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 with GRADE methodology (Grading of Recommendations, Assessment, Development, and Evaluation) and thus guided the consensus-derived recommendations.²

Definitions

Nutrition support therapy refers to the provision of enteral nutrition (EN) by enteral access device and/or parenteral nutrition (PN). Standard therapy refers to provision of intravenous 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 critically ill patient (>1 mo and <18 years) expected to require a length of stay (LOS) >2–3 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; therefore, these guidelines 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 8 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

From the ¹Division of Critical Care Medicine, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA; ²Clinical Nutrition Department, Children's Hospital Colorado, Aurora, Colorado, USA; ³Division of Critical Care, Children's Hospital of Philadelphia, University of Pennsylvania School of Nursing, Philadelphia, Pennsylvania, USA; ⁴Section of Critical Care, Department of Pediatrics, Texas Children's Hospital, Baylor College of Medicine, Houston, Texas, USA; ⁵Division of Nutrition Therapy, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; ⁶Department of Pharmacy, Betty H. Cameron Women's and Children's Hospital, New Hanover Regional Medical Center, Wilmington, North Carolina, USA; ⁷Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, Illinois, USA; ⁸Biostatistics, Department of Anesthesiology, Perioperative and Pain Medicine, Boston Children's Hospital, Boston, Massachusetts, USA; ⁹Pediatric Gastroenterology and Nutrition, Medical College of Wisconsin, Milwaukee, Wisconsin, USA; and ¹⁰Division of Epidemiology and Biostatistics, Department of Kinesiology and Nutrition, University of Illinois, Chicago, Illinois, USA.

These guidelines are being copublished by the Society of Critical Care Medicine (SCCM) in *Pediatric Critical Care Medicine* (PCCM), 2017;XX:XX-XX. Minor differences in style may appear in each publication, but the article is substantially the same in each journal.

All authors completed both the American Society for Parenteral and Enteral Nutrition and Society of Critical Care Medicine conflicts-of-interest form for copyright assignment and financial disclosure. The authors of these guidelines have reported all potential conflicts or financial disclosures. There was no funding or contribution from industry, nor were any industry representatives present at any of the committee meetings.

Financial disclosure: None declared.

Conflicts of interest: None declared.

Received for publication September 28, 2016; accepted for publication May 3, 2017.

Corresponding Author:

Nilesh M. Mehta, MD, Bader 634, Boston Children's Hospital, 300 Longwood Avenue, Boston MA 02115 USA.
Email: nilesh.mehta@childrens.harvard.edu

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

Questions and Recommendations	Evidence/GRADE
<p><i>Q1A:</i> What is the impact of nutrition status on outcomes in critically ill children? <i>R1A:</i> 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 nutrition assessment within 48 h of admission. Furthermore, as patients are at risk of nutrition deterioration during hospitalization, which can adversely affect clinical outcomes, we suggest that the nutrition status of patients be reevaluated at least weekly throughout hospitalization.</p>	<p>Quality of evidence: very low GRADE recommendation: strong</p>
<p><i>Q1B:</i> What are the best practices to screen and identify patients with malnutrition or those at risk of nutrition deterioration in the PICU? <i>R1B:</i> On the basis of observational studies and expert consensus, we recommend that weight and height/length be measured on admission to the PICU and that z scores for body mass index for age (weight for length <2 y) or weight for age (if accurate height is not available) be used to screen for patients at extremes of these values. In children <36 mo 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 nutrition assessment and interventions.</p>	<p>Quality of evidence: very low GRADE recommendation: strong</p>
<p><i>Q2A:</i> What is the recommended energy requirement for critically ill children? <i>R2A:</i> On the basis of observational cohort studies, we suggest that measured energy expenditure by IC be used to determine energy requirements and guide prescription of the daily energy goal.</p>	<p>Quality of evidence: low GRADE recommendation: weak</p>
<p><i>Q2B:</i> How should energy requirement be determined in the absence of IC? <i>R2B:</i> If IC measurement of resting energy expenditure is not feasible, we suggest that the Schofield or Food Agriculture Organization / World Health Organization / United Nations University equations may be used <i>without</i> 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.</p>	<p>Quality of evidence: very low GRADE recommendation: weak</p>
<p><i>Q2C:</i> What is the target energy intake in critically ill children? <i>R2C:</i> On the basis of 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 nutrition outcomes. On the basis of 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.</p>	<p>Quality of evidence: low GRADE recommendation: weak</p>
<p><i>Q3A:</i> What is the minimum recommended protein requirement for critically ill children? <i>R3A:</i> On the basis of evidence from RCTs and as 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.</p>	<p>Quality of evidence: moderate GRADE recommendation: strong</p>
<p><i>Q3B:</i> What is the optimal protein delivery strategy in the PICU? <i>R3B:</i> On the basis of 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.</p>	<p>Quality of evidence: moderate GRADE recommendation: weak</p>
<p><i>Q3C:</i> How should protein delivery goals be determined in critically ill children? <i>R3C:</i> 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.</p>	<p>Quality of evidence: moderate GRADE recommendation: strong</p>

(continued)

Table 1. (continued)

Questions and Recommendations	Evidence/GRADE
<p><i>Q4A:</i> Is EN feasible in critically ill children? <i>R4A:</i> On the basis of 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. On the basis of observational studies, we suggest that interruptions to EN be minimized in an effort to achieve nutrient delivery goals by the enteral route.</p>	<p>Quality of evidence: low GRADE recommendation: strong</p>
<p><i>Q4B:</i> What is the benefit of EN in this group? <i>R4B:</i> 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 h 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.</p>	<p>Quality of evidence: low GRADE recommendation: weak</p>
<p><i>Q5A:</i> What is the optimum method for advancing EN in the PICU population? <i>R5A:</i> On the basis of 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.</p>	<p>Quality of evidence: low GRADE recommendation: weak</p>
<p><i>Q5B:</i> What is the role of a nutrition support team or a dedicated dietitian in optimizing nutrition therapy? <i>R5B:</i> On the basis of observational studies, we suggest a nutrition support team, including a dedicated dietitian, be available on the PICU team, to facilitate timely nutrition assessment, and optimal nutrient delivery and adjustment to the patients.</p>	<p>Quality of evidence: low GRADE recommendation: weak</p>
<p><i>Q6A:</i> What is the best site for EN delivery: gastric or small bowel?? <i>R6A:</i> Existing data are insufficient to make universal recommendations regarding the optimal site to deliver EN to critically ill children. On the basis of observational studies, we suggest that 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.</p>	<p>Quality of evidence: low GRADE recommendation: weak</p>
<p><i>Q6B:</i> When should EN be initiated? <i>R6B:</i> On the basis of expert opinion, we suggest that EN be initiated in all critically ill children, unless it is contraindicated. Given observational studies, we suggest early initiation of EN, within the first 24–48 h 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.</p>	<p>Quality of evidence: low GRADE recommendation: weak</p>
<p><i>Q7A:</i> What is the indication for and optimal timing of PN in critically ill children? <i>R7A:</i> On the basis of a single RCT, we do not recommend the initiation of PN within 24 h of PICU admission.</p>	<p>Quality of evidence: moderate GRADE recommendation: strong</p>
<p><i>Q7B:</i> What is the role of PN as a supplement to inadequate EN? <i>R7B:</i> For 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. Based on a single RCT, supplemental PN should be delayed until 1 wk after PICU admission for patients with normal baseline nutrition state and low risk of nutrition deterioration. On the basis of expert consensus, we suggest PN supplementation for children who are unable to receive any EN during the first week in the PICU. For patients who are severely malnourished or at risk of nutrition deterioration, PN may be supplemented in the first week if they are unable to advance past low volumes of EN.</p>	<p>Quality of evidence: low GRADE recommendation: weak</p>
<p><i>Q8:</i> What is the role of immunonutrition in critically ill children? <i>R8:</i> On the basis of available evidence, we do not recommend the use of immunonutrition in critically ill children.</p>	<p>Quality of evidence: moderate GRADE recommendation: strong</p>

EN, enteral nutrition; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IC, indirect calorimetry; PICU, pediatric intensive care unit; PN, parenteral nutrition; Q, question; R, recommendation; RCT, randomized controlled trial; RDA, recommended daily allowance.

Table 2. Language for Guidelines Recommendations.

Quality of Evidence	Weighing Risks vs Benefits	GRADE Recommendations	Clinical Guideline Statement
High to very low	Net benefits outweigh harms	Strong	We recommend.
High to very low	Trade-offs for patient are important	Weak	We suggest.
High to very low	Uncertain trade-offs	Further research needed	We cannot make a recommendation at this time.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

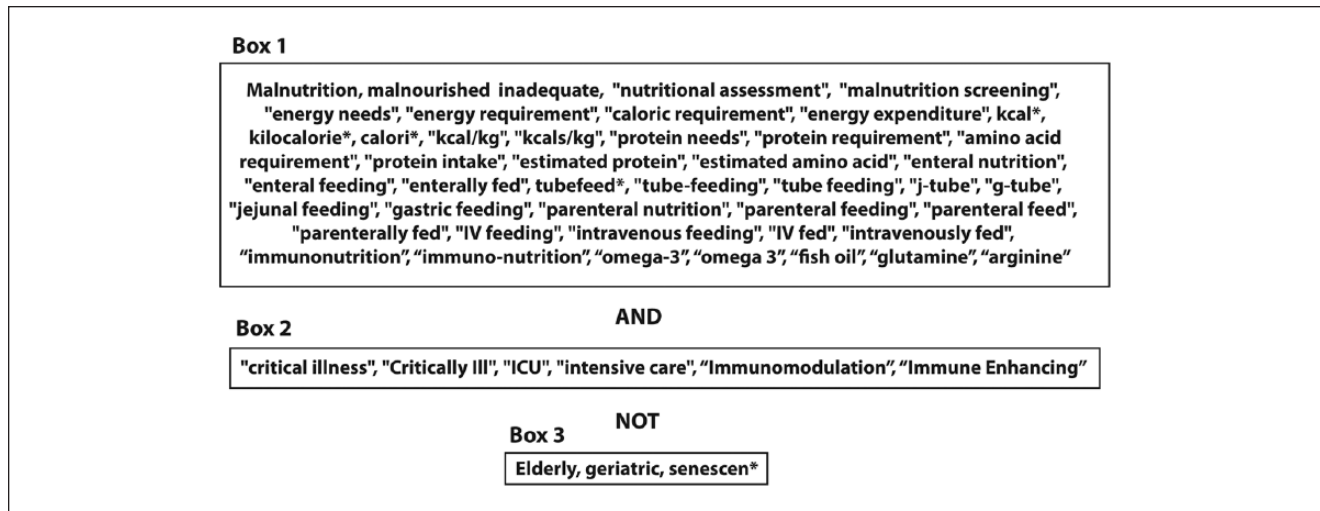


Figure 1. Overview of the literature search strategy.

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 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 with 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 also had to 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 accepted citations that had the terms *pediatric**, *paediatric**, *infan**, *adolescen**, or *child** in at least 1 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 with text-based terms (Figure 1). As an added protection against MeSH miscategorization of citations, this text-based search was then used to search the MEDLINE database, restricted to yield only 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 on EMBASE-indexed non-MEDLINE clinical trials was created and implemented for the EMBASE database.

Results

In total, 2032 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 1661 citations. In total, the search for clinical trials yielded 1107 citations, whereas the cohort search yielded 925. Each citation was reviewed by at least 2 reviewers to examine eligibility for inclusion in guideline development. After careful review, 16 RCTs and 37 cohort studies appeared to answer 1 of the 8 pre-identified question groups for this guideline. We then reviewed these studies and abstracted the relevant data with a standardized form. After review of the abstracted data, evidence tables were generated for each question. Given the evidence tables, we used an iterative process to develop practical recommendations for each question with 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 guideline question. Each table is accompanied by a discussion on the rationale for the recommendations and suggested areas for future investigation for the questions.

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 nutrition 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 intensive care units (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 among 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 not often been replicated in subsequent studies.^{11–13} Despite these limitations, there have been a number of small and large studies published over the past decade. Observational cohort and case-control 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 detail in the 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 nutrition status. It is therefore overly simplistic to expect that one strategy will be applicable to all patients. Nutrition support must be individualized according to the baseline nutrition status and vulnerabilities of patients, anticipated time to volitional feeding, and the risk-to-benefit ratio of intended nutrition therapies. Therefore, the recommendations provided here are useful starting points on which to build customized nutrition therapy for individual patients.

Question 1A: What is the impact of nutrition 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 (see Table 3). We recommend that patients in the PICU undergo detailed nutrition assessment within 48 hours of admission.

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

Quality of evidence. Very low.

GRADE recommendation. Strong.

Question 1B: What are the best practices to screen and identify patients with malnutrition or those at risk of nutrition deterioration in the PICU?

Recommendation 1B. On the basis of observational studies and expert consensus, we recommend that weight and height/length be measured at admission to the PICU and that z scores for body mass index (BMI) for age (weight for length, <2 years) or weight for age (if accurate height is not available) be used to screen for patients at extremes of these values. For children <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 nutrition interventions.

Quality of evidence. Very low.

GRADE recommendation. Strong.

Rationale. Malnutrition is prevalent in children admitted to the PICU.^{6,7,14,15} Although variables used to define malnutrition are inconsistent across reports, underweight and overweight status have both 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 nutrition deterioration.¹⁷ A large portion of children admitted to the PICU is at risk for nutrition deterioration; therefore, periodic nutrition

Table 3. Impact of Nutrition Status on Outcomes and Best Practices to Detect Malnutrition or Risk of Nutrition Deterioration.

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Results/Outcome	Comments
Bechard et al ⁴	Prospective, observational cohort (combined data set from 2 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 = 1622 Mechanically ventilated, critically ill children, 1 mo to 18 y old, with an expected PICU stay of at least 3 d, and dependent on enteral or parenteral nutrition support Mean age (SD): 4.5 y (5.1 y)	54.2%, normal weight; 17.9%, underweight; 14.5%, overweight; 13.4%, obese Outcomes (vs normal nutrition status) 60-d mortality: Higher in underweight: OR, 1.53 (CI 1.24–1.89; <i>P</i> < .001) Likelihood of discharge alive: for each additional day in the hospital, underweight had 29% (HR, 0.71; 95% CI, 0.60–0.84; <i>P</i> < .001) and obese had 18% (HR, 0.82; 95% CI, 0.68–0.99; <i>P</i> = .04) lower chance of being discharged. Hospital-acquired infection: higher in underweight: OR, 1.88 (95% CI, 1.18–3.01; <i>P</i> = .008) Higher in obese: OR, 1.64 (95% CI, 1.33–2.03; <i>P</i> < .001) VFD: Underweight associated with 1.3 fewer VFD vs normal weight (95% CI, –2.1 to –0.6; <i>P</i> = .001), 1.6 fewer VFD vs overweight (95% CI, –2.4 to –0.9; <i>P</i> < .001), 1.2 fewer VFD vs obese (95% CI, –1.9 to –0.6; <i>P</i> < .001). No significant differences in VFD among overweight and obese	45% of the cohort was malnourished (obese, overweight, underweight) on admission. Underweight and obese status associated with poor outcomes vs normal nutrition 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 nutrition status of children receiving CRRT	n = 174 PICU patients receiving CRRT Malnutrition: < 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 y 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 nutrition status, and serum albumin level was used to determine protein status.

(continued)

Table 3. (continued)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Results/Outcome	Comments
de Souza Menezes et al ⁶	Prospective, observational; single center	To determine the nutrition 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 (<i>z</i> score, <-2) based on weight for age (<2 y) or BMI (≥ 2 y) 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 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; <i>P</i> = .024).	Center with high prevalence of malnutrition showing independent impact on duration of MV. Limitations: single-center study; methodologic issues with sample size calculation.
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 = 1077 Malnutrition based on weight-for-age <i>z</i> 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 (<i>P</i> = .043).	>50% of patients admitted to this Brazilian PICU were malnourished. Malnourished patients had higher inflammatory markers vs well-nourished patients.

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

reevaluation is essential.^{15,18} Nutrition 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 1 study but has not been shown to predict outcomes in critically ill children.¹⁹

In a limited resource setting, timely and detailed nutrition 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 among 2567 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 *z* scores based on weight for age and BMI for age (or weight for length for children <2 years) 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 children receiving mechanical ventilation.⁴ Due to the 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 the 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 nutrition status in high-risk patients. A uniform definition of malnutrition must be employed, and validated methods for nutrition assessment must be developed and implemented in the PICU. Subsequently, the impact of malnutrition on clinical outcomes in the PICU population should be examined.

Question 2A: What is the recommended energy requirement for critically ill children?

Recommendation 2A. On the basis of 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 (see Table 4).

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 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. On the basis of 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 nutrition outcomes. Per 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.

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 $\pm 10\%$ 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 for critically ill children is independent of nutrition status, initial diagnosis, or severity of the acute illness.^{30–32,34} MREE may be decreased during deep sedation, neuromuscular blockade, or severe hypothyroidism, or increased with temperature >38°C and distress/activity.^{30,31,33} 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

Table 4. Recommended Energy Requirement for Critically Ill Children.

Reference	Study Design; No. of Sites	Study Aim(s)	Population (n), Eligibility	Results/Outcome	Comments
Joffrand 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 ($P = .031$) and increased by 8% per degree centigrade body temperature ($P = .003$). DRI strongly overestimated MREE Protein intake ≥ 1.5 g/kg/d protein 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 y (1.0–10.4 y)	Inadequate vs adequate caloric intake and outcomes Adequate calories defined as $\geq 80\%$ Schofield equation by third day of ARDS PICU mortality: 60.5% vs 34.6%; $P = .003$ PICU-free days: 0 (0–15) vs 0 (0–17); $P = .687$ Ventilator-free days: 0 (0–4) vs 3 (0–12); $P = .068$ Multiple organ dysfunction: 72.5% vs 53.8%; $P = .093$	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 y)	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 among patients: median, 37.2 kcal/kg/d (range, 16.8–66.4) 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.
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 y (1.4)	32 IC measurements MREE vs Harris-Benedict: 5 of 32 IC measurements greater than estimation MREE: $70.2\% \pm 3.8\%$ of Harris-Benedict MREE vs Schofield: 3 of 32 IC measurements greater than estimation MREE: $69\% \pm 4.5\%$ 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

(continued)

Table 4. (continued)

Reference	Study Design; No. of Sites	Study Aim(s)	Population (n), Eligibility	Results/Outcome	Comments
Meyer et al ³²	Prospective, observational cohort; multicenter 3 PICUs	To develop equations to estimate energy requirements and to compare 3 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 3 equations developed, $R^2 > 0.8$ for each equation Inotropes, neuromuscular blockade, temperature, C-reactive protein, and organ dysfunction scores did not impact MREE 3 new equations vs current equations vs MREE (n = 30); 25% of estimates, including 3 new equations, within 10% of MREE; 75% of estimations, including 3 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 (ie, exclusion of patients who cannot have MREE measured), and no outcomes reported
Mehta et al ⁸	Prospective, cohort with consecutive patients enrolled; multicenter 31 PICUs in 8 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 h Mean age (SD): 4.5 y (5.1 y)	Mortality lower with energy intake 33.3%–66.6% vs <33.3% prescribed goal (OR, 0.27 [95% CI, 0.11–0.67]), with >66.7% vs <33.3% (OR, 0.14 [95% CI, 0.03–0.61]); $P = .002$	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 > 48 h
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 y (0.1–28 y)	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; $P = .04$) vs normal (median, 33 d) or hypometabolism (median, 50 d)	The study described the risk of cumulative energy imbalance with 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.

(continued)

Table 4. (continued)

Reference	Study Design; No. of Sites	Study Aim(s)	Population (n), Eligibility	Results/Outcome	Comments
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), $P < .0001$; positive correlation between protein balance and energy intake ($r = 0.77$; $P < .0001$)	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 3 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 y (1.6 mo to 32 y)	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.
Sy et al ²⁵	Prospective cohort; single center	To estimate MREE with bicarbonate kinetics and to compare bicarbonate kinetics with MREE estimated via FAO/WHO/UNU and Schofield equations in 3 groups: 1 receiving PN, 1 receiving EN, and 1 receiving glucose-electrolytes	n = 31 Critically ill children Mean age (SD), PN group (n = 12): 7.8 y (7.4 y) EN group (n = 7): 3.3 y (4.1 y) Glucose-electrolytes group (n = 12): 6.3 y (5.0 y)	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 y (6.8 y)	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

(continued)

Table 4. (continued)

Reference	Study Design; No. of Sites	Study Aim(s)	Population (n), Eligibility	Results/Outcome	Comments
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 y (5.87 y)	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 y (6 y)	TEE was approximately 122% of MREE No differences in TEE, MREE, activity-related energy expenditure, PAL between sepsis and surgery groups	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
Havalad et al ³⁰	Retrospective cohort; single center	To compare MREE with 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 y (6.1–16.2 y)	40% of estimates within 10% of MREE 43% patients had MREE greater than the estimate Bland-Altman: poor agreement between MREE and all 4 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 h of admission; energy intake not reported; and actual MREE values not reported.
Hardy et al ²⁹	Prospective cohort; single center	To compare MREE with BMR estimated by various methods	n = 52 35 ventilated 17 spontaneously breathing Median age (range): 4.5 y (0–22 y)	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; $r = 0.72$, $P < .01$ 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; no outcomes reported

ARDS, acute respiratory distress syndrome; BMR, basal metabolic rate; CRR, 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; PICU, pediatric intensive care unit; PN, parenteral nutrition; RQ, respiratory quotient; TEE, total energy expenditure.

candidates for targeted MREE with IC, especially if this resource is limited (Appendix).³¹

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.^{40,41} When an equation to estimate energy requirements is used, it is essential to vigilantly monitor for potential signs of overfeeding (hyperglycemia, hypertriglyceridemia, increased CO₂ 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, overpredict 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 CO₂ (VCO₂) was recently developed among children receiving mechanical ventilation and found to be more accurate than equation-estimated energy expenditure.^{42,43} The increased use of devices that provide bedside VCO₂ measurement in the PICU may allow this equation to replace the Schofield or WHO equations for determination of energy requirement in patients receiving mechanical ventilation.

Observational data suggest a positive association between adequacy of energy intake and improved outcomes in the PICU population.^{8,36,44} Intake of > two-thirds of estimated energy goal in a large multicenter prospective cohort and >80% of estimated energy goal in a smaller single-center retrospective cohort was significantly associated with reduced mortality in critically ill children receiving mechanical ventilation.^{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 > two-thirds of energy goal, achievement of 100% of estimated energy requirement may not be necessary in all patients.^{8,24,25,40,41}

Future direction. Future studies must examine the optimal energy dose that is associated with improved nutrition 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. On the basis of evidence from RCTs and support from observational cohort studies, we recommend

a minimum protein intake of 1.5 g/kg/d (see Table 5). 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 children receiving mechanical ventilation.

Quality of evidence. Moderate.

GRADE recommendation. Strong.

Question 3B: What is the optimal protein delivery strategy in the PICU?

Recommendation 3B. On the basis of 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 enteral and parenteral (and 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 of patients receiving mechanical ventilation in the PICU, 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 a cohort study of 76 children receiving mechanical ventilation, 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 multicenter (n = 59) observational study of 1245

Table 5. Recommended Protein Requirement for Critically Ill Children.

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
Randomized controlled trials						
Geukers et al ⁴⁹	RCT (double blind); single center	To investigate the short-term (<48 h) 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)	EN initiated within 24 h 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 $\mu\text{mol/kg/min}$ Net valine balance: 0.54 vs 0.24 $\mu\text{mol/kg/min}$ No differences between groups regarding cardiac intraoperative times	Unable to demonstrate improvement in protein balance (with 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.
¹ de Betue et al ⁵⁰ and ² de Betue et al ⁴⁸	RCT; 2 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)	EN started within 24 h of PICU admission; advanced by 25% of target volume every 12 h 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 nutrition intake: 119 \pm 25 vs 84 \pm 15 kcal/kg/d; 3.1 \pm 0.3 g/kg/d vs 1.7 \pm 0.2 g/kg/d protein Whole body protein balance: 0.73 \pm 0.5 vs 0.02 \pm 0.6 g/kg/h (<i>P</i> = .026) Protein synthesis: 9.6 \pm 4.4 vs 5.2 \pm 2.3 g/kg/d (<i>P</i> = .019) Protein breakdown: 8.9 \pm 4.3 vs 5.2 \pm 2.6 g/kg/d (<i>P</i> = .046) Nitrogen balance: 274 \pm 127 vs 137 \pm 53 mg/kg/d (<i>P</i> < .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
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 y (1.2 y)	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 (<i>P</i> < .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

(continued)

Table 5. (continued)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
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 h Median age (IQR): 7 mo (3–13 mo)	Unit feeding protocol: Continuous EN started within 24 h of PICU admission to reach approximately 60 kcal/kg/d within first 24 h IC, nitrogen balance, serum urea, serum albumin level, total proteins, prealbumin, transferrin, retinol binding Study measurement times: baseline, 24 h, 72 h, 5 d Control diet: breast milk (protein, 1.1 g/100 mL) or cow milk-based formula (protein, 1.6 g /100 mL), or pediatric formula (protein, 2.6 g/100 mL) Experimental diet: same as control with supplementation of protein, 1.1 g/100 mL	Intervention diet well tolerated No difference in IC measurements between groups Experimental vs control nutrition intake Mean 71.9 vs 65.9 kcal/kg/d (not significant) Mean 3.1 vs 1.7 g/kg/d (<i>P</i> = .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 (6 control, 4 experimental); no discussion on associations with mortality, duration of mechanical ventilation, or length of stay; and small sample size analyzed
van Waardenburg et al ⁵¹	RCT (double blind); 2 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 h Mean age (SD): experimental, 2.7 mo (0.5 mo); control, 3.0 mo (0.6 mo)	Continuous EN target = 130 mL/kg/d; started at 25% of target, advanced 25% every 12 h 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 nutrition intake: 112 ± 13 vs 82 ± 4 kcal/kg/d (<i>P</i> < .01); 2.8 ± 0.3 vs 1.5 ± 0.1 g protein/kg/d (<i>P</i> < .01) Cumulative nitrogen balance, days 2–5: 866 ± 113 vs 297 ± 71 mg/kg/d (<i>P</i> < .01) Increased gastric residual volumes in protein-enhanced formula group (<i>P</i> < .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
Chaloupecky et al ⁴⁷	RCT; single center	To evaluate the effect of nutrition support on the hypercatabolic reaction within 7 d following cardiac surgery	n = 37 Postcardiac surgery Mean age (SD): 6.7 mo (3.4 mo)	EN introduced day 2 Experimental group: PN with AA 0.8 ± 0.1 g/kg/d Control group: 10% dextrose containing intravenous 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 (<i>P</i> = .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

(continued)

Table 5. (continued)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
Observational studies						
Jotterand Chaparro et al ⁶	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 h Median age (IQR): 21 mo (4–35 mo)		Minimum 1.5 g/kg/d protein and 58 kcal/kg/d required to achieve nitrogen and energy balance in children up to 4 y 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 y) Limitations: small number of older children studied and patients with longer PICU stays had more measurements which may influence results
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 y (1.0–10.4 y)		Inadequate vs adequate protein intake ICU mortality: 60.2% vs 14.3%; $P = .002$ PICU-free days: 0 (0–15) vs 0 (0–14); $P = .940$ Ventilator-free days: 0 (0–4) vs 12 (3–19); $P = .005$ Multiple organ dysfunction: 70.7% vs 50%; $P = .136$ 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: nutrition status was not documented, and its impact on outcomes is not shown; measured resting energy expenditure was not used
Mehta et al ⁹	Prospective cohort; multicenter; 59 PICUs in 15 countries	To examine the association between protein intake and 60-d mortality	N = 1245 Critically ill children requiring mechanical ventilation (≥ 48 h) Median age (IQR): 1.7 y (0.4–7.0 y)		n = 985 received EN Mean percentage delivery of prescribed: energy, 36% \pm 35%; protein, 37% \pm 38% Adequate enteral protein intake was significantly associated with 60-d mortality ($P < .001$) after adjustment for disease severity, site, PICU days, and energy intake Mean enteral protein intake <20% vs $\geq 60\%$ of prescribed goal, OR for 60-d mortality: 0.14 (95% CI, 0.04–0.52; $P = .003$)	Adequate protein intake was associated with lower mortality Results generalizable to children on mechanical ventilation in PICUs with >8 beds Limitations: noninterventonal, observational study

(continued)

Table 5. (continued)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
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 \pm neuromuscular blockade Median age (range): 6 y (2–14 y)		Anabolism was associated with increased protein intake: median 1.1 (range, 0.7–2.2) g/kg/d vs catabolism median 0.1 (0–1.8) g/kg/d ($P < .0001$) Positive correlation: protein intake and balance, $R = 0.63$ ($P < .0001$) Positive balance for phosphate and magnesium with protein intake 0.5–1 g/kg/d Negative correlation: creatinine clearance and protein balance, $R = -0.45$ ($P < .0001$) 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 $\geq 50\%$ of goal energy with the Holliday-Segar formula were associated with a positive protein balance, except in septic patients. Limitations: small sample size
Zappitelli et al ⁵⁶	Retrospective collaborative registry	To evaluate protein and caloric prescription and to evaluate factors associated with over prescription and underprescription of protein and calories	n = 195 Critically ill children and young adults with acute kidney injury receiving CRRT Mean age (SD): 8.8 y (6.8 y)		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 caloric intake: younger age ($P = .04$), higher initial protein or calories at initiation of CRRT ($P < .0001$), longer duration of CRRT ($P < .003$)	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

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; PICU, pediatric intensive care unit; PN, parenteral nutrition; RCT, randomized controlled trial; RSV, respiratory syncytial virus.

children receiving mechanical ventilation from 15 countries, 985 subjects received EN; delivery of >60% of prescribed enteral protein goal was significantly associated with decreased 60-day mortality (<20% vs >60%; odds ratio, 0.14 [95% CI, 0.04–0.52]; $P = .003$) 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 these studies. However, the safety of protein intake >3 g/kg/d in children >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 recommendation of a minimum of 1.5 g/kg/d should also be applied to this population, based on 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, nutrition status (eg, muscle mass and function), and relevant clinical outcomes (eg, 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. On the basis of observational studies, we recommend EN as the preferred mode of nutrient delivery to the critically ill child (see Table 6). 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. On the basis of 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 hours 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.

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.^{61–63,67,68} 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's decision to start EN 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 2 large international prospective cohort studies of children receiving mechanical ventilation, enteral delivery of > two-thirds of the energy goal and >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 5105 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 a retrospective cohort of 107 children with acute respiratory distress syndrome, enteral delivery of adequate calories ($\geq 80\%$ 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

Table 6. Feasibility and Benefits of Enteral Nutrition.

Reference	Study Design; No. of Sites	Study Aims	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 y (IQR, 1.0–10.4 y)	28 (26.2%) of patients received early EN (within 24 h of ARDS) PICU mortality was lower in patients who received adequate calories (34.6% vs 60.5%; $P = .025$) and adequate protein (14.3% vs 60.2%; $P = .002$) 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 with 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 = 1245 Critically ill children receiving mechanical ventilation for ≥ 48 h Median age (IQR): 1.7 (0.4–7.0) y	n = 985 received EN The mean \pm SD delivery of enteral energy and protein was $36\% \pm 35\%$ and $37\% \pm 38\%$, respectively. The adequacy of enteral protein intake was significantly associated with 60-d mortality ($P < .001$) 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 > 8 beds were included; the energy intake goals were estimated by dietitians at each site; and variability of nutrition practices at the participating sites
Mikhailov et al ⁶⁶	Retrospective cohort study; multicenter database	To determine whether early EN (within 48 h of admission) is associated with lower mortality, shorter LOS, and shorter duration of mechanical ventilation	n = 5105 Critically ill children with PICU LOS ≥ 96 h Median age (IQR): 2.4 (0.5–9.8) y	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 [95% CI, 0.34–0.76]; $P = .001$), 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 h; and inaccuracies of nutrition data recorded in health records
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 ≥ 1 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 ($P < .001$) and had a lower mortality ($P < .01$) vs the nonfed group. The Vasoactive-Inotropic Score in the nonfed group was higher only on day 1 ($P < .05$) vs the fed group. Gastrointestinal outcomes were not different between the 2 groups.	The authors found no adverse effects with the use of vasoactive medications during EN delivery. Large sample size Limitations: the effect of > 1 vasoactive drug on intolerance to EN is not known. Retrospective study with limitations of clinical and nutrition data in health records
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.	The study showed that patients with vs without AKI are more likely to be underfed. 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 h Documented nutrient intake by all routes (PN and EN) in the first 8 d in PICU	Actual energy intake for all patient-days was $75.7\% \pm 56.7\%$ of estimated BMR. Actual protein intake for all patient-days was $40.4\% \pm 44.2\%$ of estimated requirements.	Patients in this large tertiary PICU study received < half of recommended protein intake. Limitations: results may not be applicable to other PICUs; and energy and protein needs based on reference values

(continued)

Table 6. (continued)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Results/Outcome	Comments
Mehta et al ⁸	Prospective cohort study; multicenter, 31 PICUs in 8 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 y (5.1 y)	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 h 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 >8 beds were included; variability in staff skills, availability and adherence to protocols, and resource availability could have influenced the results
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 h Median age (IQR): 7.2 y (1.7–15.3 y)	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 \pm 3.1 times per patient (range, 1–13), for a total of 88 episodes accounting for 1483 h 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 h	Daily average intake met 60% required kilocalories and 85% prescribed kilocalories Gastrointestinal complications and use of vasoactive drugs (α -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-h period Age: 1 mo to 20 y	Dopamine at ≥ 6 μ g/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%); 4 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; PICU, pediatric intensive care unit; PN, parenteral nutrition.

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. On the basis of observational studies, we suggest the use of a stepwise algorithmic approach to advance EN in children admitted to the PICU (see Table 7). 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. On the basis of observational studies, we suggest that a multidisciplinary nutrition support team, including a dedicated dietitian, be available on the PICU team to facilitate timely nutrition 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 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, 9 of the 31 participating PICUs reported the use of an EN algorithm.⁷³ These algorithms defined the rate of EN advancement and 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 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 nutrition practices, such as timely assessment and documentation of nutrition status, development of an optimal nutrition prescription, serial follow-up, and monitoring for safe nutrient delivery, as 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 the presence of a dedicated dietitian for an average of 0.4 full-time equivalents per 10 beds.⁸ In a subsequent multicenter study of 59 PICUs, the presence of a dedicated dietitian was a significant and independent predictor of adequate enteral protein intake.⁹ Hence, dietitians are 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 (eg, 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 nutrition 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 (see Table 8). On the basis of observational studies, we suggest that 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 for patients unable to tolerate gastric feeding or for those at high risk for aspiration. Existing data are insufficient to make recommendations regarding the use of continuous versus intermittent gastric feeding.

Table 7. Optimum Method for Advancing Enteral Nutrition.

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
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	The EN protocol: start with 0.5 mL/kg/h, advance by the same rate every 4–6 h 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 kcal/kg/d 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.
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 LOS >24 h	The protocol included nutrition 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 d to 1 d ($P < .05$), with a higher proportion of patients reaching this goal (99% vs 61%, $P = .01$). Decrease in avoidable EN interruptions (3 vs 51, $P < .0001$) 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 stepwise EN algorithm. Limitations: No difference in clinical outcomes.
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	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 h vs 20 h) 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.

(continued)

Table 7. (continued)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
Meyer et al ⁷⁹	Time series, single center	To examine the impact of introducing a series of enteral feeding protocols on nutrition practice in a PICU over a 9-y period.	n = 400 Over a 9-y period and spanning 4 studies.	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 NJT feeding algorithm) were introduced.	Over the 4 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, 4.5 h Patients receiving EN: 89%, 81%, 99%, 96% Patients receiving PN: 11%, 19%, 1%, 4% Patients reaching 50% of EAR by day 3: 15%, 26%, 58%, 59% Patients reaching 70% of EAR by day 3: 6%, 10%, 35%, 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.
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	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 h, $P < .001$ 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
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 (2–204) mo	Initiation of a feeding protocol in the first 12 h of admission to PICU.	Energy intake approached predicted basal metabolic rate the second day (43 ± 1.7 kcal/kg/d vs 43.2 ± 1.1 kcal/kg/d) and predicted energy expenditure (based on stress factors) the fifth day (66.2 ± 2.7 kcal/kg/d 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.

EAR, estimated average requirements; EN, enteral nutrition; ICU, intensive care unit; LOS, length of stay; NGT, nasogastric tube; NJT, nasojejunal tube; PICU, pediatric intensive care unit; PN, parenteral nutrition.

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

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
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 with 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	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%; <i>P</i> = .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
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) 2 of 19 randomized to postpyloric group were unable to have feeding tube placed after 24 h and 4 abdominal radiographs; moved to the gastric group	Gastric vs postpyloric feeding Methylene blue: 0.2 mL/100 mL formula Endotracheal specimen every 8 h; 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) h; <i>P</i> = .0002 Median (95% CI) number of abdominal radiographs: 4 (3–4) vs 1 (1–1), <i>P</i> = .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
Horn et al ⁷⁷ and Chaboyer ⁸³	RCT—convenience sample, single center	¹ To examine the relationship between 2 gastric feeding regimens—continuous and intermittent—and tolerance as measured by the number of stools and prevalence of diarrhea (≥3 stools/24 h) 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 (1 subject removed due to only 1 d of feeding; final n = 23) Median age: 8 mo (1–153 mo) Random assignment to feeding regimen	Experimental group: continuously fed with pump Control group: feedings delivered every 2 h over 20–30 min with 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 (h), median (range): 13.0 (1–63) vs 18.5 (3–231); <i>P</i> = .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)

(continued)

Table 8. (continued)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
Observational studies						
Camarie et al ⁸⁹	Retrospective cohort; multicenter 6 PICUs	To determine the factors associated with delayed EN Patients divided into 2 groups: early EN (≤ 48 h) and delayed EN (> 48 h) from PICU admission	n = 444 Median age (IQR): 4.0 y (0.5–11.9 y)		EN was started at median of 20 h 88 of 444 children (19.8%) had delayed EN Risk factors associated with delayed EN: noninvasive (OR, 3.37 [95% CI, 1.69–6.72]) and invasive positive-pressure ventilation (OR, 2.06 [95% CI, 1.15–3.69]), severity of illness (OR for every 0.1 increase in PIM2 score, 1.39 [95% CI, 1.14–1.71]), procedures (OR, 3.33 [95% CI, 1.67–6.64]), and gastrointestinal disturbances (OR, 2.05 [95% CI, 1.14–3.68]) within 48 h 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 nutrition 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
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 h of admission	n = 5105 Critically ill children with PICU LOS ≥ 96 h Median age (IQR): 2.4 y (0.5–9.8 y)		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 (95% CI 0.34–0.76); $P = .001$ 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
Mehta et al ⁸	Prospective cohort study; multicenter 31 PICUs in 8 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 h Mean age (SD): 4.5 y (5.1 y)		Mean prescribed goals Energy: 64 kcal/kg/d Protein: 1.7 g/kg/d EN started in ≤ 48 h 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 ≥ 8 beds were included; and variability in nutrition practice and resources could have influenced the performance of individual sites

(continued)

Table 8. (continued)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
Taha et al ⁸⁶	Retrospective cohort; single center	To evaluate the impact of the time of initiation of nutrition support and achieving full caloric intake on PICU LOS and disposition status at discharge	n = 109 Median age (range): 13 y (8–18 y) Children with severe isolated TBI Median Glasgow Coma Scale on admission to the ICU: 3		19 patients died before starting nutrition and 7 died before achieving full caloric intake The time to start nutrition support was correlated with PICU LOS ($r = 0.49$; $P < .01$) PICU LOS was shorter when patients achieved full caloric intake sooner ($r = 0.57$; $P < .01$)	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 nutrition and discharge policies
Tume et al ⁸⁷	Prospective cohort; single center	1. To compare actual caloric intake with estimated requirements 2. Determine whether feeding guideline adherence resulted in improved nutrition intake	n = 47 Median age (range): 10 mo (0.03–168 mo)		EN initiation ≤ 6 h 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, $P = .004$	A majority of patients received $< 50\%$ of prescribed energy goal. Adherence to feeding guidelines improved nutrition intake. Limitations: small sample size; study limited to 24 h; and no clinical outcomes reported
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); $P = .0001$		Patients with shock vs those without shock: More gastrointestinal complications: 20 (30.7%) vs 42 (9.1%), $P = .020$; more gastric distention/residue: 10 (15.4%) vs 23 (5%), $P = .004$; more diarrhea: 13 (20%) vs 21 (4.6%), $P = .0001$; 1 vs 0 duodenal perforation resulting in death; definite suspension of EN: 6 (9.2%) vs 5 (1%), $P = .0001$; higher mortality: 18 (27.7%) vs 32 (6.9%), $P = .0001$	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.
Sánchez et al ⁸⁸	Prospective cohort; single center	To compare tolerance and complications associated with early vs late transpyloric EN Early EN definition: < 24 h from PICU admission	n = 526 Critically ill children admitted to PICU and received transpyloric EN n = 202 early EN n = 324 late EN		Early vs late EN: EN initiation: 0.7 ± 0.2 vs 5.3 ± 7.4 d, $P < .001$ No difference in mortality, nosocomial pneumonia, maximum caloric intake, diarrhea Supplemental parenteral nutrition: 0.2 ± 1.4 vs 0.9 ± 2.8 d Low K^+ (16.3% vs 29.9%; $P < .05$) Low Ca^{++} (3.5% vs 12.1%; $P < .05$) Abdominal distention: 3.5% vs 7.8%; $P < .05$	Early EN < 24 h was achieved in $> one-third$ 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)

Reference	Study Design; No. of Sites	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
López-Herce et al ⁶⁵	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); <i>P</i> = .001 n = 38 (71.6%) of patients with ARF required continuous renal replacement therapy		ARF vs no ARF Maximum intake: 77 (26.7) vs 85 (24.9) kcal/kg/d; <i>P</i> = .029 Shock: 49% vs 8.2%; <i>P</i> = .0001 Mortality: 30.1% vs 7.1%; <i>P</i> = .0001 Gastrointestinal complications: 24.5% vs 9.9%; <i>P</i> = .008 Abdominal distention, high gastric residual volume: 17% vs 5%; <i>P</i> = .003 EN suspended: 1.2 vs 9.4%; <i>P</i> = .0001 EN initiation <48 h 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 2 other studies.
Petrillo-Albarano et al ⁷¹	Retrospective, before/after cohort; single center	To examine the implementation of an early EN protocol (≤6 h 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)		Postintervention vs preintervention Time to goal EN, median (IQR): 14 (9–21.5) vs 32 (12–78) h; <i>P</i> < .0001 Less diarrhea: <i>P</i> = .009 Less constipation: <i>P</i> = .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.
Brassoulis et al ⁷⁸	Prospective study; single center	To investigate the feasibility, adequacy, and efficacy of early gastric feeding (≤12 h from admission)	n = 71 Critically ill children requiring mechanical ventilation Median age (range): 54 mo (2–204 mo)		Caloric intake approached predicted BMR on day 2 and estimated needs (BMR × 1.5) on day 5 Correlation between caloric intake and severity of illness: pediatric Risk of Mortality score: <i>r</i> = -0.35; <i>P</i> = .003; Therapeutic Intervention Scoring System: <i>r</i> = -0.37; <i>P</i> = .002	This study showed that use of a gastric EN protocol increased caloric intake during the first 5 d of admission to the PICU

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.

Quality of evidence. Low.

GRADE recommendation. Weak.

Question 6B: When should EN be initiated?

Recommendation 6B. On the basis of expert opinion, we suggest that EN be initiated in all critically ill children, unless it is contraindicated. Given the 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 perceived or demonstrated risks of aspiration of gastric contents into the tracheobronchial tree. The use of small intestinal (postpyloric) feeding in 2 small RCTs did not demonstrate reduced aspiration when compared with gastric feeding.^{81,82} The postpyloric route was associated with a higher proportion of goal nutrition delivery in 1 study⁸² 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 as either a continuous or an intermittent modality. In 2 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 among 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 for 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 >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 versus

delayed EN (<24 vs ≥48 hours), 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: What is the indication for and optimal timing of PN in critically ill children?

Recommendation 7A. On the basis of a single RCT, we do not recommend the initiation of PN within 24 hours of PICU admission (see Table 9).

Quality of evidence. Moderate.

GRADE recommendation. Strong.

Question 7B: What is the role of PN as a supplement to inadequate EN?

Recommendation 7B. For 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 for patients with normal baseline nutrition state and low risk of nutrition deterioration. On the basis of expert consensus, we suggest PN supplementation in children who are unable to receive any EN during the first week in the PICU. For patients who are severely malnourished or at risk of nutrition 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 for 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, the 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 3-center RCT (PEPaNIC trial [ie, “Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit”]) 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) when compared with the early PN group (receiving PN within 24 hours 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

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

Reference	Study Design; No. of Sites	Population (n), Eligibility	Study Aims	Intervention	Results/Outcome	Comments
Fivez et al ⁹⁰	Randomized controlled trial; 3 centers	n = 1440 Term newborn—17 y > 24 h expected PICU stay STRONGKids Nutrition score > 2 (0, low risk of malnutrition; 1–3, medium 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 h of admission) Primary end points: 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 h 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; <i>P</i> < .001 Patients in PICU ≥ 8 d: 159 of 717 vs 216 of 723; <i>P</i> < .001 Hospital LOS: 17.2 ± 1.0 vs 21.3 ± 1.3; <i>P</i> < .001 Acquired infections: 77 vs 134; <i>P</i> < .001; significant differences in bloodstream and airway infections Mechanical ventilation duration (d): 4.4 ± 0.3 vs 6.4 ± 0.7; <i>P</i> = .001 Hypoglycemia (<40 mg/dL in first week): 65 vs 35; <i>P</i> = .001	PN use within 24 h 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 was not provided.

EN, enteral nutrition; LOS, length of stay; PICU, pediatric intensive care unit; PN, parenteral nutrition; STRONGKids, Screening Tool for Risk of Impaired Nutritional Status and Growth.

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 through 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. Since most children were receiving significant amounts of EN, the results of the PEPaNIC trial may 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 nutrition assessment/screening tool used in the study (STRONGkids) has not been validated for 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 <80% goal to trigger supplemental PN at the 2 time points. A majority of children in this study had energy expenditure estimated with equations that have been discredited in critically ill children (see 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 overfed. In addition, glycemic control protocols were different in the 3 centers. Multiple problems exist with 1 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 bloodstream infection. The presence of indwelling devices (eg, central venous catheters) in the 2 groups was not reported. It is not clear how the investigators distinguished 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 PICU. The optimal timing of supplemental PN in children failing to

meet their nutrient delivery goals enterally must be individualized based on the nutrition 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 nutrition requirements during the first week of critical illness. These trials must account for the varying baseline nutrition status of patients and their individualized energy and protein goals.

Question 8: What is the role of immunonutrition in critically ill children?

Recommendation 8. On the basis of available evidence, we do not recommend the use of immunonutrition in critically ill children (see Table 10).

Quality of evidence. Moderate.

GRADE recommendation. Strong.

Rationale. Several dietary components—including glutamine, arginine, nucleotides, ω -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 (eg, to attenuate inflammation or provide nutrients depleted by stress). Terms used to describe this therapy include immunonutrition, immunonutrients, immunonutrient-enhanced diet, immune-enhancing nutrition, immunomodulating nutrition, pharmaconutrition, pharmaconutrients, and pharmaceutical nutrients. RCTs comparing immunonutrition with standard nutrition among critically ill children have used a variety of nutrients, delivered via the enteral or parenteral route, in heterogeneous populations, and with 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 1 pilot RCT and 1 retrospective cohort, investigators examined the use of an enteral formula containing ω -3 fatty acids, γ -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. 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 ω -3 fatty acids or to a standard pediatric formula were also underpowered and unable to demonstrate outcome differences.^{93,94} In 2 studies, infants requiring PN were randomized to receive intravenous lipid emulsion as ω -3 fatty acids, alone or in combination with medium-chain and long-chain (ω -6) fats or a 100% soybean oil–based lipid (ω -6).^{95,96} These studies were designed to evaluate the effects of the 2 lipid formulations on inflammatory biomarkers; relevant clinical outcomes for critically ill children were not evaluated. Lipids containing ω -3 versus 100% ω -6 fatty acids were associated with lower plasma proinflammatory cytokines and potential for reduced

Table 10. Role of Immunonutrition.

Reference	Study Design	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
Jordan et al ⁹⁸	RCT	To determine whether GLN 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.	Experimental group (n = 49): standard PN + GLN. Control group (n = 49): standard PN	At day 5, patients in the PN + GLN group had significantly higher levels of HSP-70 as compared with controls (68.6 vs 5.4, $P = .014$). 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.	GLN 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.
¹ Larsen et al ⁹⁵ and ² Larsen et al ⁹⁷	RCT	Examine effects of 2 different lipid emulsions on plasma phospholipids and 3 immune biomarkers	n = 32 Infants with congenital heart disease scheduled for open heart surgery with cardiopulmonary bypass Mean age (SD): 40 (0.6) wk gestational age, 3.5 ± 0.5 kg, and 10.6 d at time of surgery	n = 16 Experimental group: Lipoplus: 50% medium-chain triglycerides, 40% long-chain triglycerides, 10% fish oil n = 16 Control group: Intralipid: 100% soybean oil Subjects were randomized to receive 1 of 2 lipid emulsions with TPN, for 1–4 d preoperative and 10 d postoperative Lipids started at 0.5 g/kg, increased to max 3.5 g/kg/d Enteral intake was limited to at 30 kcal/kg/d	¹ Experimental vs control groups: lower procalcitonin 1 day postoperatively ($P = .01$), lower ω -6 to ω -3 ratio ($P = .0001$), higher ω -3 concentration ($P = .001$), higher plasma phospholipid EPA ($P < .05$); 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 ($P < .05$) On postoperative day 10, those with high PRISM III scores exhibited a 45% lower lymphocyte concentration ($P < .05$) ² TNF- α concentration was lower in the experimental vs control group (5.9 vs 14.8 pg/mL, $P = .003$) Plasma TNF- α was positively correlated with hospital LOS in the control group ($P = .01$), and negatively correlated with LOS in the treatment group ($P = .004$), with a significant time by treatment interaction ($P = .02$)	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.
Nehra et al ⁹⁶	RCT	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 intravenous fat emulsion in reducing the incidence of cholestasis in neonates compared with the traditional soybean oil-based intravenous fat emulsion	Both groups received intravenous fat emulsion at 1 g/kg/d and kept constant during the study period. Experimental group: received fish oil-based intravenous fat emulsion Control group: received soybean oil-based intravenous 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.

(continued)

Table 10. (continued)

Reference	Study Design	Study Aims	Population (n), Eligibility	Intervention	Results/Outcome	Comments
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 (0.9) y	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 h of initiation of EN.	No significant differences between the 2 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 = .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
Carcello 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 h of PICU admission	Experimental group: enteral: 20 mg/d zinc; selenium, 1–3 y: 40 mcg/d, 3–5 y: 100 mcg/d, 5–12 y: 200 mcg/d, adolescent: 400 mcg/d; 0.3 g/kg/d glutamine; IV: 0.2 mg/kg/d (<10 mg/dose) metoclopramide every 12 h, from <72 h 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 = .16 PICU LOS: median 9 vs 11 d; P = .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): Immune compromised patients—1.57 (0.53–3.73) vs 6.09 (3.33–10.32); P = .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, immune compromised 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.
Brassoulis et al, ⁹³ Brassoulis et al, ⁹⁴ and Brassoulis et al ⁹⁹	RCT	To compare outcomes in critically ill children receiving an immune-enhancing formula or standard formula ¹ NB, nutrition indices, antioxidant catalysis ^{2,3} Cytokines, hospital acquired infections, nutrition 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 TBI	Randomized to immunonutrition formula (GLN, 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 NGT starting <12 h 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, mechanical ventilation duration ^{1,2,3} Diarrhea significantly more frequent ^{1,2,3} Positive NB in significantly higher proportion of patients on day 5 ^{1,2} Significantly fewer positive gastric cultures ³ 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 small single-center studies of immunonutrition vs standard formula are underpowered to demonstrate important outcome differences

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; BMR, basal metabolic rate; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid; GLN, glutamine; HSP-70, heat shock protein 70; IL, interleukin; IV, intravenous; LOS, length of stay; LTB4, leukotriene B4; MV, mechanical ventilation; NB, nasogastric tube; PICU, pediatric intensive care unit; PN, parenteral nutrition; PRISM III, Pediatric Risk of Mortality score; RCT, randomized controlled trial.

ICU LOS.⁹⁷ Clinical outcomes of critically ill children requiring PN who were 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 as compared with whey protein (1.57 vs 6.09; $P = .011$). No 2 trials of immunonutrients in children are similar, and none demonstrated superiority of immunonutrition versus standard nutrition among critically ill children in terms of clinical outcomes.

Prior studies of critically ill adults have demonstrated reduced hospital LOS and mortality with glutamine-supplemented PN.¹⁰¹ Based on these observations, in a recent large multicenter 2-by-2 factorial trial of critically ill adults receiving mechanical ventilation 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 adults receiving mechanical ventilation showed no infectious benefits and a possibility of harm, with a significantly higher 6-month mortality among medical patients randomized to a formula containing glutamine, ω -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 for 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 provide 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 or suggestions 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 nutrition strategy for individual patients can be customized. The guidelines reiterate the importance of nutrition assessment—particularly, the detection of malnourished patients who are most vulnerable and therefore potentially may benefit from timely nutrition 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 prescriptions, 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 are areas 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 nutrition needs of the critically ill child in the complex PICU environment.

Appendix. Targeted Indirect Calorimetry

Children who are at high risk for metabolic alterations are suggested candidates for targeted measurement of resting energy expenditure in the PICU.³¹ This includes the following:

- Underweight, overweight, or obese
- Children with >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 ventilator support for >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 LOS >4 weeks may benefit from IC to assess adequacy of nutrient intake.

References

- Mehta NM, Compher C; ASPEN Board of Directors. ASPEN clinical guidelines: nutrition support of the critically ill child. *JPEN J Parenter Enteral Nutr.* 2009;33:260-276.
- Druyan ME, Compher C, Boullata JI, et al; American Society for Parenteral and Enteral Nutrition Board of Directors. Clinical guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients: applying the GRADE system to development of ASPEN clinical guidelines. *JPEN J Parenter Enteral Nutr.* 2012;36:77-80.
- McKeever L, Nguyen V, Peterson SJ, et al. Demystifying the search button: a comprehensive PubMed search strategy for performing an exhaustive literature review. *JPEN J Parenter Enteral Nutr.* 2015;39:622-635.
- Bechard LJ, Duggan C, Touger-Decker R, et al. Nutritional status based on body mass index is associated with morbidity and mortality in mechanically ventilated critically ill children in the PICU. *Crit Care Med.* 2016;44:1530-1537.
- Castillo A, Santiago MJ, López-Herce J, et al. Nutritional status and clinical outcome of children on continuous renal replacement therapy: a prospective observational study. *BMC Nephrol.* 2012;13:125.
- de Souza Menezes F, Leite HP, Koch Nogueira PC. Malnutrition as an independent predictor of clinical outcome in critically ill children. *Nutrition.* 2012;28:267-270.
- Delgado AF, Okay TS, Leone C, et al. Hospital malnutrition and inflammatory response in critically ill children and adolescents admitted to a tertiary intensive care unit. *Clinics (Sao Paulo).* 2008;63:357-362.
- Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children-an international multicenter cohort study. *Crit Care Med.* 2012;40:2204-2211.
- Mehta NM, Bechard LJ, Zurakowski D, et al. Adequate enteral protein intake is inversely associated with 60-d mortality in critically ill children: a multicenter, prospective, cohort study. *Am J Clin Nutr.* 2015;102:199-206.
- Ross PA, Newth CJ, Leung D, et al. Obesity and mortality risk in critically ill children. *Pediatrics.* 2016;137:e20152035.
- Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ.* 2009;180:821-827.
- van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* 2001;345:1359-1367.
- Yamada T, Shojima N, Noma H, et al. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. *Intensive Care Med.* 2017;43:1-15.
- Briassoulis G, Zavras N, Hatzis T. Malnutrition, nutritional indices, and early enteral feeding in critically ill children. *Nutrition.* 2001;17:548-557.
- Hulst J, Joosten K, Zimmermann L, et al. Malnutrition in critically ill children: from admission to 6 months after discharge. *Clin Nutr.* 2004;23:223-232.
- Mehta NM, Corkins MR, Lyman B, et al; American Society for Parenteral and Enteral Nutrition Board of Directors. Defining pediatric malnutrition: a paradigm shift toward etiology-related definitions. *JPEN J Parenter Enteral Nutr.* 2013;37:460-481.
- Becker P, Carney LN, Corkins MR, et al; Academy of Nutrition and Dietetics; American Society for Parenteral and Enteral Nutrition. Consensus statement of the Academy of Nutrition and Dietetics / American Society for Parenteral and Enteral Nutrition: indicators recommended for the identification and documentation of pediatric malnutrition (undernutrition). *Nutr Clin Pract.* 2015;30:147-161.
- Hulst JM, van Goudoever JB, Zimmermann LJ, et al. The effect of cumulative energy and protein deficiency on anthropometric parameters in a pediatric ICU population. *Clin Nutr.* 2004;23:1381-1389.
- Vermilyea S, Slicker J, El-Chammas K, et al. Subjective global nutritional assessment in critically ill children. *JPEN J Parenter Enteral Nutr.* 2013;37:659-666.
- Chourdakis M, Hecht C, Gerasimidis K, et al. Malnutrition risk in hospitalized children: use of 3 screening tools in a large European population. *Am J Clin Nutr.* 2016;103:1301-1310.
- Dokken M, Rustøen T, Stubhaug A. Indirect calorimetry reveals that better monitoring of nutrition therapy in pediatric intensive care is needed. *JPEN J Parenter Enteral Nutr.* 2015;39:344-352.
- Mehta NM, Bechard LJ, Dolan M, et al. Energy imbalance and the risk of overfeeding in critically ill children. *Pediatr Crit Care Med.* 2011;12:398-405.
- Teixeira-Cintra MA, Monteiro JP, Tremeschin M, et al. Monitoring of protein catabolism in neonates and young infants post-cardiac surgery. *Acta Paediatr.* 2011;100:977-82.
- Mtaweh H, Smith R, Kochanek PM, et al. Energy expenditure in children after severe traumatic brain injury. *Pediatr Crit Care Med.* 2014;15:242-249.
- Sy J, Gourishankar A, Gordon WE, et al. Bicarbonate kinetics and predicted energy expenditure in critically ill children. *Am J Clin Nutr.* 2008;88:340-347.
- Zappitelli M, Goldstein SL, Symons JM, et al; Prospective Pediatric Continuous Renal Replacement Therapy Registry Group. Protein and calorie prescription for children and young adults receiving continuous renal replacement therapy: a report from the Prospective Pediatric Continuous Renal Replacement Therapy Registry Group. *Crit Care Med.* 2008;36:3239-3245.
- Taylor RM, Cheeseman P, Preedy V, et al. Can energy expenditure be predicted in critically ill children? *Pediatr Crit Care Med.* 2003;4:176-180.
- Framson CM, LeLeiko NS, Dallal GE, et al. Energy expenditure in critically ill children. *Pediatr Crit Care Med.* 2007;8:264-267.
- Hardy CM, Dwyer J, Snelling LK, et al. Pitfalls in predicting resting energy requirements in critically ill children: a comparison of predictive methods to indirect calorimetry. *Nutr Clin Pract.* 2002;17:182-189.
- Havalad S, Quaid MA, Sapiega V. Energy expenditure in children with severe head injury: lack of agreement between measured and estimated energy expenditure. *Nutr Clin Pract.* 2006;21:175-181.
- Mehta NM, Bechard LJ, Leavitt K, et al. Cumulative energy imbalance in the pediatric intensive care unit: role of targeted indirect calorimetry. *JPEN J Parenter Enteral Nutr.* 2009;33:336-344.
- Meyer R, Kulinskaya E, Briassoulis G, et al. The challenge of developing a new predictive formula to estimate energy requirements in ventilated critically ill children. *Nutr Clin Pract.* 2012;27:669-676.
- White MS, Shepherd RW, McEniery JA. Energy expenditure in 100 ventilated, critically ill children: improving the accuracy of predictive equations. *Crit Care Med.* 2000;28:2307-2312.
- van der Kuip M, de Meer K, Westertep KR, et al. Physical activity as a determinant of total energy expenditure in critically ill children. *Clin Nutr.* 2007;26:744-751.
- Oosterveld MJ, Van Der Kuip M, De Meer K, et al. Energy expenditure and balance following pediatric intensive care unit admission: a longitudinal study of critically ill children. *Pediatr Crit Care Med.* 2006;7:147-153.
- Jotterand Chaparro C, Laure Depeyre J, Longchamp D, et al. How much protein and energy are needed to equilibrate nitrogen and energy balances in ventilated critically ill children? *Clin Nutr.* 2016;35:460-467.
- van der Kuip M, Oosterveld MJ, van Bokhorst-de van der Schueren MA, et al. Nutritional support in 111 pediatric intensive care units: a European survey. *Intensive Care Med.* 2004;30:1807-1813.
- Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr.* 1985;39(suppl 1):5-41.
- World Health Organization. *Energy and Protein Requirements: Report of a Joint FAO/WHO/UNU Expert Consultation.* Geneva, Switzerland: World Health Organization; 1985. Technical Report Series 724.

40. Bechard LJ, Feldman HA, Venick R, et al. Attenuation of resting energy expenditure following hematopoietic SCT in children. *Bone Marrow Transplant.* 2012;47:1301-1306.
41. Mehta NM, Costello JM, Bechard LJ, et al. Resting energy expenditure after Fontan surgery in children with single-ventricle heart defects. *JPEN J Parenter Enteral Nutr.* 2012;36:685-692.
42. Kerklaan D, Augustus ME, Hulst JM, et al. Validation of ventilator-derived VCO₂ measurements to determine energy expenditure in ventilated critically ill children. *Clin Nutr.* 2017;36:452-457.
43. Mehta NM, Smallwood CD, Joosten KF, et al. Accuracy of a simplified equation for energy expenditure based on bedside volumetric carbon dioxide elimination measurement—a two-center study. *Clin Nutr.* 2015;34:151-155.
44. Wong JJ, Han WM, Sultana R, et al. Nutrition delivery affects outcomes in pediatric acute respiratory distress syndrome [published online March 9, 2016]. *JPEN J Parenter Enteral Nutr.*
45. Bechard LJ, Parrott JS, Mehta NM. Systematic review of the influence of energy and protein intake on protein balance in critically ill children. *J Pediatr.* 2012;161:333-339.e1.
46. Botrán M, López-Herce J, Mencía S, et al. Enteral nutrition in the critically ill child: comparison of standard and protein-enriched diets. *J Pediatr.* 2011;159:27-32.e1.
47. Chaloupecký V, Hucín B, Bláskal T, et al. Nitrogen balance, 3-methylhistidine excretion, and plasma amino acid profile in infants after cardiac operations for congenital heart defects: the effect of early nutritional support. *J Thorac Cardiovasc Surg.* 1997;114:1053-1060.
48. de Betue CT, van Waardenburg DA, Deutz NE, et al. Increased protein-energy intake promotes anabolism in critically ill infants with viral bronchiolitis: a double-blind randomised controlled trial. *Arch Dis Child.* 2011;96:817-822.
49. Geukers VG, Dijsselhof ME, Jansen NJ, et al. The effect of short-term high versus normal protein intake on whole-body protein synthesis and balance in children following cardiac surgery: a randomized double-blind controlled clinical trial. *Nutr J.* 2015;14:72.
50. de Betue CT, Joosten KF, Deutz NE, et al. Arginine appearance and nitric oxide synthesis in critically ill infants can be increased with a protein-energy-enriched enteral formula. *Am J Clin Nutr.* 2013;98:907-916.
51. van Waardenburg DA, de Betue CT, Goudoever JB, et al. Critically ill infants benefit from early administration of protein and energy-enriched formula: a randomized controlled trial. *Clin Nutr.* 2009;28:249-255.
52. Verbruggen SC, Schierbeek H, Coss-Bu J, et al. Albumin synthesis rates in post-surgical infants and septic adolescents; influence of amino acids, energy, and insulin. *Clin Nutr.* 2011;30:469-477.
53. Verbruggen SC, Coss-Bu J, Wu M, et al. Current recommended parenteral protein intakes do not support protein synthesis in critically ill septic, insulin-resistant adolescents with tight glucose control. *Crit Care Med.* 2011;39(11):2518-2525.
54. Carlotti AP, Bohn D, Matsuno AK, et al. Indicators of lean body mass catabolism: emphasis on the creatinine excretion rate. *QJM.* 2008;101:197-205.
55. Martinez EE, Pereira LM, Gura K, et al. Gastric emptying in critically ill children [published online January 1, 2017]. *JPEN J Parenter Enteral Nutr.*
56. Ikeda S, Kudsk KA, Fukatsu K, et al. Enteral feeding preserves mucosal immunity despite in vivo MAdCAM-1 blockade of lymphocyte homing. *Ann Surg.* 2003;237:677-685.
57. Kudsk KA, Stone JM, Carpenter G, et al. Enteral and parenteral feeding influences mortality after hemoglobin-*E coli* peritonitis in normal rats. *J Trauma.* 1983;23:605-609.
58. Li J, Kudsk KA, Gocinski B, et al. Effects of parenteral and enteral nutrition on gut-associated lymphoid tissue. *J Trauma.* 1995;39:44-51.
59. Sano Y, Gomez FE, Kang W, et al. Intestinal polymeric immunoglobulin receptor is affected by type and route of nutrition. *JPEN J Parenter Enteral Nutr.* 2007;31:351-356.
60. Fukatsu K, Zarzaur BL, Johnson CD, et al. Enteral nutrition prevents remote organ injury and death after a gut ischemic insult. *Ann Surg.* 2001;233:660-668.
61. Mehta NM, McAleer D, Hamilton S, et al. Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. *JPEN J Parenter Enteral Nutr.* 2010;34:38-45.
62. de Oliveira Iglesias SB, Leite HP, Santana e Meneses JF, et al. Enteral nutrition in critically ill children: are prescription and delivery according to their energy requirements? *Nutr Clin Pract.* 2007;22:233-2339.
63. Rogers EJ, Gilbertson HR, Heine RG, et al. Barriers to adequate nutrition in critically ill children. *Nutrition.* 2003;19:865-868.
64. King W, Petrillo T, Pettignano R. Enteral nutrition and cardiovascular medications in the pediatric intensive care unit. *JPEN J Parenter Enteral Nutr.* 2004;28:334-338.
65. Panchal AK, Manzi J, Connolly S, et al. Safety of enteral feedings in critically ill children receiving vasoactive agents. *JPEN J Parenter Enteral Nutr.* 2016;40:236-241.
66. Mikhailov TA, Kuhn EM, Manzi J, et al. Early enteral nutrition is associated with lower mortality in critically ill children. *JPEN J Parenter Enteral Nutr.* 2014;38:459-466.
67. Kyle UG, Akcan-Arikan A, Orellana RA, et al. Nutrition support among critically ill children with AKI. *Clin J Am Soc Nephrol.* 2013;8:568-574.
68. Kyle UG, Jaimon N, Coss-Bu JA. Nutrition support in critically ill children: underdelivery of energy and protein compared with current recommendations. *J Acad Nutr Diet.* 2012;112:1987-1992.
69. Kaufman J, Vichayavilas P, Rannie M, et al. Improved nutrition delivery and nutrition status in critically ill children with heart disease. *Pediatrics.* 2015;135:e717-e725.
70. Hamilton S, McAleer DM, Ariagno K, et al. A stepwise enteral nutrition algorithm for critically ill children helps achieve nutrient delivery goals. *Pediatr Crit Care Med.* 2014;15:583-589.
71. Petrillo-Albarano T, Pettignano R, Asfaw M, et al. Use of a feeding protocol to improve nutritional support through early, aggressive, enteral nutrition in the pediatric intensive care unit. *Pediatr Crit Care Med.* 2006;7:340-344.
72. Yoshimura S, Miyazu M, Yoshizawa S, et al. Efficacy of an enteral feeding protocol for providing nutritional support after paediatric cardiac surgery. *Anaesth Intensive Care.* 2015;43:587-593.
73. Martinez EE, Bechard LJ, Mehta NM. Nutrition algorithms and bedside nutrient delivery practices in pediatric intensive care units: an international multicenter cohort study. *Nutr Clin Pract.* 2014;29:360-367.
74. Elke G, Felbinger TW, Heyland DK. Gastric residual volume in critically ill patients: a dead marker or still alive? *Nutr Clin Pract.* 2015;30:59-71.
75. McClave SA, Taylor BE, Martindale RG, et al; Society of Critical Care Medicine; American Society for Parenteral and Enteral Nutrition. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *JPEN J Parenter Enteral Nutr.* 2016;40:159-211.
76. Ozen N, Tosun N, Yamanel L, et al. Evaluation of the effect on patient parameters of not monitoring gastric residual volume in intensive care patients on a mechanical ventilator receiving enteral feeding: a randomized clinical trial. *J Crit Care.* 2016;33:137-144.
77. Horn D, Chaboyer W, Schluter PJ. Gastric residual volumes in critically ill paediatric patients: a comparison of feeding regimens. *Aust Crit Care.* 2004;17:98-100, 102-103.
78. Briassoulis GC, Zavras NJ, Hatzis MD, Hatzis TD. Effectiveness and safety of a protocol for promotion of early intragastric feeding in critically ill children. *Pediatr Crit Care Med.* 2001;2:113-121.

79. Meyer R, Harrison S, Sargent S, et al. The impact of enteral feeding protocols on nutritional support in critically ill children. *J Hum Nutr Diet.* 2009;22:428-436.
80. Wakeham M, Christensen M, Manzi J, et al. Registered dietitians making a difference: early medical record documentation of estimated energy requirement in critically ill children is associated with higher daily energy intake and with use of the enteral route. *J Acad Nutr Diet.* 2013;113:1311-1316.
81. Kamat P, Favalaro-Sabatier J, Rogers K, et al. Use of methylene blue spectrophotometry to detect subclinical aspiration in enterally fed intubated pediatric patients. *Pediatr Crit Care Med.* 2008;9:299-303.
82. Meert KL, Daphtary KM, Metheny NA. Gastric vs small-bowel feeding in critically ill children receiving mechanical ventilation: a randomized controlled trial. *Chest.* 2004;126:872-878.
83. Horn D, Chaboyer W. Gastric feeding in critically ill children: a randomized controlled trial. *Am J Crit Care.* 2003;12:461-468.
84. López-Herce J, Mencía S, Sánchez C, et al. Postpyloric enteral nutrition in the critically ill child with shock: a prospective observational study. *Nutr J.* 2008;7:6.
85. López-Herce J, Sánchez C, Carrillo A, et al. Transpyloric enteral nutrition in the critically ill child with renal failure. *Intensive Care Med.* 2006;32:1599-1605.
86. Taha AA, Badr L, Westlake C, et al. Effect of early nutritional support on intensive care unit length of stay and neurological status at discharge in children with severe traumatic brain injury. *J Neurosci Nurs.* 2011;43:291-297.
87. Tume L, Latten L, Darbyshire A. An evaluation of enteral feeding practices in critically ill children. *Nurs Crit Care.* 2010;15:291-299.
88. Sánchez C, López-Herce J, Carrillo A, et al. Early transpyloric enteral nutrition in critically ill children. *Nutrition.* 2007;23:16-22.
89. Canarie MF, Barry S, Carroll CL, et al; Northeast Pediatric Critical Care Research Consortium. Risk factors for delayed enteral nutrition in critically ill children. *Pediatr Crit Care Med.* 2015;16:e283-e289.
90. Fivez T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. *N Engl J Med.* 2016;374:1111-1122.
91. Jacobs BR, Nadkarni V, Goldstein B, et al; Nutritional Immunomodulation in Children with Lung Injury Study Group. Nutritional immunomodulation in critically ill children with acute lung injury: feasibility and impact on circulating biomarkers. *Pediatr Crit Care Med.* 2013;14:e45-e56.
92. Mayes T, Gottschlich MM, Kagan RJ. An evaluation of the safety and efficacy of an anti-inflammatory, pulmonary enteral formula in the treatment of pediatric burn patients with respiratory failure. *J Burn Care Res.* 2008;29:82-88.
93. Briassoulis G, Filippou O, Hatz E, et al. Early enteral administration of immunonutrition in critically ill children: results of a blinded randomized controlled clinical trial. *Nutrition.* 2005;21:799-807.
94. Briassoulis G, Filippou O, Kanariou M, et al. Comparative effects of early randomized immune or non-immune-enhancing enteral nutrition on cytokine production in children with septic shock. *Intensive Care Med.* 2005;31:851-858.
95. Larsen BM, Field CJ, Leong AY, et al. Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and down-regulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants. *JPEN J Parenter Enteral Nutr.* 2015;39:171-179.
96. Nehra D, Fallon EM, Potemkin AK, et al. A comparison of 2 intravenous lipid emulsions: interim analysis of a randomized controlled trial. *JPEN J Parenter Enteral Nutr.* 2014;38:693-701.
97. Larsen BM, Goonewardene LA, Joffe AR, et al. Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial. *Clin Nutr.* 2012;31:322-329.
98. Jordan I, Balaguer M, Esteban ME, et al. Glutamine effects on heat shock protein 70 and interleukines 6 and 10: randomized trial of glutamine supplementation versus standard parenteral nutrition in critically ill children. *Clin Nutr.* 2016;35:34-40.
99. Briassoulis G, Filippou O, Kanariou M, et al. Temporal nutritional and inflammatory changes in children with severe head injury fed a regular or an immune-enhancing diet: a randomized, controlled trial. *Pediatr Crit Care Med.* 2006;7:56-62.
100. Carcillo JA, Dean JM, Holubkov R, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. The randomized comparative pediatric critical illness stress-induced immune suppression (CRISIS) prevention trial. *Pediatr Crit Care Med.* 2012;13:165-173.
101. Wischmeyer PE, Dhaliwal R, McCall M, et al. Parenteral glutamine supplementation in critical illness: a systematic review. *Crit Care.* 2014;18:R76.
102. Heyland D, Muscedere J, Wischmeyer PE, et al; Canadian Critical Care Trials Group. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med.* 2013;368:1489-1497.
103. van Zanten AR, Sztark F, Kaisers UX, et al. High-protein enteral nutrition enriched with immune-modulating nutrients vs standard high-protein enteral nutrition and nosocomial infections in the ICU: a randomized clinical trial. *JAMA.* 2014;312:514-524.
104. Bertolini G, Iapichino G, Radrizzani D, et al. Early enteral immunonutrition in patients with severe sepsis: results of an interim analysis of a randomized multicentre clinical trial. *Intensive Care Med.* 2003;29:834-840.