Nutritional Support in the Pediatric ICU

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Case Scenario

A 12-month-old female with no significant past medical history is admitted to the medical-surgical ICU following a dog bite resulting in extensive injuries to the maxillofacial area and neck. The infant weighs 8 kg (5th %; weight-for-age z-score − 1) and is 70 cm long (10th %; height-for-age z-score − 0.8). Given the severity and location of injuries, an emergent surgical airway was secured, and she was taken to the operating room for wound debridement and tracheostomy. She returned to the intensive care unit for postoperative management. The surgical team was unable to place a nasogastric tube in the operating room given the location of her injuries. The extent of her injury had left a significant portion of open and denuded mucosa involving her mandible and lateral neck similar to a burn injury. Finally, the surgical team requested deep sedation and, if necessary, paralysis to ensure adequate tract formation given her new tracheostomy for at least 5 days.

This vignette illustrates several questions regarding the assessment of nutritional needs and provision of optimal nutrients during critical illness. Specific questions related to this vignette include:

- What was the baseline nutritional status of the patient?
- Was she at risk for further nutritional deterioration during her hospitalization?
- What type of metabolic stress response should we expect during the acute and convalescent phase of this injury?
- How should we determine the optimal energy and protein requirements during the acute and subacute phases of recovery?
- What is the best route for nutrient delivery, enteral versus parenteral?
- Is there a role for supplementation with micronutrients to aid in wound healing?

In this chapter, we will review the current evidence and concepts related to these questions and

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provide recommendations to guide bedside practice.

Introduction

Providing optimal nutrition to infants and children during critical illness is a vital aspect of their care. On admission, the prevalence of malnutrition in critically ill children is staggering – ranging between 20% and 47% in recent studies [1–6]. Additionally, nutritional status may further deteriorate during critical illness as a result of increased metabolic demands, failure to accurately estimate energy needs and inadequate nutrient delivery [7]. Malnutrition remains underrecognized in critically ill infants and children and has been associated with deleterious outcomes such as a higher rate of infectious complications, prolonged duration of mechanical ventilation, longer lengths of stay, increased resource utilization, and higher mortality [3–6, 8–14]. Individualizing nutritional support for critically ill children is challenging yet essential, as they represent a heterogeneous population in relation to age, disease process, comorbidities, presenting nutritional status, and metabolic response to stress. The provision of optimal nutrition during critical illness requires screening and identification of those at risk for nutritional deterioration, a detailed comprehension of the metabolic stress response, accurate estimates or measurement of energy expenditure to guide energy prescriptions, determination of the optimal route and timing of nutrient delivery, monitoring for intolerance to nutrient delivery, and the development of meaningful outcome measures to assess the impact of nutritional interventions. Updated guidelines from the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM) in 2017 highlight the current literature related to several aspects of bedside practice and identify key areas for further investigation [15]. As higher-quality studies including randomized controlled trials and other pragmatic study designs become available, these unanswered questions should coalesce into uniform evidence-based guidelines.

Defining Malnutrition

The definition of malnutrition in pediatrics is inconsistent across publications. To address this concern, ASPEN recently published guidelines unifying the diagnosis of pediatric malnutrition to facilitate early identification of those at risk, compare prevalence among centers, develop screening tools, implement uniform thresholds for intervention, and formulate evidence-based recommendations (Fig. 8.1) [16]. The new guidelines include recommendations for use of anthropometric variables, growth, chronicity of malnutrition, etiology, pathogenesis, and impact on functional outcomes to define pediatric malnutrition. The recent consensus statement concluded with the following definition of pediatric malnutrition [16]:

> An imbalance between nutrient requirements and intake, resulting in cumulative deficits of energy, protein or micronutrients, that may negatively affect growth, development and other relevant outcomes.

Following the development of a uniform definition, a standardized set of diagnostic indicators was generated to document malnutrition in routine clinical practice [17]. The recommended indicators include (1) weight-for-length *z*-score or body mass index (BMI), (2) length-for-age *z*-score, (3) mid-upper arm circumference (MUAC), or (4) velocity of weight gain or loss over time. Simple anthropometry on admission to the intensive care unit can predict clinical outcomes and must be prioritized [4, 5, 11, 12]. Ultimately, the acceptance of a uniform definition and validated diagnostic indicators of pediatric malnutrition should facilitate evidence-based clinical practice and advance research in the area of critical care nutrition.

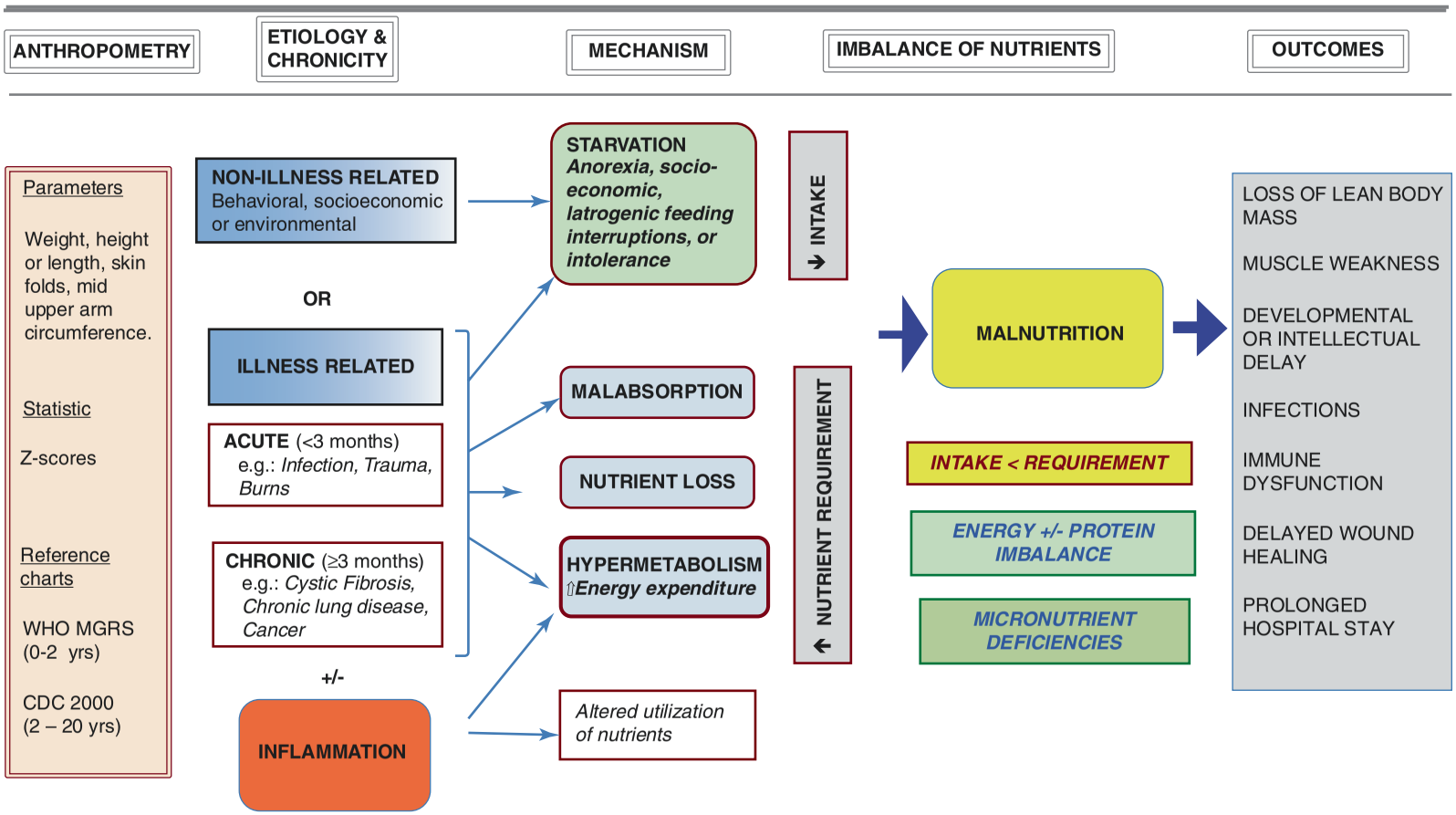

Fig. 8.1 ASPEN's new definition for pediatric malnutrition in hospitalized children. (Reprinted with permission [16]. Abbreviations: *WHO* World Health Organization, *MGRS* Multicenter Growth Reference Study, *CDC* Centers for Disease Control and Prevention)

Screening for Malnutrition

Given the concerns for preexisting malnutrition and further nutritional deterioration while critically ill, a detailed nutritional assessment should be performed on patients at risk for malnutrition or nutritional deterioration early during their hospitalization. The nutritional assessment should include a detailed dietary history, recent changes in anthropometry, alterations to their functional status (i.e., ability to perform normal daily activities), and a nutrition-focused physical examination. Due to limited resources, a detailed nutritional assessment on every patient may not be feasible. Thus, developing a validated screening tool to identify those at risk for malnutrition at admission and facilitate allocation of limited resources to those who would benefit the most from early nutritional intervention is necessary. The current ASPEN/SCCM guidelines suggest that within 48 h of admission a weight and height/length be measured in order to facilitate calculation of *z*-scores for body mass index (BMI) or weight-for-length measurements [15].

There are several screening tools currently available (Table 8.1), but none have been validated to identify those at risk for malnutrition in the pediatric ICU population. The Pediatric Yorkhill Malnutrition Score (PYMS), the Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP), and the Screening Tool for Risk of Impaired Nutritional Status and Growth (STRONGkids) were recently evaluated in 2,567 children across

Table 8.1 Available screening tools to evaluate the presence and severity of malnutrition in pediatric patients upon admission. Abbreviations: *mo* months old, *hrs* hours, *yo* years old

Screening tool	Variables	Population	Outcome
Pediatric Subjective Global Nutritional Assessment (SGNA) [18]	Food intake Ability to eat Difficulty retaining food Pain Disease severity	Pediatric patients >1 mo admitted to medical or surgical ward for ≥48 hrs	Weight loss >2% during admission
Pediatric Nutritional Risk Score (NRS) [19]	Weight and height Ideal body weight BMI-for-age MUAC Triceps skinfold thickness Mid-arm muscle area Handgrip strength Albumin Transferrin Hemoglobin Total lymphocyte count	Pediatric patients >1 mo and < 18 yo requiring major elective surgery	Major/minor infectious complications Major/minor noninfectious complications Postoperative LOS Non-prophylactic antibiotic use Unplanned reoperation Readmission
Pediatric Yorkhill Malnutrition Score (PYMS) [20]	BMI History of recent weight loss Changes in nutritional intake Current medical condition's effect on nutritional status	Pediatric patients 1 to 16 yo admitted to medical or surgical ward	Compare PYMS score to full dietitian's assessment of malnutrition risk
Screening Tool for Risk of Impaired Nutritional Status and Growth (STRONGkids) [21]	Subjective clinical assessment High-risk disease Nutritional intake Weight loss	Pediatric patients 1 mo to 18 yo admitted to medical or surgical ward	Weight-for-length/height z-score Prevalence of acute malnutrition Hospital LOS
Screening Tool for the Assessment of Malnutrition in Pediatrics (STAMP) [22]	Diagnosis' impact on nutrition Dietary intake Weight and height	Pediatric patients 2–17 yo admitted to medical or surgical ward for >24 hrs	Compare STAMP score to full dietitian's assessment of malnutrition risk

Europe [23]. The study demonstrated that the identification and classification of malnutrition risk varied across the screening tools and were unable to detect a considerable portion of undernourished children. Based on these findings, the authors recommended that none of the screening tools could be utilized in clinical practice. In the absence of a validated formal screening tool, most centers rely on admission weight-for-age or BMI-for-age *z*-scores to identify those at risk for nutritional deterioration in the ICU. This approach is reasonable and necessary, as clinical outcomes (i.e., rate of infectious complications, length of stay, duration of mechanical ventilation, and mortality rate) in the ICU have been associated with poor nutritional status at admission using various anthropometric measurements [4, 5, 11, 12]. Specifically, one multicenter, retrospective cohort study demonstrated admission BMI *z*-score-predicted mortality for children receiving mechanical ventilation [13]. Although there are challenges with obtaining accurate anthropometrics upon admission to the ICU, the association of malnutrition with poor clinical outcomes should prioritize procurement of these measurements.

The development of a validated pediatric nutrition screen specific for critically ill children is therefore paramount for the assessment of nutritional risk in a timely and accurate manner. Until an appropriate screening tool is established, the development and implementation of a nutrition support team (i.e., interdisciplinary team comprised of physicians, dietitians, nurses, and pharmacists with specialty training in nutrition) in the ICU should be considered, as they have been shown to improve surveillance for those at risk for malnutrition and aid in individualized nutritional prescriptions [24].

Metabolic Stress Response

A basic understanding of the metabolic stress response can assist in the accurate assessment of energy expenditure and help tailor individualized nutritional prescriptions in the critically ill. Increased counter-regulatory hormones, such as glucagon, cortisol, and epinephrine, induce insulin and growth hormone resistance in response to stress after injury, infection, surgery, or trauma [25]. This neuroendocrine response drives the catabolism of endogenous protein, carbohydrate, and fat (Fig. 8.2) [27]. Protein catabolism is the sine qua non of the metabolic stress response. The continuous degradation and decreased synthesis of muscle protein, resulting in a net negative nitrogen balance, result in a large pool of free amino acids. The free amino acids are redistributed, from visceral proteins (i.e., albumin), which comprise erythrocytes, granulocytes, lymphocytes, and other solid tissue organs, to inflammatory response proteins (i.e., C-reactive protein, fibrinogen, haptoglobin) that aid in wound healing and tissue repair. The remaining free amino acids are shuttled to the liver to partake in gluconeogenesis. In addition, carbohydrate breakdown leads to an increase in glucose oxidation and thus gluconeogenesis [28]. Gluconeogenesis is essential in critical illness as it ensures adequate energy reserves for glucose-dependent organs such as the brain, red blood cells, and renal medulla. Finally, the metabolic stress response increases fatty acid oxidation as well, providing ketones as a secondary fuel source for the brain [29].

The provision of protein, carbohydrate, and fat does not suppress the metabolic stress response during critical illness as it does during starvation [30, 31]. As a result, protein, carbohydrate, and lipid catabolism continue despite nutrient intake. Protein breakdown often exceeds protein synthesis and if unmatched by adequate concomitant intake can result in loss of lean body mass and nutritional deterioration [31]. The loss of muscle mass is not isolated to skeletal muscle alone, but may affect cardiac and diaphragmatic muscles resulting in cardiorespiratory insufficiency. Likewise, the provision of carbohydrate does not stop gluconeogenesis but instead results in "stress hyperglycemia" [32]. Finally, increased lipid demand in the setting of limited fat stores and inadequate provision can lead to essential fatty acid deficiency, especially in preterm infants [33, 34].

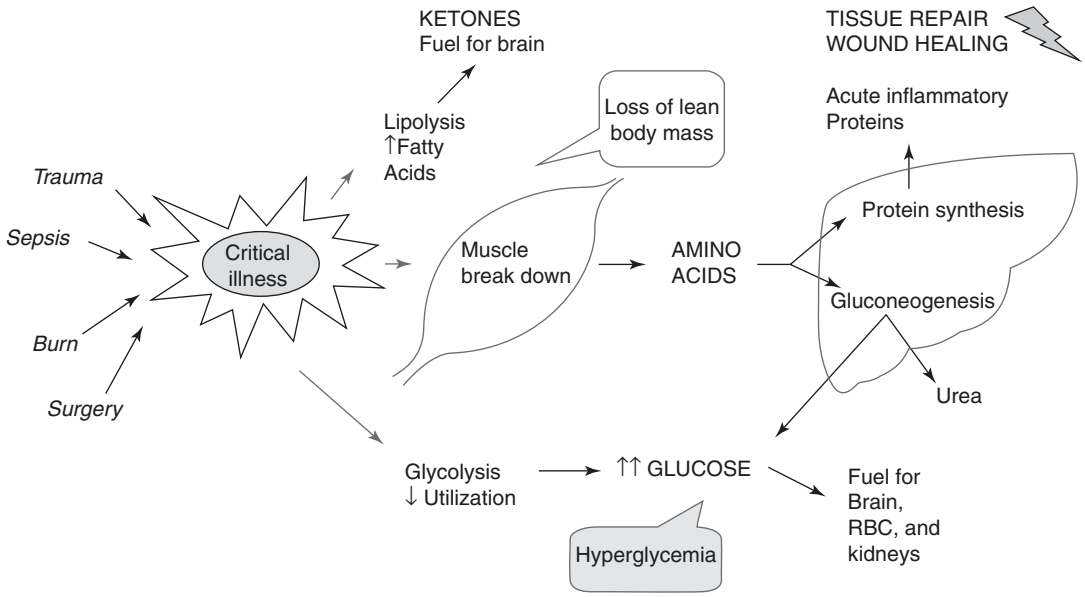

Fig. 8.2 Pathways of the metabolic stress response during critical illness. (Reprinted with permission [26])

Determining Energy Requirements

The metabolic state during critical illness is dynamic and unpredictable, ranging from hypometabolism (<90% of predicted measured resting energy expenditure) as a result of sedation, mechanical ventilation, and targeted temperature management to hypermetabolism (>110% of predicted measured resting energy expenditure) as seen in severe burn injuries [35–39]. Inaccurate energy estimates can result in underfeeding or overfeeding with potential negative clinical consequences [26, 40–43]. Underfeeding can lead to poor wound healing, impaired oxygen utilization, increased infection risk, poor neurodevelopmental outcomes, and increased mortality, while overfeeding can result in hypertriglyceridemia, hyperglycemia, hepatic steatosis and cholestasis, increased carbon dioxide production, and uremia [44–46].

Indirect calorimetry (IC) remains the gold standard and current ASPEN/SCCM guideline recommendation to measure resting energy expenditure in critically ill children [43, 47, 48]. IC, which is typically performed using a metabolic cart, measures oxygen consumption (VO_2) and carbon dioxide production (VCO_2) to calculate the respiratory quotient (RQ), which is calculated as $RQ = VCO_2/VO_2$. RQ values range from 0.6 to 1.4 based on the type of substrate utilized by the patient. Carbohydrate oxidation results in higher carbon dioxide production and therefore higher RQ, whereas lipolysis is associated with comparatively lower VCO_2 measurements and hence a lower RQ. Mixed fuel utilization results in typical RQ ranging from 0.8 to 1.2. Although carbohydrate excess may increase the RQ value, the use of RQ as a measure of overfeeding is not recommended [49]. IC has several limitations as it is not reliable in children that weigh less than 5 kg, those supported with an inspired O_2 concentration greater than 60%, or in patients with a sizeable air leak (i.e., around endotracheal tube, chest tube).

Though IC is deemed the gold standard for measuring energy expenditure in critically ill children, the majority of ICUs lack the resources and expertise to operationalize IC in their daily clinical management [50–53]. When IC is not available and despite substantial evidence against their accuracy, clinicians utilize predictive equations based on patient demographics to estimate resting energy expenditure (Table 8.2) [39, 43, 52–57]. If predictive equations are utilized, the

Table 8.2 Available predictive equations to calculate resting energy expenditure. Abbreviations: *yo* years old, VCO_2 volumetric carbon dioxide production (mL/min), RQ_{macro} respiratory quotient based on the ratio of carbohydrate to fat in the diet

Schofield	**<3 yo** Male: REE = 60.9 * weight (kg) – 54 Female: REE = 61 * weight (kg) – 51 **3–10 yo** Male: REE = 22.7 * weight (kg) + 495 Female: REE = 22.5 * weight (kg) + 499 **10–18 yo** Male: REE = 17.5 * weight (kg) + 651 Female: REE = 12.2 * weight (kg) + 746
World Health Organization (WHO)	**<3 yo** Male: REE = (60 * weight (kg)) – 54 Female: REE = (6.1 * weight (kg)) – 51 **3–10 yo** Male: REE = (22.7 * weight (kg)) + 495 Female: REE = (22.5 * weight (kg)) + 499 **10–18 yo** Male: REE = (17.5 * weight (kg)) + 651 Female: REE = (12.2 * weight (kg)) + 746
Harris-Benedict	**Male** REE = 66.5 + (13.75 * weight (kg)) + (5.003 * height (cm)) = (6.775 * age) **Female** REE = 655 + (9.563 * weight (kg)) + (1.85 * height (cm)) – (4.676 * age)
Recommended Daily Allowance (RDA)	<6mo REE = 108 kcal/kg/day 6mo-1yo REE = 98 kcal/kg/day 1-3yo REE = 102 kcal/kg/day 4-6yo REE = 90 kcal/kg/day 7-10yo REE = 70 kcal/kg/day 11-14yo Male: REE = 55 kcal/kg/day Female: REE = 47 kcal/kg/day 15-18yo Male: REE = 45 kcal/kg/day Female: REE = 40 kcal/kg/day
VCO_2-derived	REE = [3.941 (VCO_2/RQ_{macro}) + 1.106 (VCO_2)] * 1440

ASPEN/SCCM guideline currently recommends using either the Schofield or World Health Organization (WHO) equation without the addition of "stress" or "activity" correction factors [52]. Moreover the guidelines recommend against using the Harris-Benedict equation and Recommended Daily Allowances (RDA) to determine resting energy expenditure, as they have been shown to overestimate resting energy expenditure in critically ill patients and lead to overfeeding [58].

As IC is not universally available and predictive equations are inaccurate, there is an impetus to develop consistent, accurate, accessible, and innovative ways to measure resting energy expenditure in the critically ill. Volumetric carbon dioxide measurement (VCO_2) represents one promising means to accomplish this goal. By synthesizing physiologic data into a simplified equation, VCO_2 measurement was recently modeled into an equation to predict resting energy expenditure in mechanically ventilated children and was found to be more accurate than currently available predictive equations [59, 60]. As continuous VCO_2 measurements in mechanically ventilated patients are increasing in availability in most ICUs, this equation may replace previous predictive equations in the future.

Determining Nutrition Prescription

Total Energy Goals

Several observational studies have demonstrated improved clinical outcomes when adequate energy intake is achieved in the PICU [3, 48, 61]. In spite of this finding, children admitted to the ICU have been shown to not achieve adequate energy requirements during their first week of admission [50, 62, 63]. Based on cohort studies and presumed hypometabolism in a variety of pediatric disease states, the current ASPEN/SCCM guidelines recommend achieving at least two thirds of prescribed energy requirements by the end of the first week of critical illness [3, 37, 42, 61, 64, 65].

Total Protein Goals

Based on several randomized controlled and prospective, multicenter cohort trials a minimum of 1.5 g/kg/day of protein delivery should be achieved to encourage a positive nitrogen balance according to the ASPEN/SCCM guidelines [48, 66–70]. Specifically, to avoid cumulative protein deficits, ASPEN's recent guidelines recommend higher protein intake goals than those recommended by the Dietary Reference Intake (DRI), which were historically based on healthy children (Table 8.3) [71]. The rationale for increased protein goals is related to increased protein breakdown and turnover during critical illness. In support of higher protein intake goals, a large, multicenter prospective study demonstrated higher enteral protein intake to be associated with lower mortality in mechanically ventilated children (Fig. 8.3) [6]. The optimal protein intake for critically ill infants, however, is likely higher and may be around 2.5–3 g/kg/day based on previous cohort studies [67, 70, 72]. Increasing protein goals beyond 3 g/kg/day and especially in infants less than 1 month of age has not been adequately studied and may lead to a rising blood urea nitrogen level. Finally, as pediatric formulas were not designed for critically ill children, prescribed standard formulas have a limited protein/energy ratio that may restrict the amount of protein delivered [73]. To overcome this dilemma, the field is currently examining the feasibility and efficacy of adding modular protein supplements (i.e., Beneprotein®) to standard formulas in children, a practice embraced by adult ICUs for the last decade [73, 74].

On the other hand, a secondary analysis of the Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) trial demonstrated that supplying greater than 1 gm/kg/day of protein was associated with worse clinical outcomes (i.e., increased infectious complications and longer duration of mechanical ventilation), as opposed to carbohydrate and fat

Table 8.3 Recommended daily protein intake (g/kg/day) for pediatric patients. Abbreviations: *DRI* Dietary Reference Intake, *ASPEN* American Society for Parenteral and Enteral Nutrition [71]

	Age range	Recommended protein intake (g/kg/day)
DRI 2005	0–6 months	1.52
	7–12 months	1.2
	1–3 years	1.05
	4–13 years	0.95
	14–18 years	0.85
ASPEN 2009	0–2 years	2–3
	2–3 years	1.5–2
	3–18 years	1.5

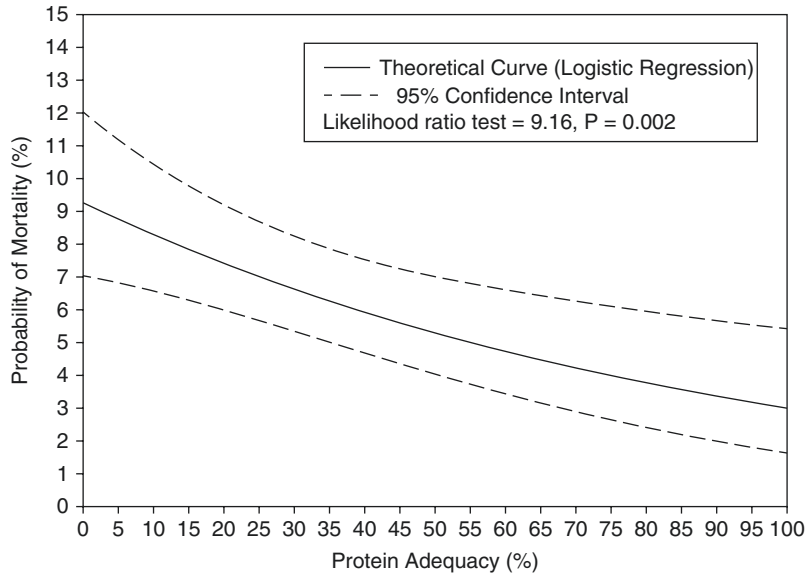

Fig. 8.3 Relation between enteral protein intake adequacy and 60-day mortality in mechanically ventilated children (n = 1245). (Reproduced with permission [6])

[75]. These findings were similar to those represented in a secondary analysis from a similar adult randomized controlled trial [76]. Critical review of the study cautions against a change in daily clinical practice however, as the study was observational in nature and not developed as a dosing study, unique clinical outcomes were developed as primary outcome measures, reference macronutrient doses used in the study were higher than recommended by the ASPEN/SCCM guidelines, and there was no examination of the interaction between different macronutrient levels. Hence, until further studies are available to clarify the conflicting data, use of the ASPEN/SCCM guidelines for protein delivery in critically ill patients is appropriate.

Determining the Delivery Route of Nutrition

Enteral Nutrition

Enteral nutrition (EN) is the preferred mode of nutrient delivery in critically ill children. Regardless of most diagnoses, sedative, and vasoactive use, EN has been shown to be safe and beneficial [77, 78]. As timing of EN initiation has been associated with nutritional adequacy, initiation of EN within 24–48 h of ICU admission, known as "early EN," is preferred according to the ASPEN/SCCM guidelines [6, 79–81]. Furthermore, achieving two thirds of the prescribed energy and protein goals via EN within the first week of critical illness may be associated with improved clinical outcomes [3, 6]. Early EN has demonstrated a lower risk of infection, reduced LOS, improved anthropometrics, and improved survival when compared to EN initiated later [61, 79, 82–84].

When initiating EN, the question remains whether to begin with gastric or postpyloric feeds. Currently, initiating feeds via the gastric route is preferred and physiologic; however there is no evidence to support this recommendation from the ASPEN/SCCM guidelines. Considering postpyloric feeds requires available technical expertise in placing the feeding tube and may result in a delay in initiation of EN [85–87]. However, postpyloric feeds may be beneficial in patients who suffer from feeding intolerance and are at risk for aspiration [88, 89]. One randomized controlled trial demonstrated reduced gastric residual volumes (GRVs) in patients who were fed postpyloric compared to gastric, although two randomized controlled trials have not demonstrated a reduction in the rate of aspiration [85, 86].

Another consideration when initiating EN is to whether to begin with continuous versus intermittent feeds. Existing data is currently conflicting and insufficient for the ASPEN/SCCM guidelines to recommend one practice as opposed to the other. The only evidence currently available consists of two randomized controlled trials that demonstrated no difference in EN tolerance between continuous and intermittent feeds [90, 91]. Based on these data, the delivery method for enteral nutrition can be determined by provider preference.

Once EN is initiated, maintenance of EN remains challenging, as interruptions are common [92, 93]. Barriers to optimal EN include delayed initiation, mechanical feeding tube issues, perceived feeding intolerance, noninvasive positive-pressure ventilation use, and prolonged fasting around procedures including intubation and extubation (Fig. 8.4) [81, 92, 94]. A prospective cohort study found that over half of the interruptions to EN in the PICU were avoidable [92]. These avoidable interruptions were associated with a threefold increase in parenteral nutrition (PN) use and a significant delay in achieving the prescription goal; thus an effort to minimize interruptions is of paramount importance. Methods to minimize avoidable interruptions include careful consideration regarding timing of procedures, guideline development and adherence around duration of fasting, and a dedicated team of nurses and support from interventional radiology to assist in the successful and expedient placement of feeding tubes.

Once EN is initiated, there is no uniform method to advancing EN. A stepwise algorithmic approach to advancing EN in the ICU has been shown to improve time to goal prescription,

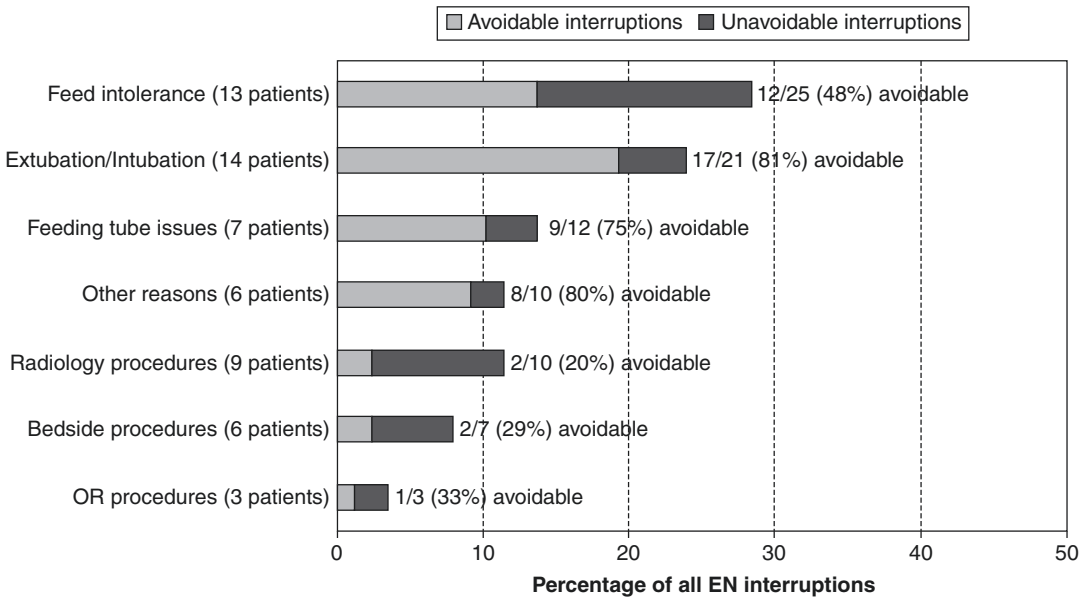

Fig. 8.4 Reasons for interruptions to enteral nutrition, both avoidable and unavoidable [92]. (Reproduced with permission)

increase the percent of patients who achieve their prescription goal, reduce interruptions to nutrition, decrease PN use, and improve nutritional and clinical outcomes (Fig. 8.5) [80, 95–98]. Devising an algorithm for use in the ICU should provide guidance on detecting and managing intolerance to ensure appropriate and expedient EN advancement [50].

Perceived feeding intolerance is one of the primary reasons for interrupting EN. Currently, feeding intolerance lacks a uniform description and could possibly refer to gastroesophageal reflux, vomiting, constipation, diarrhea, or malabsorption. Traditionally, gastric residual volume (GRV) was used to define feeding intolerance; however its accuracy has been questioned, and it is no longer recommended in adult ICUs [73, 99–101]. As there are no comparable pediatric studies to support this move, the use of GRVs is cautiously recommended in the most recent ASPEN/SCCM guidelines [15]. Despite a lack of definitive data in pediatrics, many centers use prokinetic agents (i.e., erythromycin, metoclopramide), antiemetics, acid suppression, antidiarrheals, and laxatives as adjuncts to EN.

The benefits of EN have been demonstrated in both human and animal studies. Gastrointestinal mucosal integrity and motility may improve when EN is prescribed [102]. These beneficial effects of EN are likely related to engaged gut-associated lymphoid tissue (GALT), mucosal immunity, and improved gastrointestinal blood flow [103–106]. Additional studies are required to further understand the benefits of providing early EN. Universally advanced and clearer stepwise algorithms need to be developed and should be supported by evidence considering gastric versus postpyloric, continuous versus intermittent, and methods to obviate interruptions to EN.

Parenteral Nutrition

When enteral nutrition fails, parenteral nutrition (PN) is advised [15, 107]. In addition, when EN is not feasible or contraindicated, such as following major abdominal surgery, when there are concerns for intestinal ischemia or in a low cardiac output state, PN should be considered. Furthermore, if a patient is severely malnour-

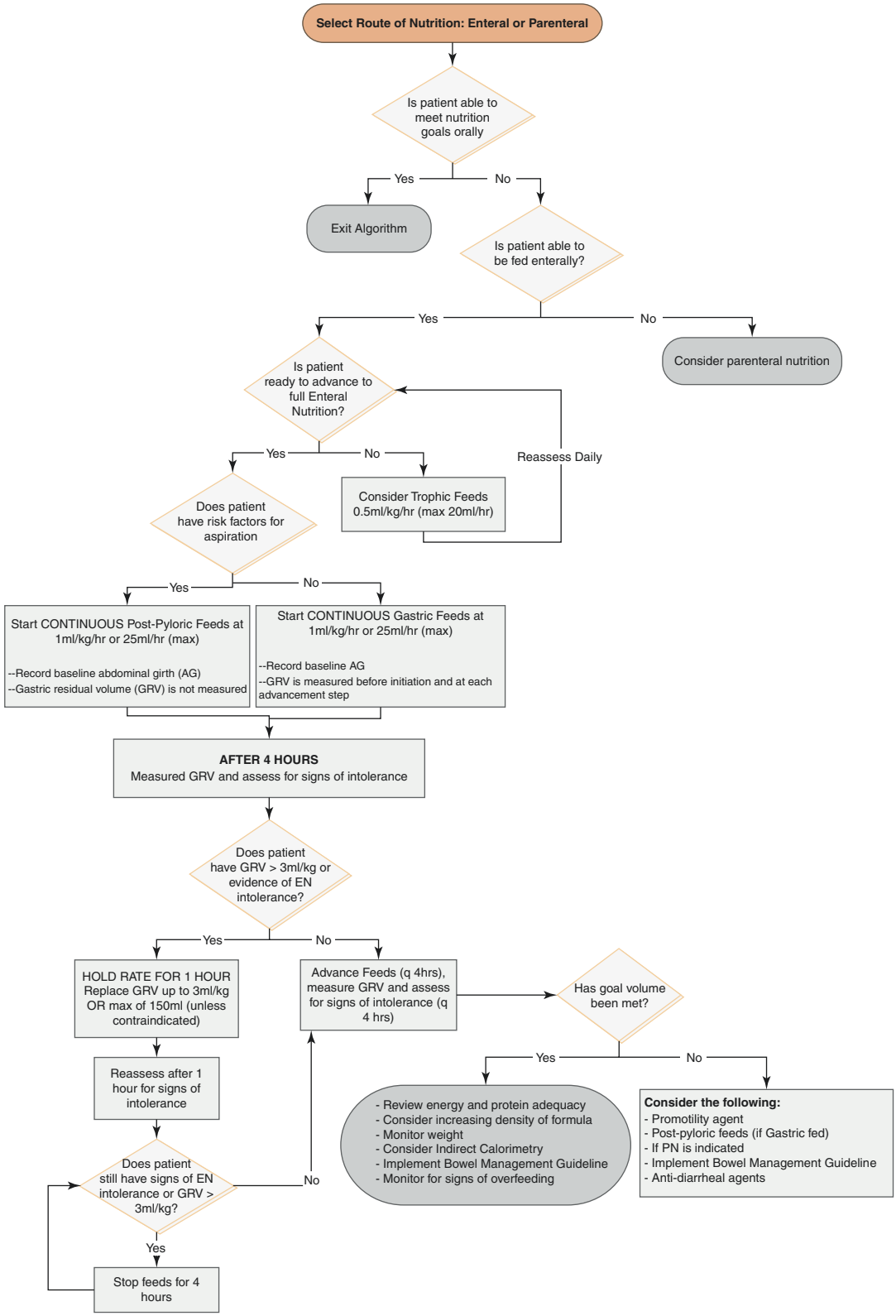

Fig. 8.5 Example of a stepwise algorithm for initiating and advancing enteral nutrition [95]. (Reproduced with permission)

ished, at high risk for nutritional deterioration during their hospitalization (i.e., severe burn injury), or a neonate (<30 days old) and not able to achieve energy and protein goals via EN, PN should be initiated.

The optimal timing for initiation of PN remains controversial. Adult studies have reported a potential benefit when PN is initiated after day 3 if nutritional goals are not met by EN but inferior clinical outcomes if PN is initiated earlier [108–111]. Prior to the publication of the PEPaNIC trial, there was a dearth of randomized, controlled trials addressing the effects of PN on clinical outcomes in children [112, 113]. The PEPaNIC trial was a three-center trial in critically ill children who were randomized to receive either an early (<24 h) or late (>7 days) PN strategy. The study demonstrated improved outcomes in the children who received the late PN strategy, specifically by lowering the rate of new infections, decreasing ICU length of stay, shortening the duration of mechanical ventilation, and decreasing renal replacement therapy utilization. Several issues regarding the study methods need to be reviewed: the portion of the calories that were provided via PN was small; energy goals were calculated by predictive equations, putting the subjects at risk for overfeeding; and subjects at risk for malnutrition were treated similarly to those well-nourished and identified using the STRONGkids screening tool, which has not been previously validated in the ICU population [114]. Hence, the current ASPEN/SCCM guidelines recommend exercising caution when applying these results broadly in clinical practice, particularly in vulnerable newborns and severely malnourished children [15]. Furthermore, the recent publication of NUTRIREA-2, a study examining the safety of early enteral versus parenteral nutrition in mechanically ventilated adults with shock, demonstrated no difference in hospital-acquired infections among the two groups and not surprisingly demonstrated an increased rate of feeding intolerance in the enteral group [115]. In summary, the ASPEN/SCCM guidelines advise against initiating PN within the first 24 h of admission and to consider a delayed PN approach in children who are not severely malnourished. Following that recommendation, the timing of supplemental PN needs to be made on an individualized basis and should take in consideration the nutritional and clinical status of the patient.

The macronutrient composition of PN and particularly the alternative lipid emulsions are being extensively studied. Recommendations for protein intake mirror the current enteral recommendations, although further research into the route of protein supplementation and its effects on clinical outcomes is needed [15]. With the recent Food and Drug Administration's (FDA) approval of alternative lipid formulations, emerging literature has indicated benefits in utilizing olive oil- and fish oil-based lipids. Non-soy-based lipid formulations have demonstrated a trend toward improved survival, shorter duration of mechanical ventilation, and ICU length of stay [116, 117]. These clinical improvements are thought to be secondary to higher antioxidant content, immune modulating, and less inflammatory properties [118]. As an additional benefit, these lipid formulations have been shown to reduce the incidence and possibly reverse PN-associated liver disease in patients with short gut syndrome and PN dependence [119].

Additional studies are required to determine the optimal timing for PN initiation and the role of supplemental PN for critically ill children in general. Ongoing research regarding the potential benefits of alternative lipid formulations may lead to a uniform recommendation in the future.

Role of Micronutrients as Immunonutrition

The role of micronutrients as immunomodulators in critically ill patients surfaced as an area of research over a decade ago. Micronutrients and antioxidants were hypothesized to diminish inflammation or replete nutrients depleted by stress. Glutamine, arginine, selenium, copper, and zinc are a few of the studied micronutrients to date. Several randomized controlled trials comparing various forms of immunonutrition have been undertaken and have yet to demonstrate any clinical benefit [120–123]. Furthermore,

a majority of these studies combine the micronutrients making it difficult to interpret the impact of a single micronutrient. Two such examples are glutamine and arginine supplementation. Clinical outcomes in critically ill children prescribed glutamine did not differ when compared to control; however in several adult studies, glutamine has been associated with an increased mortality rate [124, 125]. Likewise, arginine, hypothesized to improve immune function and wound healing, was associated with increased mortality in septic patients in an adult trial [126]. Thus, the potential for harm, paucity of pediatric data, and poor quality of designed studies have led the recent ASPEN/SCCM guidelines to not recommend immunonutrition [15].

Case Scenario Conclusion

To highlight the issues raised in this chapter, we conclude with our recommended management of the patient in the opening vignette.

Anthropometric measurements were obtained upon admission, and the patient was described as "well-nourished" based on her normal weight-for-age and height-for-age z-scores. However, given her diagnosis and expected trajectory, she was deemed high risk for experiencing nutritional deterioration while hospitalized. As enteral access was not secured in the operating room and the likelihood of obtaining enteral access within the first 5 days of her admission was low, she was prescribed parenteral nutrition. While sedated, paralyzed, and mechanically ventilated, her total energy and protein goals were calculated to be two-thirds her resting energy expenditure, as estimated by the Schofield equation and ASPEN guidelines. We did not add additional micronutrients to her parenteral nutrition. After her first tracheostomy change and on day 6 of admission, indirect calorimetry was performed and found her to be slightly hypermetabolic – 110% predicted resting expenditure – at which time we adjusted our total energy and protein goals. Given the anticipated prolonged duration of critical illness, she returned to the operating room on day 7 of admission, and a gastrostomy tube was placed. Nutrition was transitioned from exclusively parenteral to enteral nutrition over the next 48 h. To aid our nutrition support care team in tailoring their nutrition prescription, indirect calorimetry was performed weekly while she was in the ICU and continued to show her to be mildly hypermetabolic. She maintained weight during her first 2 weeks of critical illness and then began to gain weight during week 3. She was weaned from mechanical ventilation over her first month of illness and transferred to the surgical ward with a tracheostomy collar in place.

Key Points

1. Malnutrition is prevalent in critically ill children. Simple anthropometric assessment on admission must be prioritized to allow early detection of severely malnourished children who are likely to have worse clinical outcomes.
2. The new definition of pediatric malnutrition includes anthropometry, growth, chronicity of malnutrition, etiology and pathogenesis, and impact on functional outcomes. Screening tools that reliably identify malnourished or at-risk patients in the PICU need to be developed.
3. The metabolic stress response is unpredictable. The catabolism of protein is the characteristic feature and may result in loss of lean mass, which has been associated with poor clinical outcomes. Higher protein delivery is necessary to achieve a positive protein balance. However, the optimal protein dose asso-

ciated with improved clinical outcomes during critical illness is being investigated.
4. Indirect calorimetry remains the gold standard to estimate energy expenditure. Predictive equations to estimate energy expenditure may be inaccurate.
5. Adequacy of nutritional delivery, defined by optimal energy and protein intake, is associated with improved clinical outcomes. Hence, a timely and safe nutrient delivery strategy is an essential part of critical care.
6. Early enteral nutrition is safe and associated with improved clinical outcomes.
7. Supplemental parenteral nutrition should be considered if energy and protein goals have not been achieved via enteral nutrition within the first week of illness.
8. Immunonutrition is currently not recommended.

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