Chapter 17
Nutritional Considerations for Infants and Children During Critical Illness and Surgery

Joyce L. Owens, Sheila J. Hanson, and Jennifer McArthur

Key Points

- Children are susceptible to the negative consequences associated with a prolonged metabolic response to stress.
- Resting energy expenditure in critically ill children may vary but is predominantly hypometabolic.
- The optimal energy, protein, and nutrient requirements in critically ill children are unknown.

Keywords Metabolic response • Metabolic response to stress • Critical illness • Surgery • Cytokines • Critical illness • Immunoparesis • Malnutrition • Obesity • Nutrition assessment • Energy requirements • Resting energy expenditure • Pharmaconutrition • Macronutrients and micronutrients • Antioxidants • Nutrition support

Introduction

This chapter provides a basic overview of the metabolic response to stress. A considerable amount of knowledge regarding the metabolic response to stress has been obtained by studies in adults. Many factors are involved in the physiological response to stress, thereby impacting nutritional needs throughout this phase of illness. Current interest has propelled studies in pediatrics identifying unique characteristics of this response during critical illness and in several forms of surgery including general, cardiac, and minimally invasive surgery (MIS).

Children have different age-related nutrient and energy requirements than adults due to their need for growth and development. Although there are many nutritional screening tools designed to identify individuals at nutritional risk, only a few have been validated. Predictive equations are used extensively to determine energy requirements in adults and children but are highly prone to both over and underestimating of energy requirements in the hospitalized patient [1, 2]. While better knowledge on optimal energy requirements during critical illness is needed, there is an even greater paucity of data regarding the optimal macronutrient and micronutrient needs in critical illness. Pharmaconutrition is the study of the pharmacologic benefits of therapeutic use of specific nutrients in various disease

J.L. Owens, R.D., C.D., C.N.S.C. (✉) • S.J. Hanson • J. McArthur
Department of Pediatric Critical Care, Medical College of Wisconsin and Children's Hospital of Wisconsin, 9000 W. Wisconsin Avenue, Milwaukee, WI 53201, USA
e-mail: jowens@mcw.edu

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states and trauma. This is an emerging area of research. Despite the obvious importance of providing nutrition during critical illness, there are numerous barriers to initiating and sustaining nutritional support. These will be reviewed.

Metabolic Response to Stress: Overview

Stress is defined as a disruption of the body's homeostasis [1]. In response to stress the human body initiates sequential responses termed the metabolic response to stress. This response is aimed at dealing with noxious stimuli that could potentially alter health and well-being. Noxious stimuli may include, but are not limited to, infection, trauma, and/or surgery. Infants, children, and adults all experience the metabolic response to stress, though it varies somewhat in the different age groups [1].

Over the past 20 years there has been a substantial increase in the knowledge and awareness of the metabolic response during critical illness, trauma, and surgery. Short-term response to stress in the human body is beneficial, but prolonged stress may actually cause harm. Increased knowledge has facilitated ongoing changes in medical practices, treatment, and research to minimize the potential detrimental effects that can occur. During prolonged periods of stress, infants and young children, more so than adults, are particularly susceptible to the detrimental effects of stress [2–4].

Cytokines are chemical messengers that regulate both local and systemic immune function and are initiated by nuclear factor kappa β (NF-kβ) [1, 5]. Cytokines play an integral role in regulation of the inflammatory response to stress, infection, trauma, and surgery. Various types of cytokines have been identified and characterized as anti-inflammatory, proinflammatory, or both. Upon release into the circulatory system, cytokines exhibit autocrine and paracrine functions as well as modulation of gene expression in specific cells [1].

The initiation of cytokine production alters macronutrient metabolism (protein, carbohydrate, and lipid). Short term, this is an adaptive mechanism. Once the body's limited glycogen stores are depleted through glycogenolysis, gluconeogenesis ensues. Gluconeogenesis is the provision of energy from a nonglucose source (protein, fat) and associated with elevated levels of catecholamines (epinephrine, norepinephrine, dopamine) and counterregulatory hormones (cortisol, glucagon). This results in insulin resistance and decreased levels of growth hormones. This in turns provokes catabolism of skeletal muscle (Fig. 17.1, Metabolic Response) [6, 7]. The catabolism of muscle results in mobilization of free amino acids. This mobilization yields a decreased synthesis of structural proteins such as albumin

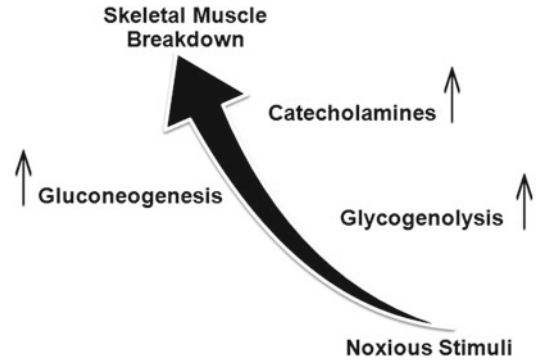

Fig. 17.1 Metabolic response overview of the pathway to skeletal muscle breakdown

and other protein constituents required for tissue repair. As a consequence, there is increased synthesis of nonstructural proteins, such as C-reactive protein, fibrinogen, enzymes, cytokines, and production of glucose via gluconeogenesis [2, 4, 7]. Prolonged skeletal muscle catabolism can result in negative consequences especially in infants and young children due to their limited muscle (protein) reserves. This can potentially lead to respiratory and heart muscle compromise. Due to the elevated levels of catabolic hormones (catecholamines and counterregulatory), growth is halted during this phase. Approximately one-third of energy needs in infants are for growth.

Contrary to starvation, providing exogenous glucose or excessive energy does not halt these mechanisms but instead excessive amounts generate lipogenesis. Providing exogenous protein has a major role in minimizing muscle protein loss but does not halt the metabolic process and a negative protein balance continues [3].

General Characteristics of Metabolic Response in Critical Illness

Proinflammatory cytokines that are in the body in increased levels during sepsis, trauma, and the postperative period promote increased lipolysis of adipose tissue but may alter lipase function [8]. Excessive lipid administration may result in impairment of leukocyte and platelet function, impaired pulmonary function, and hypertriglyceridemia. Consequences are an increase in serum fatty acids, fatty liver, tachypnea, and hypercarbia. Little data is available depicting the ability of infants to oxidize lipids during critical illness or sepsis [8].

The type of anesthetic agents used during surgery or in critical illness helps offset the metabolic response to stress. For example, the opioid anesthetic fentanyl has been shown not only to decrease muscle protein breakdown but also to reduce the postoperative endocrine stress response thereby blunting the intensity of the physiological response to stress [1].

General Characteristics of Metabolic Response After Surgery

Surgical stress induces the inflammatory response as outlined in the metabolic response to stress overview. A portion of the cytokines or chemical mediators generated during the response are derived from the surgical wound as a direct result of local cellular injury followed by release of cytokines into the systemic circulation [1].

Stimulation of the immune response is thought to eliminate opportunistic microbial organisms while immuneparesis reduces this immune response initiating the healing phase. The metabolic response to surgery is also impacted by the extent of fasting prior to surgery. Fasting prior to surgery exaggerates the stress response which is accompanied by an increased level of insulin resistance postoperatively [1].

Numerous fluctuations in the metabolic response to stress and its consequences fluctuate by age [1, 2]. An attenuated immune response is seen in surgical neonates less than 48 h old in comparison to an older infant or young child. Adolescents tend to have a longer duration of metabolic stress response than infants and young children. One possible explanation for the lessened response in the younger infant is the higher synthesis of intrinsic opioids during the perinatal period thereby blunting the metabolic response. This theory is further supported by the presence of the inflammatory cytokine interleukin-6 (IL-6) seen in older children but not in neonates [1].

Infants and young children have an increased surface area (body and head) in comparison to bodyweight. Such factors place them at greater risk for dissipation of body heat compared to adults. What protects adults and older children from hypothermia is brown fat. The predominant role of brown fat

is thermogenesis. The lack of brown fat compared to adults contributes to heat loss in infants. Also, during surgery decreased heat production is noted, yielding a lower body core temperature. This may be related to several factors modulating thermoregulation such as anesthetic medications or open body cavities. Both muscle relaxants and anesthesia impede the body's ability to generate heat through shivering, thus the increase in energy expenditure generated through shivering is insignificant during surgery [1, 4].

Interleukin-6 (IL-6) is the most consistently elevated postoperative cytokine identified in the postoperative period in adults, older infants, and children, although it is not detected after all types of surgeries. Prolonged elevated levels of IL-6 can occur due to complex infections or surgeries. IL-6 levels appear to peak 6–24 h after surgery and return to baseline generally by postoperative day 2. Diminished or the complete absence of IL-6 levels are associated with minor surgeries. The metabolic response including level of acute phase reactants, immune and endocrine response is proportional to the magnitude of surgery. Reducing postoperative metabolic derangements may help minimize postoperative complications [1]. Stimulation of the immune response is thought to eliminate opportunistic microbial organisms while a period of decreased immunological challenge referred to as immunoparesis reduces this immune response (stimulation) to initiate the healing phase [1].

Tumor necrosis factor-alpha (TNF-α) is a potent mediator in the stress response. It is rarely detected in minor or uncomplicated surgeries. However, a wide variety of levels have been found in major surgeries. Elevated levels in infants correlate with severity of surgery and likelihood of death [1].

Cardiac Surgery

Postoperatively, elevated IL-10 levels are seen in moderate and severe surgical stress. IL-10 is a potent immune-suppressive cytokine. In pediatric cardiac surgical patients IL-10 is particularly elevated. The elevated levels are observed after the start of bypass and generally decline to postoperative levels 2–3 days after surgery [1]. Elevated levels have been demonstrated to correlate with surgery severity and likelihood of death. Following cardiopulmonary bypass neonates are at risk for an exaggerated inflammatory response. The exaggerated response is manifested by capillary leak syndrome, general edema, and multisystem organ dysfunction (MOD). Subsequently, modified ultrafiltration (MUF), a unique form of continuous renal replacement therapy is utilized to extract cytokines thereby attenuating the inflammatory response. Despite the inflammatory state seen in cardiopulmonary bypass (CPB), children also develop impaired immune function after CPB. Following CPB there is evidence that children with monocyte hypofunction have a greater risk for sepsis [9].

Minimally Invasive Surgery

Significant elevation in circulating levels of TNF-α does not generally accompany minimally invasive surgery (MIS). Examples of MIS surgery include minimally invasive cardiac surgery and laparoscopy. MIS inflicts less surgical trauma and subsequently has the potential to decrease the intensity of the metabolic response to stress. MIS may also modulate thermoregulation especially in infants and young children as it alleviates the need to open body cavities and the subsequent loss of body heat. Unfortunately, current data reveals conflicting results. Some studies have found no sizable reduction in the levels of cytokines post-MIS compared to traditional surgical techniques. The majority of studies showing a reduction of cytokines levels to date have been in major surgeries. There is a theoretical concern that this downregulation of the metabolic response could potentially lead to the healing mechanism not being effectively initiated [1]. See Fig. 17.2 for an overview of the cytokine profile following surgery.

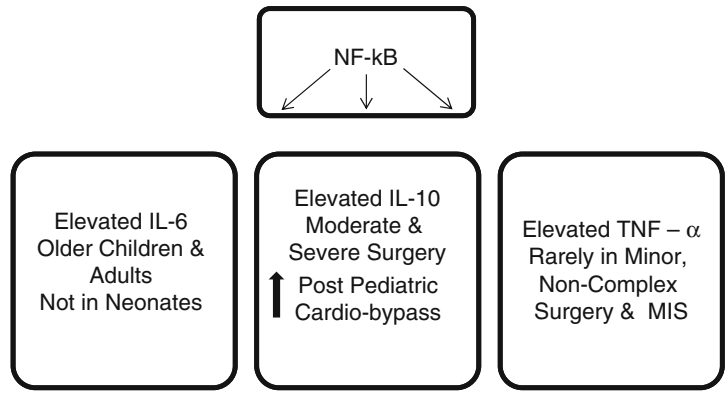

Fig. 17.2 Postoperative Cytokine Profile of Infants, Children and Adults NF-κB = nuclear factor kappa B, IL = interleukin, TNF-α = tumor necrosis factor alpha, MIS = minimally invasive surgery, ↑ = markedly elevated

Additional Considerations During Pediatric Critical Illness

Malnutrition

Critically ill infants and children with preexisting acute or chronic disease are at increased risk for malnutrition and MOD [10]. Hospitalized children (44%) with a variety of acute and chronic diseases may develop malnutrition [7]. Malnutrition facilitates physiologic aberrations with subsequent gastrointestinal alteration, immune impairment (cell mediated and phagocytosis), and the imbalance of micronutrients. A higher incidence of protein-energy malnutrition (PEM) occurs in children with congenital heart disease. Risk factors leading to PEM are energy deficits associated with increased work of breathing and/or cardiac failure; malabsorption as a consequence of lower cardiac function, elevated right-side heart pressure, and/or impaired gastrointestinal function accompanied by decreased intake [7]. Depletion of endogenous antioxidants during oxidative stress is another possible contributing factor in the development of MOD during critical illness [5], by the initiation of reactive oxygen species following ischemia or reperfusion injury [11].

Burns

Burn injury induces a considerable metabolic response to stress. The degree of response directly correlates with the size of injury up to a plateau of 40% of total body surface area burn. The metabolic response to burns is increased proteolysis, nitrogen loss, and lipolysis induced by the upregulation of catabolic hormones including catecholamines, glucagon, and cortisol. The elevation of acute phase reactants catecholamines, and cytokines has been shown in the severely burned pediatric patient to endure up to 3 years postinjury [12]. The inflammatory response initiated by burns is not restricted to the local wound. Burns affect such organs as the gastrointestinal tract causing gut permeability and a suppression of immune function through decrease synthesis and function of neutrophils, macrophages, and T-lymphocytes through impaired phagocytosis. Critically ill children with burns are also at risk of malnutrition, loss of muscle mass, and infections [10, 13]. Children who have suffered burn injury and inhalation injury have increased mortality. As the pediatric burn patient's length of time in the pediatric intensive care unit (PICU) increases so their their for a cumulative energy deficit. Factors independent of the length of stay contributing to this energy deficit involve length of mechanical ventilation and required surgical interventions [7].

In severe burns, protein catabolism is extensive leading to a negative nitrogen balance as well as loss of muscle mass partially related to cortisol. Anabolic hormones crucial to protein synthesis such

as insulin-like growth factor (IGF-1) and growth hormone are reduced following significant burn injury. Protein synthesis plus wound healing requires a positive nitrogen balance. Tachycardia and lipolysis may persist leading to fatty liver infiltration and cardiac failure. A decrease in lean body mass has been confirmed to ensue up to 1 year following injury and impediment of linear growth has been described up to 2 years following injury [7]. In a randomized control trial involving 205 severely burned pediatric patients over a 9-year period, the patients that received recombinant human growth (rhGH) demonstrated higher lean body mass, reduced scarring, and an attenuated inflammatory response. In another study involving 180 severely burn pediatric patients with ≥40% TBSA, females were found to have attenuated inflammatory response in contrast to males. Insulin therapy has proven to be of benefit to severely burn pediatric patients in which hyperglycemia is a hallmark finding. In a prospective randomized trial, 239 pediatric patients with burns >30% TBSA were randomized to receive intensive insulin therapy (IIT). Compared to controls, the IIT group had less insulin resistance, and sepsis attenuated inflammatory response measured by decreased levels of IL-6 and demonstrated improved organ function. The mortality rate for the IIT group was 4% compared to the controls at 11% [14].

Pediatric Obesity

Pediatric obesity is considered an epidemic worldwide. Despite this, the pediatric obese critically ill child has not been intensively studied. Higher complication rates appear to manifest in the critically ill obese child and adolescent as longer mechanical ventilation days and prolonged PICU stays compared to lean pediatric trauma patients [10, 15]. In addition, obese children have altered polyunsaturated fatty acid (PUFA) levels (low ω-3 PUFA to ω-6 PUFA ratio). It is unknown if this may contribute to a heightened inflammatory response during critical illness [10]. Obese individuals have a higher distribution of white adipose (fat) tissue (WAT). WAT is comprised of adipocytes, endothelial cells, fibroblasts, leukocytes, and macrophages. WAT is characterized as both an endocrine and paracrine organ, and as such is a mediator in metabolism and inflammation. The role of WAT is to store and mobilize fat for body energy and secrete hormones termed adipokines or adiopocytokines. These cells secrete various types of cytokines, adiponectin, growth factors, leptin, TNF-α, etc. Adiponectin increases the sensitivity of the liver and muscle to insulin, and adiponectin levels are depressed in obesity. Inflamed adipose tissue enhances insulin resistance [16]. These factors may potentially contribute to the increased complications seen in critically ill obese pediatric patients.

Nutrition Assessment and Energy Requirements

Nutrition Assessment

The nutrition screen is designed to identify individuals who are either malnourished or at nutritional risk by assessing characteristics that have been shown to correlate with nutrition problems. Only a very limited number of screens have been validated. Effective nutrition screens are generally quick and reliable, with adequate sensitivity and specificity, and with good positive and negative predicted values [17]. The nutrition assessment is a more comprehensive assessment. It involves interpretation of data to determine if a nutrition problem exists and to what extent. Five distinct areas have been recognized that should be evaluated in the comprehensive assessment; food/nutrition history, biochemical parameters, medical test and procedures, patient history, anthropometric data, as well as a nutrition-focused examination. The nutrition-focused examination helps to evaluate nutrient deficiencies and an estimation of body composition [17]. Once the comprehensive assessment

Table. 17.1 Protein Needs [19]

Protein needs	Age 0–2 years 2–3 g/kg/day
Protein needs	Age 2–13 years 1.5–2 g/kg/day
Protein needs	Age 13–18 years 1.5 g/kg/day

Protein provision requires ongoing reevaluation. Adjust protein provision ↑ or ↓ based on clinical condition, medication and medical therapy

has been completed, the next step is to develop estimated protein and energy goals. Important nutritional goals are to preserve skeletal muscle protein, support wound healing, and the inflammatory response [2, 7].

Energy Requirements in the Critically Ill Child

The basal metabolic rate (BMR) is the energy required to support body temperature, respiratory and cardiac function, and maintain the integrity of the body cells. It is ~65–75% of total energy expenditure (TEE) [1]. TEE is comprised of diet-induced thermogenesis, BMR, and activity [18]. Resting energy expenditure (REE) is 10% above the BMR to account for thermogenesis. Energy needs are acutely altered and variable postinjury and critical illness [19, 20]. To account for the wide range of alterations in energy metabolism during critical illness, measured resting energy expenditure (MREE) is obtained from indirect calorimetry (IC), the most accurate assessment of energy needs [4, 19]. Another method used to obtain MREE is respiratory mass spectrometry [21]. IC is the most frequently used method to obtain MREE. IC determines REE by measuring the volume of oxygen consumed (VO_2) compared to the volume of carbon dioxide produced (CO_2) and does not utilize temperature changes to determine energy needs. IC cannot determine accurate energy measurements in patients with chest tubes in place, endotracheal tube with air leak, extracorporeal membrane oxygenation (ECMO), and high inspired oxygen fraction (FIO_2>0.6) [3]. Indications for IC include children that are underweight, overweight, burns, failure to be weaned or requiring escalation in mechanical ventilation support, neurologic trauma, and hypoxia and/or ischemia. Additional indications for IC include hypometabolic state (hypothyroidism, hypothermia, and pentobarbital coma) or hypermetabolic state (dysautonomic storms, status epilepticus, SIRS) [19].

Numerous studies have used IC to determine MREE in critically ill children. The results have found children of many ages to be hypometabolic during critical illness and postsurgery. Table 17.1 provides a summary of several studies in which MREE was obtained by IC in hospitalized pediatric patients and their age ranges [22–24]. Mehta et al. in a prospective cohort study measuring MREE in critically ill pediatric patients found that in 62% of patients physicians inaccurately assessed their metabolic state, 72% of patients were hypometabolic, and 83% of patients were overfed resulting in excessive cumulative energy (calories). This study further demonstrates that predicated equations are inaccurate, with escalating inaccuracies when stress factors are added to predictive equations to determine energy needs. Children under the age of two are extremely vulnerable to overfeeding [25]. In another study, Briassoulis et al. evaluated the cytokine profile and metabolic patterns (normometabolic, hyper- or hypometabolic based on MREE) of critically ill pediatric patients. During the early phase of illness patients in this study were hypometabolic. Elevated levels of cytokines did not correspond with the hypometabolic state. Only VO_2 and VCO_2 were found to be independently associated with hypometabolism which was associated with an increase in mortality [26]. Both adults and children in some studies have been found to have increased energy expenditure during the early postoperative

Table 17.2 Summary of measured resting energy (MREE) obtained by indirect calorimetry in critically ill pediatric patients. The summary includes the age range, median age, and metabolic status defined as hypometabolic (HYPO), hypermetabolic (HYPER), and normometabolic (NORM)

Research study	Age range	Median age	Researcher's conclusion of metabolic status
Mehta et al. [59]	0. 1–25.8 years	2 years	HYPO, HYPER, & NORM Predominate HYPO
Framson et al [22]	2–17 years	5 years	HYPO
Nydegger et al. [23]	Less than 1 month	16 days	HYPER prior to corrective heart surgery. NORM one week post surgery
Avitzur et al. [24]	3.2–12.3 months	Noncyanotic 12.3 months cyanotic 3.2 months	NORM

Table 17.3 Breakdown of specific energy requirement expressed as kcal/kg/day, needed for basal growth and replacement of excreta losses in neonates 4

Calorie partition in neonates	
Basal metabolic needs	40–70 kcal/kg/day
Growth needs	50–70 kcal/kg/day
Replacement for excreta losses	20 kcal/kg/day
Total	100–120 kcal/kg/day

period while other studies have found no elevation in REE. In children with congenital heart defects, studies using IC have found an increased energy expenditure prior to surgical correction followed by normalization of energy expenditure postcorrective surgery [27]. The optimal energy (calorie) provision following major stress and critical illness is unknown. The most accurate assessments are serial IC measurements due to the variability of MREE during critical illness and the known inaccuracy of predictive equations. Due to the alteration in the hormonal milieu during critically illness and stress, growth does not occur until the convalescent phase of illness [28]. Table 17.2 provides an example of caloric partition in neonates which impacts energy needs during critical illness. Three commonly used predictive equations used to predict REE are given in Table 17.3 for use as a guide when IC is not available or feasible [29, 30]. The impact of stress factors remains unclear and may potentially have more effect in the older child and teenager, more research is needed. The necessity for ongoing revaluation of energy and protein provision in the critically pediatric patient cannot be overemphasized. More research is greatly needed in this area.

Macronutrients, Micronutrients, and Pharmaconutrition

Dietary reference intakes (DRIs) are specific nutrient requirements for age groups and gender for healthy individuals in the United States and Canada [31]. DRIs do not take into account the influence of nutrient requirements in regards to drug–nutrient interactions, toxicity, or disease processes. Therefore, the optimal macronutrients and micronutrients in critical illness are unknown [7]. Macronutrients include protein, carbohydrate (CHO), and fat. Micronutrients consist of vitamins, minerals, and trace elements.

Macronutrients

Protein

Maintenance of protein (nitrogen) equilibrium is the objective in healthy adults who have a protein turnover range of 3.5g/kg/day. Healthy infants and children require a positive nitrogen balance to achieve growth and development; their base line turnover rate is 6g/kg/day [4]. Normal fractional protein synthesis rates in adults is 6-15% and higher in neonates and infants at 15–23% and 15–20% respectively [32]. In critical illness an altered hormonal milieu increases protein breakdown to supply free amino acids for synthesis of enzymes, acute phase reactants, and immunoproteins. This results in a negative protein balance.

This protein breakdown mechanism requires energy. The rate of protein synthesis from the recycling of amino acids during an inflammatory state is doubled that synthesized from dietary protein. Protein turnover in burns and extracorporeal membrane oxygenation (ECMO) is even higher [3]. A significant increase in protein turnover is seen in infants after surgery (25%) and with sepsis there is a 100% elevation of urinary nitrogen excretion [19]. The consequence of significant protein breakdown is evident by inflammation, skeletal muscle wasting, delayed wound healing, and weight loss. Protein breakdown incurred during critical illness does not subside with the provision of exogenous substrate, though the provision of higher protein may help reduce the severity of negative nitrogen balance. Protein stores in adults are nearly doubled that of infants. Therefore, infants and young children are at increased risk for the ill effects of significant protein loss during prolonged injury and/or illness [2]. Additional protein losses can occur in such conditions as the presence of an ileostomy, dialysis, or malnutrition. In these conditions protein needs may be even higher [3, 4, 33]. Medications also affect protein status. For example, glucocorticoid steroids increase proteolysis and postoperative fentanyl decreases protein breakdown in neonates [4, 32]. The addition of intravenous fat into the diet of newborn surgical infants has also been demonstrated to be a protein-sparing mechanism. Protein sparing is the result of lipid being used as an energy source during gluconeogenesis; less protein is then broken down for [2–4]. Therefore, specific protein requirements may be related to age, inflammatory state, and disease state [2, 3, 34]. Children at risk for protein depletion have a greater incidence of multiple system organ dysfunction (MSOD); those with fat store depletion have a greater probability of death in comparison to nutritional healthy children [26].

Nuclear factor kappa B (NF-kβ) activates the release of cytokines during inflammatory states. The activation of cytokines prompts the suppression of insulin receptor signaling leading to insulin resistance, which is seen in both critically ill children and adults [34]. In addition, there appears to be an association between insulin resistance and muscle wasting. A prospective randomized crossover study of critically ill septic adolescents who received parenteral nutrition (PN) containing comparable energy provision and different levels of amino acid support while maintaining tight glycemic control (glucose levels 90–110) found higher amino acid and insulin administration reduced protein breakdown. The researchers concluded that in septic adolescents with insulin resistance, providing 1.5 g/kg/day of protein is inadequate to sustain protein balance in either baseline conditions or during insulin infusion. Supplying protein at 3 g/kg/day demonstrated an impressive tendency towards stimulation of protein synthesis leading to substantial improvement in whole body protein balance even in absence of insulin [34]. The optimal protein provision for the critically ill infant and child are unknown. Current practices have been based on limited studies and data. Table 17.4 outlines clinical guidelines for protein provision for the critically ill infants and child determined by the best available evidence.

Table 17.4 Commonly used predicated equations to estimate resting energy expenditure in children in calories per day [29, 30]

Equations to estimate resting energy in children		
Schofield weight		
Age (years)	Male	Female
<3	(59.512 × W) − 30.4	(61 × W) − 51
3–10	(22.706 × W) + 504.3	(22.5 × W) + 499
10–18	(17.686 × W) + 658.2	(12.2 × W) + 746
World Health Organization *(FAO/WHO/UNU)*		
0–3	(60.9 × W) − 54	(61 × W) − 51
3–10	(22.7 × W) − 495	(22.5 × W) + 499
10–18	(17.5 × W) + 651	(12.2 × W) + 746

W weight(kg), *FAO* The Food and Agriculture Organisation, *WHO* World Health Organization, *UNU* United Nations University

Carbohydrates

Both children and adults during critical illness and injury have an elevated need for glucose, with neonates demonstrating a higher turnover rate of glucose. This is considered to be the result of their increased body surface area and mass to brain ratio. The provision of exogenous glucose in critical illness will not suppress the body's need of heightened glucose production but excess provision increases carbon dioxide synthesis. As a consequence of this heightened glucose demand, protein is readily broken down via gluconeogenesis to produce glucose [3]. Elevated plasma glucose levels are not uncommon due to insulin resistance. Variability in glucose levels and hypoglycemia are accompanied with increased length of hospital stay and mortality [19]. The risk of providing exogenous insulin to achieve tight glucose control is hypoglycemia. Therefore, the decision to use exogenous insulin to achieve tight glucose control should be made after taking into account the individual's risk for hypoglycemia given their age and clinical situation. Various insulin infusion rates and mechanisms of glucose metabolism are being studied to avoid this risk; however, the optimal glucose range to be maintained during critical illness and postsurgery are unknown.

Lipids

Lipids provide a concentrated source of energy and essential fatty acids. During critical illness, sepsis, surgery, and trauma, the turnover of lipids generally occurs at an accelerated rate. Triglycerides release glycerol moiety which can be converted to glucose. Some studies have shown decreased lipid clearance during infections. The consequence of lipid metabolism is lipid peroxidation with formation of free radicals. Proinflammatory cytokines facilitate lipolysis and triglyceride (TG) release, and potentially may impair lipase function and oxidation of fatty acids. Because of this, it is the practice at some facilities to exercise caution when initiating lipids during sepsis/SIRS. Omega-3 fatty acids may also be protective of the lungs during systemic inflammation [35]. A pediatric study examined the impact of sepsis/SIRS on the oxidation of lipids during limited CHO infusion. Respiratory quotient (RQ) levels were comparable to the controls and markers of lipid peroxidation were not altered by the lipid infusion. Even without lipid infusion, TG levels during sepsis/SIRS were significantly higher than the controls [8].

Clinically the respiratory RQ is obtained from IC. The RQ does not detect actual substrate utilization during critical illness, although a RQ>1 has been shown to correlate with overfeeding [36]. Due to limited stores, infants generally are at higher risk for essential fatty acid deficiency. Intravenous fat emulsion comprising omega-3 fatty acids (ω-3 fatty acids) or olive oil is available outside of the United States. The use of these intravenous fat emulsions in some studies demonstrate a reduction in parenteral nutrition-related cholestasis and development of liver disease [4, 10] while others have identified benefit in only a subset of patients [37].

Pharmaconutrition

Pharmaconutrition is the provision of therapeutic doses of nutrients to counteract deficiencies caused by disease or injury in the same manner as pharmacologic agents (Wischmeyer, Heyland). Arginine (ARG), glutamine (GLU), omega fatty acids, various combinations of antioxidants and probiotics are some of the most frequently studied nutrients. A general overview of their specific roles and benefits is provided below [10, 19, 38]. Pharmaconutrients can be classified by function as anti-inflammatory, cell protective, or immune-modulating [38]. More research is needed in the area of pharmaconutrients to further clarify benefits in various pediatric populations by age groups, as well as optimal dosing.

Arginine

Arginine (ARG) is an amino acid that becomes rapidly depleted in significant stressed states such as injury, trauma, or surgery due to increased demand. ARG is a substrate for the vasodilator, nitric oxide. ARG deficiency impairs immune function, especially T-lymphocytes [38]. ARG also has a crucial role in regulation of blood flow, protein synthesis, and repair of tissue and wound injury. Many of the studies outlining benefit in adults have involved immune-enhancing formulas which contain a combination of nutrients such as ARG, omega 3-fatty acids, and nucleotides. The avoidance of ARG supplementation in sepsis stems from the potential for excessive nitric oxide synthesis resulting in an exaggerated SIRS response. The American Society of Parenteral Nutrition (ASPEN), Society for Critical Care Medicine (SCCM), and the European Society for Parenteral and Enteral Nutrition (ESPEN) describe benefits or possible benefit of ARG in adults [38]. The combination of ARG and ω-3 fatty acids after major adult surgeries has shown reduction in infection and length of hospital stay in comparison to standard enteral formulas [38, 39]. In comparison to adults, children's wounds heal more rapidly and completely. Impairment of wound healing in children occurs in critical illness, prematurity, complex wounds, and with comorbidities. Use of negative pressure wound therapy (NPWT) has become increasingly popular in adults, children, and in infants due to decreased sedation needs for dressing changes, provision of a closed clean system, and direct measurement of fluid [40]. In a pediatric study involving six infants, use of an enteral ARG rich supplementation coupled with NPWT was thought to stimulate early healing of infected surgical wounds [41]. NPWT effectiveness and safety in the United States has not been established at this time in neonates, infants, and children [42]. Deficient ARG plasma levels are also found in low birth weight premature infants. ARG supplementation demonstrated improvement in both plasma levels and decreased incidence of necrotizing enterocolitis (NEC) [10, 41]. Further research is needed regarding ARG use in the pediatric population.

Glutamine

Glutamine (GLN) is the most abundant amino acid in plasma and has been studied in both pediatric and adult patients. GLN is a major energy substrate for enterocytes; rapidly proliferating immune cells, lymphocytes, macrophages, and neutrophils. GLN levels decline rapidly in critical illness [10, 35, 38, 43]. GLN plays a significant role in facilitating production of heat shock proteins (HSPs). HSPs are fundamental in cellular recovery following injury. Overall the benefits of reduced infectious complications with GLN supplementation have been found in the severely critically ill adult patient. Supplemental GLN provided parenterally may be more beneficial than enteral supplementation [43]. In a double-blind, randomized, controlled trial of surgical adult patients the investigators concluded that parenteral supplementation of glutamine dipeptide was not only safe but improved glutamine levels and decreased infection rates following cardiac, colonic, and vascular surgery but not pancreatic necrosis surgery [44]. In pediatrics, there is less support for use of GLN supplementation in critical illness. A double blind, randomized controlled trial involving neonates and infants found no change in infection, PICU length of stay, nitrogen balance, or mortality. This study noted no adverse outcomes with the administration of glutamine [45].

Fatty Acids

A pilot study using an adult immune-enhancing enteral formula in 19 critically ill severely burned pediatric patients with acute respiratory distress syndrome (ARDS) found improvement in oxygenation and pulmonary compliance [46]. The formula contained omega 3 fatty acids, eicosapentaenoic acid (EPA), and γ (gamma)-linolenic (GLA). The 2009 A.S.P.E.N guidelines did not recommend the routine use of this formula for critically ill children [19]. Skillman and Wischmeyer endorsed usage in older pediatric patients [10]. More research is needed regarding this potentially promising therapy of immune-enhancing formulas containing anti-inflammatory fatty acids and antioxidants.

Antioxidants

Antioxidants (AOXs) are present in minute amounts and inhibit or delay the oxidation of a substrate. The primary function of AOXs is to counteract oxidative stress which is prevalent in critical illness. AOX levels have been found to be low or depleted in critical illness [47]. AOXs are produced naturally and exogenously provided through food or supplements [48]. The body's natural AOX defense consists of metabolic and nutrient components. The metabolic constituents are synthesized through metabolism and examples include bilirubin, glutathione, L-arginine, and uric acid. The nutrient AOXs cannot be produced endogenously and must be acquired through food or supplement and examples include vitamin A or B-carotene, C, E, selenium, and zinc [48, 49]. In critical illness depleted AOX levels are linked to an increased formation of free radicals, exaggerated systemic inflammatory response, and cell injury leading to increased morbidity and mortality. Heyland et al. reviewed clinical trials involving high-dose AOX supplementation in critically ill patients. They concluded that AOXs have been reported safe and associated with a decrease in mortality in critically ill patients [50]. Potential benefits of AOXs during critical illness are outlined in Table 17.5. Many of the clinical trials involving AOXs have had various vitamin and mineral cocktails involving heterogeneous patients groups. A handful of these trials have been done in children. Pediatric patients with severe burns have been found to have low plasma levels of vitamin D [7, 51]. Additional losses of vitamins and minerals can occur through loss of bodily fluids, such as hemorrhaging and drains [7]. Dylewski et al. found

Table 17.5 Summary of the roles of nutrient antioxidants in critical illness [48, 49]

Antioxidant	Function
Vitamin E	Breaks free radical chains
	Decreases lipid destruction
Vitamin C	Inhabits free radical reactions jointly with vitamin E
Vitamin C and E	Reduces infectious complications post hemorrhagic shock and injury
Selenium	Protects endothelial cells
	Scavenger of free radicals jointly with vitamin E
	Decreases mortality in critical illness and septic shock

plasma and urinary selenium levels to be low in 15 pediatric patients. The researchers concluded that suboptimal selenium status may potentially impact the incidence of infections in pediatric burn patients [52].

Probiotics

Probiotics are nonpathogenic living organisms or food that have the capacity to yield health benefits through modulation of the mucosal milieu in the gastrointestinal tract when consumed in adequate amounts. The use of probiotics in several studies has revealed benefit in both adults and children in infectious diarrhea and clostridium difficile [53]. Probiotic use in premature infants may reduce the incidence of NEC [10]. Higher yield of probiotic benefit may occur with multi-strains vs. mono-strains [54]. However, there are conflicting data regarding probiotic use and safety in critical illness. In a randomized placebo controlled study of probiotics in pediatric intensive care patients, the probiotic group developed more infections than the placebo group although the difference was not statistically significant. As a consequence the study was halted [55]. In a pilot study of 56 critically ill pediatric patients of which 26 of the patients were randomized to receive Lactobacillus Casei Shirota (LCS), no growth of LCS was found in the probiotic group. The researchers concluded LCS did not increase risk of infection [56]. Further studies are warranted to evaluate the efficacy and safety of probiotics in critical illness.

Nutrition Support Barriers, Initiation, and Monitoring

Nutrition Support Barriers

Enteral nutrition (EN) is the preferable routine of nutrition support during critical illness. In adults early initiation of EN within 24–48 h is shown to decrease infectious complications, hospital length of stay, and benefits to the integrity of the intestinal mucosa in comparison to PN. EN is also more cost-effective than PN [57, 58]. Early EN has also been shown to improve nitrogen balance in the critically ill or injured patient. In severe burn patients early EN (24 h) improves nitrogen balance and the provision of caloric intake and a decrease in mortality compared to EN initiated 48 h posthospital admission [57]. Several barriers are repeatedly identified as inhibitors of the provision of EN and attainment of enteral feeding goals in the critically ill patient. Numerous studies and quality control audits measuring enteral nutrition provision compared to medical order and/or established EN goal have led to identification of these barriers. Frequent EN feeding obstacles are listed in Table 17.6

Table 17.6 Common causes for not reaching EN goal volumes [59, 60]

Elevated gastric residual volumes (GRV)
Failure to acquire enteral access or maintain access
Prolonged holding of EN for test and/or procedures
EN held in anticipated of intubation or extubation
Intolerance to EN, diarrhea, emesis
Clogged feeding tube
Fluid regulation

[59, 60]. One of the major obstacles to EN is the measuring of gastric residual volumes (GRV) which lacks efficacy and has undeservingly been used to define tolerance to enteral nutrition. Elevated GRV have been defined as evidence for intolerance of enteral nutrition based on the premise that all gastric contents must empty and gastric residuals indicate delayed gastric emptying with the associated risk of aspiration pneumonia [61]. As a consequence EN is either held or not advanced. The evidence shows little correlation between GRV with EN intolerance or increased risk of aspiration pneumonia. No augmented risk for aspiration pneumonia is associated with an elevated GRV and no decreased risk is associated with a low GRV [62, 63]. Prolonged holding of EN delivery prior and after tests and procedures such as endotracheal intubation and extubation limits delivery. The actual process of obtaining GRV increases the risk of clogging feeding tubes which furthers disrupts EN delivery. When the intact protein in enteral formula mixes with the gastric contents (acidic) the conformation of the protein is altered and coagulation may form leading to a clogged feeding tube, especially in small bore feeding tubes. Medications administered through feeding tubes increase the risk for clogging. The use of liquid medications when feasible can help reduce the risk of tube clogging as can periodic water flushes [64]. Liquid medication may reduce the risk of tube clogging but in turn may increase the risk of diarrhea due to their higher osmotic load [65]. Awaiting the return of bowels sounds is another EN obstacle. Research has demonstrated that the small bowel returns to normal function 4 h postoperatively and early EN is tolerated though bowel sounds are generally absent [61, 66]. Finally, symptoms of diarrhea and emesis are frequent occurrences in the critically ill patient. Measurement and assessment of these occurrences varies extensively, the lack of standardization to define feeding intolerance may in itself be a barrier to delivery of EN. Causes of diarrhea are multifaceted. Frequent known causes of diarrhea are disease state, dysbiosis or dysbacteriosis, antibiotics, and medications in elixir or liquid form promoting an osmotic laxative consequence. Another potential cause is inadequately absorbed fermentable fiber or lack of fiber in the enteral formula [65].

Data have shown that implementation of EN protocols that outline initiation and advancement guidelines for EN increases the delivery and tolerance of EN. Pediatric nutrition support teams increase the utilization of EN while decreasing unwarranted PN use. Protocols regarding enteral tube placement enhance staff expertise in EN tube placement thereby increasing EN delivery [67–69].

Initiation of Nutrition Support

The optimal support method selected for the critically ill and/or the critical surgical patient should be determined by age, clinical condition, underlying disease state, gastrointestinal function, and length of therapy [58]. Numerous decision trees or algorithms have been developed to guide the initiation of nutrition support. In pediatrics there is a dearth of data available to make evidence-based decisions,

Table 17.7 Suggestion for initiation of EN using an isotonic formula preferably. Initiation of EN should be based on medical condition, treatment modalities, and individualized tolerance [58]

Initiation of enteral nutrition (EN)	
Weight < 30–40 kg	Weight > 30–40 kg
Continuous infusion	Continuous infusion
Start 1–2 mL/kg/h	Start at 1 mL/kg/h
Advance to desired goal rate within 24–48 h	Advance to desired goal rate within 24–48 h
Bolus gastric feeding	Bolus gastric feeding
Start at 2.5–5 mL/kg per feed over 5–8 feedings/day gradually advancing to desired goal volume	Start at 2.5–5 mL/kg per feed over 5–8 feedings/day gradually advancing to desired goalvolume

thus clinicians are forced to rely on best practices or data obtained from adult literature. The general premise is that if the gastrointestinal tract is functional EN is utilized and PN is reserved for the nonfunctional GI tract. Gastric is the preferred method for EN delivery while postplyoric is reserved for gastroparesis, gastric outlet obstruction, pancreatitis, and patients with known reflux and aspiration of gastric contents [58]. In hemodynamic instability, EN is frequently withheld due to the requirement for vasoactive medications. Avoidance of EN also occurs during evidence of bowel ischemia [57]. EN is administered by continuous, intermittent, and bolus infusion. The American Society for Enteral and Parenteral Nutrition (A.S.P.E.N.) 2009 suggestions for initiation of EN nutrition can be found in Table 17.7. The recommendations are for initiation of full strength isotonic formula and the avoidance of diluted enteral formula. The diluting of enteral formula increases the probability of microbial contamination leading to diarrhea and EN intolerance. In addition, dilution of enteral formula lowers the formula osmolality. The lower osmolality and higher pH of the diluted formula is more supportive of microbial growth compared to full strength formula [58].

Monitoring of Nutrition Support

Monitoring of biochemical parameters should occur before nutritional support, after initiation of nutrition support, and periodically thereafter. The type of parameters monitored should be based on protocols as well as the patient's underlying illness and disease state. Patients at risk for the refeeding syndrome and metabolic complications should be monitored more closely. Complications of refeeding in malnourished patients can lead to pathophysiological and metabolic complications involving depleted levels of potassium, phosphorus, magnesium, and thiamine leading to cardiac, hepatic, respiratory, and neuromuscular consequences and even death. Depleted biochemical parameters should be corrected prior to the initiation of nutrition support [58]. Electrolyte and glucose management involves monitoring many parameters as a result of fluid shifts, renal function, bodily secretions, and increased insensible losses and may need to be reviewed on a daily basis depending on clinical condition. Abnormal phosphate, magnesium, and acid–base imbalances frequently occur during critical illness particularly in those with sepsis, SIRS, and preexisting deficiencies. In stress states there is hepatic reprioritization of protein synthesis. Protein levels are inversely related to the C-reactive protein (CPR) level. When the CRP is elevated, protein synthesis of albumin and prealbumin is decreased compared to when the CRP is less than 2. Albumin levels are also skewed independent of nutrition status by fluid status, intravenous albumin provision, trauma, sepsis, and liver disease. This is not a reliable monitor of nutrition status during these states and critical illness [2, 3, 7].

Summary and Future Research

Critically ill children like adults experience the metabolic response to stress which varies by age. Children, especially young children, due to their low protein reserves are particularly vulnerable in prolonged stress to the detrimental effects of the altered hormonal milieu. The role of nutrition support is to help preserve skeletal muscle and support organ and immune function. The optimal provision of macronutrients, micronutrients, energy, and nutrition support in critically ill children is unknown. It is well established that predictive equations inadequately predict energy needs during critical illness and indirect calorimetry is more accurate. Research in the area of nutrition support for the critically ill child is urgently needed.

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