Introduction

Metabolic demands of critical illness and underfeeding or overfeeding may expose seriously ill children to the threat of malnutrition or metabolic overload (acute metabolic syndrome). In addition, nutritional status itself affects every pediatric patient’s response to illness. Reports of poor provision of nutrition in intensive care units, as well as evidence of malnutrition [1] or overfeeding [2] in critically ill patients are still frequent. Recent studies, compared with similar surveys performed up to three decades ago, showed that there has been little improvement in nutritional status in pediatric populations in the interim [3].

Although caloric intake lower than the basic metabolic rate has been associated with higher mortality and morbidity rates [4], critically ill children have been reported to only receive a median 58.8 % of their energy requirements, which could not be optimized until the 10th intensive care day [5]. In another study, patients in the Pediatric Intensive Care Unit (PICU) received a median of 37.7 % (range, 0.2–130.2 %) of their estimated energy requirements [6]. Only 52 % achieved full estimated energy requirements at any time during their admission. Failure to estimate energy requirements accurately [7], barriers to bedside delivery of nutrients, and reluctance to perform regular nutritional assessments are responsible for the persistence and delayed detection of malnutrition in this cohort [8]. At the same time, using targeted indirect calorimetry, a high incidence of unintended overfeeding in critically ill children with a long stay has been recently detected [2]. The predominance of hypometabolism, failure of physicians to correctly predict metabolic state, use of stress factors, and inaccuracy of standard equations all contributed to cumulative energy excess in this cohort [8].

Nutritional monitoring should be an integral part of the care for every pediatric critically ill patient. Despite the

Abstract

The ideal set of variables for nutritional monitoring that may correlate with patient outcomes has not been identified. This is particularly difficult in the PICU patient because many of the standard modes of nutritional monitoring, although well described and available, are fraught with difficulties. Thus, repeated anthropometric and laboratory markers must be jointly analyzed but individually interpreted according to disease and metabolic changes, in order to modify and monitor the nutritional treatment. In addition, isotope techniques are neither clinically feasible nor compatible with the multiple measurements needed to follow progression. On the other hand, indirect alternatives exist but may have pitfalls, of which the clinician must be aware. Risks exist for both overfeeding and underfeeding of PICU patients so that an accurate monitoring of energy expenditure, using targeted indirect calorimetry, is necessary to avoid either extreme. This is very important, since the monitoring of the nutritional status of the critically ill child serves as a guide to early and effective nutritional intervention.

Keywords

Nutrition • Monitoring • PICU • Energy expenditure • Metabolic monitor • Anthropometrics

Nutrition Monitoring in the PICU

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realization of its importance and the high incidence of combination of malnutrition and low energy intake, most medical professionals seldom assess and monitor the nutritional status of hospitalized patients [9]. A survey in 111 European PICUs from 24 countries showed that a multidisciplinary nutritional team was available in 73% of PICUs. Approximately 70% of PICUs used dedicated software for nutritional support and acknowledged nutritional support as an important aspect of patient care, yet only 17% of them regularly monitored energy expenditure by indirect calorimetry. In most PICUs daily energy requirements were estimated using weight, age, predictive equations with correction factors, and a wide range of biochemical blood parameters [9].

**Assessing Nutritional Status**

**Subjective Global Nutritional Assessment (SGNA)**

The ideal set of variables for nutritional monitoring that may correlate with patient outcomes has not been identified. This is particularly difficult in the PICU patient because many of the standard modes of nutritional monitoring, although well described and available, are fraught with difficulties. Thus, repeated anthropometric and laboratory markers must be jointly analyzed but individually interpreted according to disease and metabolic changes, in order to modify and monitor the nutritional treatment. In addition, isotope techniques are neither clinically feasible nor compatible with the multiple measurements needed to follow progression. On the other hand, indirect alternatives exist but may have pitfalls, of which the clinician must be aware. Overall, among assessment instruments, only 11 original instruments and three modified ones were published with enough information to allow appropriate usage [10]. This is very important, since the monitoring of the nutritional status of the critically ill child serves as a guide to appropriately modify nutritional intervention.

Because of the 24-h 7-day-a-week time requirement for the initial nutrition screen in a PICU, many units use staff nurses to complete the screening at the time of admission. These screens are generally shorter in length than more in depth screens that include laboratory values, but have the advantage that they can be done efficiently and in a timely fashion. Certain components of nutritional assessment have been combined into a clinical tool described as the subjective global nutritional assessment (SGNA) that physicians can use to systematically document and recognize nutritional problems in their hospitalized patients [11]. It provides a systematic method for obtaining essential information about nutritional status from the history and the physical exam, such as the history of weight loss, altered food consumption, gastrointestinal derangements, decreased functional capacity, subcutaneous tissue loss, muscle wasting, and the presence of edema. It demands training but is easily learned, adds little additional effort to a routine admission history and physical examination, and is a powerful predictor of adverse outcomes [12]. Thus, SGNA has been validated by anthropometry and albumin measurement, and predicted morbidity and mortality in severely ill patients [13]. Those patients classified as severely malnourished by the SGNA presented with a consistent worsening of the traditional objective markers, had significantly more complications, remained in the hospital longer and had a higher mortality rate. Additionally, it has been shown that SGNA is a sensitive and specific nutrition assessment tool for assessing nutritional status in children having major thoracic or abdominal surgery and identifying those at higher risk of nutrition-associated complications and prolonged hospitalizations [14]. Therefore, application of the protocol as a complement of standard anthropometric tool in a PICU setting should be considered.

**Anthropometrics**

In the initial evaluation of nutritional status, only updated national or regional standard growth curves, the most rudimentary of assessment tools, are necessary. The child who suddenly or progressively deviates from an established pattern is at high risk for depletion. The height indexed to the height of the 50th percentile is useful in assessing chronic changes, but its value in acute illness is not clear. Weight is more likely to be affected by acute changes, while deviation from the height curve perhaps reflects long-standing caloric deprivation. The current body weight is often compared with the ideal body weight for height in order to roughly estimate the patient’s body habitus versus norms. These measurements can be converted to growth velocities or to height-for-age and weight-for-height Z-scores or percent of expected values to provide a measure of the degree of under- or over-nutrition in the child [15]. There are several important caveats, however, in monitoring anthropometries in the critically ill. They suffer from the influence of intra-observer and inter-observer errors and are compared with tables derived from healthy populations. Furthermore, the edema and ecchymoses often encountered in the PICU setting interfere with accurate determinations. Monitoring the weight/height/age ratios, therefore, based on the National Center for Health Statistics [16] and the World Health Organization child growth charts [17] can be used as reference but there is a risk of over- and underestimation of malnutrition rates compared with country-specific growth references [18]. For children with specific medical conditions and syndromes, specific growth references should be used for appropriate interpretation of nutritional status [19].
Body mass index (BMI) may also be used to assess nutritional status. This weight-stature index is calculated as weight in kilograms divided by height in meters squared. Although there is no consensus on how to interpret BMI in relation to nutritional status, a BMI of <15 kg/m² has been associated with significant increases in morbidity and mortality. In moderately malnourished children, percentage of standard BMI was the best predictor for serum leptin concentrations, which were low not only in severe acute malnutrition, but also in children with mild-to-moderate malnutrition without chronic disease [20]. In adults, it has been suggested that the relationship between BMI and patient outcomes is “U” shaped, with worse outcomes for both underweight (BMI <18.5 kg/m²) and morbidly obese (>40 kg/m²) patients [21, 22]. In evaluating more severe changes, chronic and acute nutritional status was defined by interpreting the Waterlow stages for chronic protein-energy malnutrition (CPEM) and acute protein-energy malnutrition (APEM) [23]. Patients classified by these criteria as CPEM or APEM are more than 2 SD from the median (Table 42.1). Another widely used anthropometric classification is the Z score [24]. It may be used for children of any age, and rates lower than −2 Z scores or less than average indicate undernutrition. Children whose rates are lower than −3 Z scores or less than 70 % in relation to average, or those who present with edema provenly due to nutrition, are considered severely undernourished.

Skinfold thickness (TSF) and circumference measurements of the arms, legs and/or trunk may be useful to characterize the changes in peripheral fat depots and muscle mass, respectively. Upper arm TSF and mid-arm circumferences (MAC) represent body-compartment measurements of adipose tissue and muscle. Arm muscle size is been calculated from arm circumference and triceps skinfold and should be useful in monitoring the depletion of lean body mass [25]. In infants, 10 % of body weight should be fat; by 5–10 months of age, this should be up to 20 %. Even in adults, compared with the BMI, the MAC was a better mortality predictor in patients with chronic obstructive pulmonary disease [26]. MAC and cutaneous TSF are determined using Lange skinfold callipers and a tape measure [27]. From these measurements, mid-arm muscle circumference (MMC), mid-arm muscle area (MMA), and mid-arm fat area (MFA) are calculated. Fat stores are assessed by measurements of TSF and MFA; somatic protein stores are assessed by MMC and MMA. Both, fat and protein stores are classified as normal, nutritionally at risk, or deficient, according to Frisancho [28, 29] and Ryan, Martinez [30] or the Standards of the Ten-State Nutritional Survey [31] tables (Table 42.2). Critically ill patients whose arm circumference values are below the fifth percentile have a higher mortality rate [32]. Acute fluid shifts and changes in circulating albumin, however, cannot only influence weight, but also arm circumference and skinfold thickness determinations. In a recent prospective study, however, in which 80 % of children received enteral nutrition, there was no statistically significant change in most anthropometric indicators evaluated in the PICU, suggesting that nutrition probably helped patients maintain their nutrition status [33]. Importantly, in children with cancer, although the weight-for-height values were normal, MAC and TSF values were significantly less than control values [34]. In a prospective PICU study, although weight and all arm anthropometrics decreased, only arm circumference and

### Table 42.1 Criteria for relative risk for malnutrition

| Waterlow stage | At risk | Greater risk | Protein-calorie malnutrition |
|----------------|---------|--------------|------------------------------|
| 0              | Normal  | >90 %        | >70–79 %                     |
| 1              | 80–89 % | <70 %        | 369 %                       |
| 2              | 70–79 % | <70 %        | 369 %                       |
| 3              | >70 %   | >70–79 %     | <69 %                       |

A. Acute protein energy malnutrition (APEM): weight for height = (actual weight)/(50th percentile weight for subject’s height and age)

B. Chronic protein energy malnutrition (CPEM): subject’s height/50th percentile height for subject’s age

### Table 42.2 Anthropometric nutritional status assessment

| Somatic protein stores: |                  |
|-------------------------|------------------|
| Midarm muscle circumference: MMC (mm) = MAC (mm) – (TSF [mm] × 3.14) |
| Midarm muscle area: MMA (mm²) = (MAC [mm] – [TSF [mm] × 3.14])²/4π |

| Fat stores: |
|-------------|
| Triceps skinfold thickness (TSF) [mm] |
| Midarm fat area (MFA) (mm²) = MAA⁻²–MMA |

### Frisancho tables

| Normal | Nutrititionally at risk | Deficient |
|--------|------------------------|-----------|
| >10 percentile | 5–10 percentile | <5 percentile |

*Midarm circumference = MAC
*Midarm area: MAA (mm²) = a/4 × (MAC/π)²
triceps skinfold thickness were significantly decreased at day 7 compared with initial measurements [33]. Thus, it has been suggested that arm anthropometry should replace the use of weight-related indices to identify malnutrition in children with co-morbidity [24].

**Obesity**

The National Health and Nutrition Examination Survey and Pediatric Nutrition Surveillance System report a tripling of the prevalence of BMI at least 95% (obesity) among US school-age children and adolescents over the past three decades [35]. International data confirm similar upward shifts in pediatric BMI distribution, especially in countries undergoing economic transitions favoring industrialized, western urban lifestyles [24]. Among adults, nearly one-third of ICU patients are obese and nearly 7% are morbidly obese, frequencies that are predicted to increase as the prevalence of obesity in the general population rises [36]. However, there is a critical lack of research on how obesity may affect complications of critical illness and patient long-term outcomes. Data of 8,813 mechanically ventilated adults >18 years who remained in the ICU for >72 h (multicenter international observational study of ICU nutrition practices that occurred in 355 ICUs in 33 countries during 2007–2009) showed that during critical illness, extreme obesity is not associated with a worse survival advantage compared to normal weight [37]. It showed, however, that among survivors, BMI ≥40 kg/m² is associated with longer time on mechanical ventilation and in the ICU.

**Malnutrition**

Adequate nutrient intake is critical for optimal cellular and organ functions, protein synthesis, immunity, repair, and capacity of skeletal, cardiac, and respiratory muscles and tissue repair [38]. Disease related malnutrition, however, frequently occur in infants and children, often with more rapidly obvious and detrimental consequences than in adults. Other factors such as age, social background, congenital heart disease, burn injury, and length of hospital stay also negatively impact nutritional status. The consequences of hospital malnutrition are well described and recognized as causing skeletal-muscle weakness, increased rate of hospital-acquired infection, impaired wound healing, prolonged convalescence, length of hospital stay, increasing mortality [39] and, consequently, the costs of providing health care [40, 41]. A number of studies have demonstrated that children with newly diagnosed diseases may already be malnourished [3]. It has also been indicated that malnutrition and nutrient store deficiencies commonly occur early in the course of critical illnesses in children [42]. In a recent study, 16.7% of patients were already depleted of protein and 31% of fat stores upon admission to the PICU [43]. Overall, 16.9% were at risk for and 4.2% had already CPEM and 21.1% were at risk for and 5.6% had already APEM. In addition, levels of many complement components are reduced and trace mineral and vitamin deficiencies are associated with profound effects on cell-mediated immunity such as impaired lymphocyte stimulation response, decreased CD4+/CD8+ cell number and function, decreased chemotaxis and function of phagocytes, and diminished secretory immunoglobulin A antibody response [44]. These changes are driven by a combination of the counter regulatory hormones and the direct and indirect action of the various inflammatory mediators such as prosta-glandin and kallikreins [45], the balance of which may be crucial in regulating the ability to generate an anabolic response [46].

### Monitoring Biochemical Markers

#### Plasma Proteins

Because of the problems associated with anthropometrics, a number of other measurements are used in conjunction both for establishing the initial nutritional status and monitoring changes. Hepatic proteins such as albumin, transthyretin (pre-albumin), transferrin, and retinol binding protein have been used as nutritional markers. Among them, the shorter half-life proteins correlate better with acute changes, and the longer-lived proteins are better for the evaluation of chronic problems. Thus, isolated starvation does not alter plasma protein concentrations reflecting the uniform loss of water and cellular mass until severe depletion is present. On the other hand, critical illness leads to a decrease of protein concentrations without severe loss of body cell mass, mainly reflecting reprioritization of liver protein synthesis.

Serum albumin represents equilibrium between hepatic synthesis and albumin degradation and losses from the body. It is also influenced by intravascular and extravascular albumin compartments and water distribution. About one-third of the albumin pool is in the intravascular compartment, and two-thirds is in the extravascular compartment. Once albumin is released into the plasma, its half-life is about 21 days. Levels of this visceral protein may decline in the setting of acute injury and illness as the liver reprioritizes protein synthesis from visceral proteins to acute-phase reactant proteins and as a consequence of increased degradation, transcapillary losses and fluid replacement [47, 48]. Albumin losses from plasma to the extravascular space increase threefold in patients with septic shock [49]. Albumin might be also altered because of factors other than malnutrition, such as in hepatic disorders, extra protein losses (nephrotic syndromes,
in fistula, peritonitis), and in cases of acute infection or inflammation. However, it has been shown that serum albumin correlates very poorly with monitoring of nutritional status based on a patient’s history and physical exam [50].

Transferrin, also referred to as prealbumin, is a transport protein for thyroid hormone. It is synthesized by the liver and partly catabolized by the kidneys. Normal serum transferrin concentrations range from 16 to 40 mg/dL; values of <16 mg/dL are associated with malnutrition. Levels may be increased in the setting of renal dysfunction, corticosteroid therapy, or dehydration, whereas physiological stress, infection, liver dysfunction, and over-hydration can decrease transferrin levels. The half-life of transferrin (2–3 days) is much shorter than that of albumin, making it a more favorable marker of acute change in nutritional status [43].

Transferrin has also been used as a marker of nutritional status. This acute-phase reactant is a transport protein for iron; normal concentrations range from 200 to 360 mg/dL. Transferrin has a relatively long half-life (8–10 days) and is influenced by several factors, including liver disease, fluid status, stress, and illness. Levels decrease in the setting of severe malnutrition, but this marker is unreliable in the assessment of mild malnutrition, and its response to nutrition intervention is unpredictable. Transferrin has not been studied as extensively as albumin and transferrin in relation to nutritional status, and the test can be expensive. It also suffers from the influence of other non-nutritional situations such as hepatic and renal failure and hormone infusion. Despite these limitations, it has been shown that transferrin and prealbumin levels improved at the end of a period of early enteral feeding in critically ill children, while survivors had higher prealbumin levels than non-survivors (22.3 versus 15.5 mg/dL) [43]. Similarly, a greater positive trend in levels of prealbumin, transferrin, retinol-binding protein, and total protein has been shown in a protein-enriched diet group [51].

**Nutritional Indices**

Nutritional indices, such as the Prognostic Nutrition Index, are mathematically derived equations that combine measurements of albumin, triceps skinfold thickness, transferrin, and delayed hypersensitivity skin testing. Each measurement has its own restrictions, as previously mentioned, but, when combined, they have been shown to increase the sensitivity of prediction of major morbidity in surgical patients [52]. Two multi-parameter nutritional status indices, the Maastricht Index (MI) [53] and the Nutritional Risk Index (NRI) [54] were used to assess the nutritional status of patients. Also, acute phase reactants such as C-reactive protein have been used as a marker of metabolic state [55]. By combining nutritional and acute stress markers, a modified form of Prognostic Inflammatory and Nutritional Index (PINI) has been shown to be significantly correlated with protein intake by the end of early enteral nutrition (EN) and to be negatively correlated to myocardial contractility in critically ill children [43].

**Nitrogen Balance**

Significant negative nitrogen balance and somatic protein depletion develops in critically ill pediatric patients, especially when they are inadequately fed, develop Multiple Organ System Failure (MOSF), or have previous chronic illness. Thus, an alternative to specific protein determinations is measurement of nitrogen balance. In the human body, only protein is composed of nitrogen, thus measurement of nitrogen excretion is a method for assessing protein metabolism and indirectly assessing metabolic stress and following up nutrition repletion. Achievement of positive protein and energy balance in relation to the basic metabolic rate using an aggressive early EN protocol improved nitrogen balance during the acute phase of stress in two-thirds of critically ill children [56]. The breakdown of muscle proteins has been proved to be sensitive to alterations in nutrient and substrate supply [57]. It has been speculated that ATP is utilized in the process of peptide bond synthesis, for the formation of the tertiary structure of proteins, and for the synthesis of tRNA, mRNA, and the nucleotides from which they are, in turn, found [58]. On the contrary, the oxidation of amino acids in muscle is stimulated by fasting, sepsis, stress, hormonal influence, and other conditions associated with negative NB [59]. It was recently shown that caloric intake and MOSF independently affect substrate utilization [60]. In particular, the incidence of negative NB was 91 % when the caloric intake was less than REE and 9 % when it was equal to or greater than REE. Without MOSF there was a trend toward positive nitrogen balance by day 7 while with MOSF, negative nitrogen balance persisted even by day 7 [51].

Nitrogen balance, in the absence of exogenous support, can be estimated from urinary urea nitrogen excretion over a 24-h period. This will constitute about 93 % of total urinary nitrogen losses. Additionally, it has been suggested that 0.5 g per day of nitrogen be added to the output to account for nitrogen lost through skin [61]. Ideally, urine output should be collected for 24 h measurements of total urinary nitrogen and additional fecal, stoma, drainage fluid, and/or other body fluid losses should be obtained to determine concentrations of daily nitrogen excretion [49]. In critically ill children, nitrogen balance estimated by total urinary nitrogen and justified for other losses differed significantly from the estimated values using urine urea nitrogen or even unjustified total urinary nitrogen (Fig. 42.1). Nitrogen drainages are usually determined by manual micro-Kjeldahl digestion or
by high-resolution liquid chromatography [62]. Nitrogen balance is then calculated by subtracting output (corrected for daily changes in total-body urea content assuming that urea is uniformly distributed in body water) from input (enteral, parenteral, and non-feeding protein), according to the following formula:

$$\text{Justified nitrogen balance (g/day)} = \text{N intake} - \left( \text{Total urinary N} + \text{change in BUN} + \text{faecal losses} + \text{other body fluid losses} + 0.5 \text{g for cutaneous losses} \right)$$

$$= \text{Change in BUN (g)} = 0.6 \times \text{weight} \times \text{BUN initial} - \text{BUN final}.$$

**Creatinine Height Index- Body Protein Turnover**

The creatinine height index may also be used to monitor nutritional status. It is derived from the measurement of 24 h urinary creatinine excretion as follows: (24 h excretion of creatinine/creatinine excretion of normal individuals of same height and sex) $\times$ 100. Thus the determined creatinine height index is compared with predicted values based on height and sex and then the somatic protein status may be calculated as follows: $<80$ % = moderate depletion of somatic protein status, $<60$ % = severe depletion of somatic protein status [53]. Any factor that might interfere with creatinine excretion, such as age, renal disease, stress or diet, might interfere with its interpretation. In a mixed critically ill pediatrics population, 27 % had mild to moderate somatic protein depletion and 5.4 % had severe somatic protein depletion on day 1 [60]. Only the persistence of stress and co-morbidity were associated with the creatinine-height index. Monitoring this index in a prospective study of early EN in a PICU, children who had severe depletion of somatic protein status on stress day 1 reached the normal range of somatic protein status on post-stress day 5 (CHI $>80$ %) [56].

Although, 3-methylhistidine excretion has been proposed as an index of skeletal muscle degradation and, therefore, proteolysis associated with stress, at least 25 % of urinary 3-methylhistidine has been also attributed to extra-skeletal sources [63]. Tracer studies of whole body protein turnover underestimate actual protein turnover because intercellular recycling of amino acids occurs, and thus some amino acids may not be in equilibrium with a tracer such as nitrogen.

**Monitoring Resting Energy Expenditure**

Energy expenditure can be difficult to predict in PICU patients because of the effects of various disease states, therapeutic interventions, stress, and each patient’s own inherent metabolic requirements. It was recently shown that there was no relationship between resting energy expenditure (REE) and clinical severity evaluated using the PRISM, PIM2 and PELOD scales or with the anthropometric nutritional status or biochemical alterations [64]. Thus, neither nutritional status nor clinical severity was shown to relate to REE which should be measured individually in each critically ill child at risk, preferably using indirect calorimetry. Risks exist for both overfeeding and underfeeding of PICU patients so that an accurate assessment of energy needs is necessary to avoid either extreme.
Indirect Calorimetry

Indirect calorimetry continues to be the ‘gold standard’ for measuring energy expenditure in the critically ill child. Unfortunately, indirect calorimetry is expensive and is not available to the majority of PICU clinicians or registered dietitians. Obviously, when a metabolic monitor is available, critically ill children’s energy requirements should be based on measured REE as the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) recommend. Traditional components of total energy expenditure (TEE) include REE, diet-induced thermogenesis and physical activity energy expenditure. The TEE is considered the REE plus a 5 % activity factor [65] and plus 15 % for day-to-day variability [66]. The magnitude of the diet-induced thermogenesis depends on the type of substrate provided, the amount of substrate ingested, and the way the body handles the substrate, ranging from 5 to 30 % [67].

Indirect calorimetry is based on the recognition that the body is a chemical furnace and, like all physical entities, must follow the basic laws of thermodynamics. In combustion, the use of energy involves the consumption of oxygen (VO₂) and production of carbon dioxide (VCO₂), nitrogenous waste, and water in a stoichiometric fashion. Further, according to the first law of thermodynamics, energy can be neither consumed nor created, but can merely change forms. When basic nutrients are converted to heat in cells, measurement of VO₂ and VCO₂ would indirectly reflect the basal metabolic expenditure involved. Mean REE and respiratory quotient (RQ) are automatically obtained using an integrated microprocessor. Respiratory quotient is calculated from gas fractions alone, according to the Haldane transformation and REE is calculated according to Weir’s equation [68] (Table 42.3).

The RQ reflects whole body substrate use, but is also affected by factors such as body habitus, acid-base disturbances, underlying metabolic conditions, or critical illness. Physiologically, RQ represents an instantaneous summary of the interplay between oxidation and synthesis of various metabolic substrates. The ratio can vary from 0.7 to 1.2. The non-protein RQ is calculated from the measured respiratory quotient (i.e. VO₂/VCO₂) after correction for protein oxidation as measured by urinary nitrogen excretion after correction for changes in serum urea levels. Thus, the non-protein RQ reflects the ‘net’ metabolism of glucose and lipids. A RQ value greater than 1 indicates that patients have been overfed, especially in excess of carbohydrate calories, which can result in net fat synthesis. Lipogenesis or net fat synthesis is also defined as a non-protein RQ >1. A high carbohydrate intake, defined as a continuous glucose infusion >8 mg*kg⁻¹*min⁻¹, to acutely ill patients may increase CO₂ production by 50–66 %. Overfeeding a respiratory compromised child might increase the RQ to >1, producing unnecessary CO₂ that he/she might be unable to eliminate creating difficulty in weaning from mechanical ventilation [69] and prolonging the length of hospitalization [70]. Thus, when there is a need for increasing energy intake, the energy source should be carefully chosen to avoid giving excess carbohydrate calories. In adults on parenteral nutrition, however, RQ >1.0 was not a specific marker of excessive caloric intake [71] whereas RQ >1.0 was reported in <30 % of all adults who were overfed [72]. Similarly, in critically ill children, a single measurement of RQ had poor sensitivity (21 % for overfeeding) when a specific cutoff of RQ >1.0 was used to classify the degree of overfeeding [73]. Therefore, the best indicator of overfeeding remains the difference between energy intake and energy expenditure as measured by metabolic monitors.

Indirect calorimetry circumvents many of the problems associated with other modes of nutritional assessment. Since the method directly measures the conversion of energy to heat, there is no need to apply age-related, population-based data to individual critically ill children. Alterations in tissue composition also will not obscure the meaning of the data. Patients may be classified as hypermetabolic (as defined by a REE >10 % of the predicted value), normometabolic (REE within the ±10 % prediction range), and hypometabolic (REE <10 % of the prediction range) [62]. Compared with a ‘normometabolic’ group, hypermetabolic patients show higher fat oxidation suggesting that fat is preferentially oxidized. A high carbohydrate intake is associated with lipogenesis and thus with an increase in thermogenesis [62]. RQ is also strongly affected by the ratio of energy intake/total daily REE and by the cumulative energy balance. Following a patient over time will allow recognition of the nature of the metabolic problem and tailoring of support to meet individual needs. Thus, during the week following PICU admission,

### Table 42.3 Measured resting energy expenditure (REE) and Respiratory Quotients (RQ)

| Fuels     | Respiratory quotients |
|-----------|-----------------------|
| Carbohydrate | RQ = 1               |
| Fat       | RQ = 0.7              |
| Protein   | RQ = 0.8              |

REES can be derived from metabolic cart measurements, using the following formulae:

\[
\text{REE Weir formula:}
\]

\[
\text{REE} = 5.68 \text{VO}_2 + 1.59 \text{VCO}_2 - 2.17 \text{Urine N}_2
\]

If urine N₂ is not entered, the REE is calculated as follows:

\[
\text{REE} = 5.466 \text{VO}_2 + 1.748 \text{VCO}_2
\]

According to Haldane transform, which states the relationship between the inspiratory (I) and expiratory (E) volume, the respiratory quotients (RQ) can be calculated from gas fractions alone:

\[
\text{VO}_2 = V_d(F_I O_2) - V_d(F_E O_2)
\]

\[
\text{VCO}_2 = V_d(F_I CO_2) - V_d(F_E CO_2)
\]

\[
\text{RQ} = \frac{\text{VCO}_2}{\text{VO}_2}
\]
REE was not shown to be different from Schofield’s Predicted Basal Metabolic Rate (PBMKR), but it was 20% lower than TEE [74]. During convalescence, for clinically stable patients, adding approximately 20–25% to the REE might better approximate TEE requirements [75]. From the median nitrogen excretion, optimal daily protein intake has been calculated as 1.9 g/kg, whereas a high protein intake (about 2.8 g/kg per day) has been shown to result in a positive nitrogen balance [62].

Monitoring nutrition of critically ill children, subjects may be divided into three groups, based on the degree of feeding as previously described [76]. Underfed is defined as a subject’s actual average energy intake being less than 90% of total energy requirements. Appropriately fed is defined as a subject’s actual average energy intake being within ±10% of TEE requirements. In overfed patients the actual average energy intake is larger than 110% of the TEE requirements. Additionally, careful monitoring with indirect calorimetry and nitrogen balance studies should help prevent inadequate protein or excessive carbohydrate intake. The non-protein RQ and the net substrate (fat, carbohydrate, and protein) oxidation rates are calculated using the Weir formula modified by Frayn [77].

The Standard Metabolic Monitor

The metabolic monitors have been widely validated and tested for accuracy and reproducibility by both in vitro and in vivo means, which enables its clinical use in PICU [78]. They measure the VO2 and VCO2 from gas exchange measurements, and calculate the REE and RQ by using the Weir equation [68], ignoring the urinary nitrogen [79]. For most children a single measurement of total daily energy expenditure provides reasonable insight as to the daily energy needs [80]. The mean percentage of between day variations in energy expenditure has been estimated at 21 ± 16%, [81] but the early phase of stress response is characterized by a greater variability in REE because of the fast biphasic metabolic response to injury in children [82]. In a previous study conducted for validation of the predictive equations in the early post-injury period, no differences with clinical relevance were found in the REE throughout the 24-h post-injury phase [83]. In another study, the within-day variation of REE in ventilated, critically ill children was only 7.2% [81] also supporting the approach that a single 30-min indirect calorimeter measurement may provide an acceptable guide to set up the nutritional support. Thus, in critically ill, ventilated children energy expenditure can be measured with acceptable accuracy but daily measurements are necessary because of huge between-day variations.

Patients receiving continuous enteral or parenteral infusions are not interrupted during the measurement. The patient is connected via an endotracheal tube to a spirometer filled with 100% O2 attached to a kymograph (closed circuit spirometry method). As the patient breathes, the oxygen is consumed and CO2 is exhaled. The water and CO2 vapor are mechanically absorbed, so that volume changes in the spirometer are due only to the consumption of oxygen. The oxygen uptake by the lungs is determined from the amount of oxygen consumed from the spirometer. Since the magnitude of tube leakage of mixed expiratory gases cannot be predicted from endotracheal tube diameter, ventilator settings, or infant activity or posture [84], lack of an air leak must be confirmed on clinical examination by absence of an audible air leak during mechanical inspiration, by determining the difference between inspired and expired tidal volumes (<15%), and/or during testing by the presence of stable minute to minute RQ values. Patients with FiO2 >0.80, with incompetent endotracheal tube cuffs, leaking chest tubes, bronchopleural fistulas losing expired gases to the environment, on other ventilators (not suitable for REE measurement) [85], or on continuous nitric oxide or CO2 inhalation may not have reliable measurements. The device permits uninterrupted patient ventilation and provides non-invasive measurement of inspired and exhaled gases. The flowmeter and the CO2 and O2 analyzers are automatically calibrated before each measurement and oxygen consumption is measured for at least 30 min each time.

Recent Advances in Monitoring REE in the Critically Ill

With the advent of newer technology, continuous and accurate metabolic monitoring in critically ill children has been possible at the bedside. Two of the most well studied metabolic monitors; the Deltatrac II NMN-200 (Datex-Ohmeda, Helsinki) and the E-COVX (former M-COVX) from Datex-Ohmeda (Helsinki) are systems that use the open circuit technique. The Deltatrac II measures gas volume in a mixing chamber and the E-COVX uses a breath-by-breath method to analyze VO2 and VCO2 [86]. The Deltatrac II, validated in different patients in the past but no longer produced, used to require a high level of technical expertise and was time consuming to calibrate. The newer compact E-COVX is able to continuously analyze VO2 and VCO2 cheaper and simpler to use, performs calibration automatically and is much smaller in size [87]. It was suggested, however, that although in adult patients it compared more [87] or less [88] favorably to the Deltatrac II, it might not provide measurement within a clinically accepted range in certain ventilation modes and in non-sedated patients [89].

Extending the previous studies we have recently shown that, despite an immediate decrease in dynamic compliance and expired tidal volume that result in inadequate or inaccurate sidestream respiratory monitoring, pulmonary mechanics
and continuous indirect calorimetry monitoring were not influenced after uneventful open endotracheal suctioning in well-sedated children [90]. Especially, when using a compact modular metabolic monitor (E-COVX), attending physicians may be able to reliably record spirometry and metabolic indices as early as 5 min after suctioning at different ventilator modes. In addition, we have shown that the influence of different ventilator modes on VO₂ and VCO₂ measurements in adequately sedated critically ill children is not significant [91]. Thus, new compact metabolic monitors, like the E-COVX metabolic module, are suitable for continuous REE monitoring in well-sedated mechanically ventilated children with stable respiratory patterns using the PRVC, SIMV, or BiVent modes of ventilation.

The Short Douglas Bag Protocol

The Douglas bag method uses the fraction of expiratory CO₂ to determine VCO₂ and calculate energy expenditure through a double in/outlet, separated by a valve, allowing airflow to and from the bag or to outside air by turning a tap. It compared favorably to the metabolic monitor in a study in which predictive equations failed to predict individual energy expenditure [92]. Intra-measurement variability was within 10% for both methods, which showed significant bias compared to Schofield equations. Considering its low cost, these data render the short and simple Douglas bag method a possible robust measure and a routinely applicable instrument for tailored nutritional assessment in critically ill children.

Alternative Methods Used to Predict Energy Expenditure

Bicarbonate Dilution Kinetics

Energy expenditure can be determined over a period of several days [93] by bicarbonate dilution kinetics if the energy equivalents of carbon dioxide (food quotient) from the diet ingested are known. Accordingly, using this method it is necessary to know the fraction of carbon dioxide produced during the oxidative process but not excreted. By measuring the dilution of 13C infused by metabolically produced carbon dioxide (continuous tracer infusion of NaH13CO3) the rates of 13CO₂ appearance were estimated in critically ill children [94]. Determining the energy expenditure by this method, it was shown that the 2001 World Health Organization and Schofield predictive equations overestimated and underestimated, respectively, energy requirements compared with those obtained by bicarbonate dilution kinetics [94].

Indirect Estimations of REE

Because protein oxidation represents 8–12% of the total energy expenditure, it has been speculated that changes in nitrogen balance are associated with changes in REE [95]. Benotti et al. proposed that an estimation of REE could be made from measurement of urea excretion and nitrogen balance [96]. In a study, in which the patients received only 5% dextrose infusion and no nitrogen, a week correlation between daily nitrogen excretion and REE, has been shown [97]. In patients receiving mixed nutritional regimens, however, we could not find any correlation or independent association of the nitrogen balance with REE [98]. Instead, the efficacy of increased protein and energy intakes to promote protein anabolism and the underlying mechanisms were studied by measuring whole body protein balance (WbPBal) using intravenous-enteral phenylalanine/tyrosine stable isotope method protocol [99].

Predictive Equations

Energy requirements can be predicted with some accuracy. Estimations are based on measurements of energy expenditure in greater reference populations. Conceptually, estimates of energy requirements refer to the mean of groups and not to individuals. Predictive equations based on measurements in a considerable number of individuals have been developed for REE and also for TEE. Most of these equations are valid for adults. Alternatively, since patients in an ICU environment are rarely in a basal state, Kinney et al. have defined REE as the measured energy expenditure in a quiet supine individual. PBMR of assumed (non-measured) REE in ventilated, critically ill children, has usually been calculated using the Talbot’s tables, Harris-Benedict, Caldwell-Kennedy, Schofield, Food and Agriculture/World Health Organization/United Nation Nation, Maffeis, Fleisch, Kleiber, Dreyer, and Hunter equations, using the actual and ideal weight [100].

The formulae most frequently used in practice (e.g. the FAO/WHO/UNU prediction equations or Schofield’s formulae) are based on measurements in considerable numbers of participants (i.e. more than 7,500 3–18-year-old children in the case of the FAO/WHO/UNU who were investigated between 1910 and 1980 in different areas all over the world) [101]. For children and adolescents a sufficient database on REE has only recently been established [102]. Henry et al. developed new equations to estimate REE in children aged 10–15 years [103]. These equations were based on measurements of REE by indirect calorimetry in 195 school children (40% boys, 60% girls). Sex, weight, height, puberty stage and skinfolds were used to develop more specific regression equations. In adults, and probably in adolescences, the
predicted basal metabolic rate (PBMR) is a function of sex, age, height, and weight and can be calculated using the Harris-Benedict equations [104]. It has been suggested that until more accurate prediction equations are developed, the following should be utilized: Schofield-HW equation [105] for field studies with a mixed population of obese and non-obese children and adolescents; the FAO/WHO/UNU equation in girls; and the Schofield-W equation in non-obese children [106]. Corresponding Predicted Energy Expenditure (PEE) is estimated by PBMR multiplied by stress-related correction factors (Table 42.4). In critically ill children PBMR and PEE are often obtained according to FAO/WHO/UNU, Schofield-HW, and Seashore [107] equations and in adolescents after the Harris-Benedict equations [108].

Lessons Learned From Adult Studies

As shown recently, seven prediction equations applied to critically ill patients were rarely within 10 % of the measured REE [109]. In 34 mechanically ventilated cancer adult patients the Harris-Benedict PBMR without added stress and activity factors correlated better with measured REE than did the clinically estimated PEE based on recommendations of the American Society for Parenteral and Enteral Nutrition [110]. Thus indirect calorimetry is now suggested as the method of choice to estimate caloric requirements in critically ill, mechanically ventilated adult patients [111].

Current clinical practice guidelines suggest that an adequate energy goal to be monitored for most ICU patients is approximately equivalent to the measured or estimated REE multiplied by 1.0–1.2 [112]. Although, an alternative method is to initially use 20–25 kcal per kilogram of body weight as the total caloric target range for most adults in the ICU [113], a REE monitoring period of about 12 min for patients on controlled ventilation and 21 min for those on assisted mode was found to be enough for a successful daily REE estimation in the majority of cases (difference between TDEE and REE <5 %) [45]. In addition, it has been shown that indirect calorimetry with 5-min steady state test correlated very well with the 30-min steady state test in both mechanically ventilated and spontaneously breathing patients [114]. A 5-min period of measurement, if variation in that measurement is less than 5 % [115], or multiple short measurement periods (twice 15 min) or a single 20-min measurement have also been shown accurate in approximating TDEE [116]. Later in the period of hospitalization multiple factors influence the REE and due to these factors, there can be a significant variability in the daily REE, ranging from 4 to 56 %. Occasionally, attention to the RQ has been considered important in roughly evaluating substrate utilization and/or nutritional support and in determining overfeeding and underfeeding [117].

The Pediatric Experience

The unreliability of prediction equations to determine caloric requirements in ventilated, critically ill children is well established. Obesity, malnutrition, dehydration, excess body water, or population differences may impose difficulty in accurately monitoring body weight, height or other variables used in the prediction equations [111]. In particular, most of the predictive equations overestimate REE in critically ill children during the early post-injury period [83]. Similarly, recommended daily allowances and energy expenditure predicted by using a stress-related correction to the PEE grossly overestimate REE [98, 100]. In fact, in critically ill mechanically ventilated children, REE is close to PBMR and in many patients it is lower than PBMR and associated with higher morbidity [98]. Since a proportion of children do not become hypermetabolic during the acute phase of critical illness [98], agreement between REE and PEE remains broad [118, 119], confirming therefore that PEE equations are inappropriate for use in critically ill children [120, 121]. Although none of the remaining methods stood out as being more precise, the recommended dietary allowance for energy has been shown to be the least accurate and differed significantly even from the other predictive methods, overestimating energy expenditure in 50 of 52 children [122]. In young children (birth to 3 years) with failure to thrive WHO, Schofield weight-based, and Schofield weight- and height-based equations were all within 10 % accuracy <50 % of the time [123]. Agreement between measured resting energy expenditure and equation-estimated energy expenditure was poor, with mean bias of 72.3 ± 446 kcal/day (limits of agreement −801.9 to +946.5 kcal/day).

Besides disparity between equation-estimated PEE, REE, and TDEE among critically ill children, a high incidence of underfeeding or overfeeding and a wide range of metabolic alterations were also recorded [124], strongly suggesting that nutritional repletion should be ideally based on indirect calorimetry. Hopefully, targeted indirect calorimetry on high-risk patients selected by a dedicated nutrition team may prevent cumulative excesses and deficits in energy balance [124].

Body-Composition Tests

Body-composition methods, such as nuclear magnetic resonance, whole-body conductance and impedance, neutron activation, hydrodensitometry and other techniques, have been evaluated as additional nutritional assessment tools in healthy populations and in athletes [125]. Except for a few studies from investigative centers, very little research has been done to prove the utility of these methods in sick patients. It is extremely difficult to perform these tests in bedridden children, those who are connected to ventilators,
Table 42.4  Equations used to estimate PBMR and PEE

1a. **Harris-Benedict equation**: (kilocalories/day) (after age 15) [204]
Males: \(66.473 + (13.7516 \times Wt) + (5.0033 \times Ht) − (6.755 \times Age)\)
Females: \(665.0955 + (9.5634 \times Wt) + (1.8496 \times Ht) − (4.6756 \times Age)\)

1b. \(\text{PEE} = \text{PBMR} \times \text{correction factor for stress (1.4–2.0)}\)

| Stress components | % |
|-------------------|---|
| Elevated body temperature (per °C above 37 °C) | 12 |
| Severe infection/sepsis | 10–30 |
| Recent extensive operation | 10–30 |
| Fracture/trauma | 10–30 |
| Burn wounds | 50–150 |
| ARDS | 20 |

2a. **FAO/WHO/UNU equation**: (kilocalories/day)

| Age | Equation |
|-----|----------|
| <3 years | Boy\(\sim(60.9 \times Wt) − 54\) |
| | Girl\(\sim(61 \times Wt) − 51\) |
| 3–10 years | Boy\(\sim(22.7 \times Wt) + 495\) |
| | Girl\(\sim(22.5 \times Wt) + 499\) |
| 10–18 years | Boy\(\sim(17.5 \times Wt) + 651\) |
| | Girl\(\sim(12.2 \times Wt) + 746\) |

3a. **Schofield – WH [204] equations** (MJ/day) (1 kcal = 4.186 kJ)

| Age | Equation (boy) | Equation (girl) |
|-----|----------------|-----------------|
| <3 years | \(\sim(0.0007 \times Wt) + (6.349 \times Ht) − 2.584\) | \(\sim(0.068 \times Wt) + (4.281 \times Ht) − 1.730\) |
| 3–10 years | \(\sim(0.082 \times Wt) + (0.545 \times Ht) + 1.736\) | \(\sim(0.071 \times Wt) + (0.677 \times Ht) + 1.553\) |
| 10–18 years | \(\sim(0.068 \times Wt) + (0.574 \times Ht) + 2.157\) | \(\sim(0.035 \times Wt) + (1.948 \times Ht) + 0.837\) |

2b–3b. Correction factors (% of PBMR added to PBMR)

| Condition | Correction |
|-----------|------------|
| Elevated temperature | +12 % per °C above 37° |
| ARDS | +20 % |
| Sepsis | +10–30 % depending on severity |
| Trauma | +10–30 % depending on severity |
| Surgery | +10–30 % depending on severity |

4a–b. **Seashore’s equation** for PBMR and PEE (kilocalories/day) (infants and children up to age 15)

Estimation of energy requirements

| PBMR | Add |
|------|-----|
| \([55 − (2 \times \text{Age in years})] \times \text{Weight in kg}\) | |
| **Maintenance**:<sup>a</sup> | PBMR + 20 % |
| **Activity**:<sup>b</sup> | PBMR + 0–25 % |
| **Sepsis**: | PBMR + 13 % for each 1 °C above normal |
| **Simple trauma**: | PBMR + 20 % |
| **Multiple injuries**: | PBMR + 40 % |
| **Burns**: | PBMR + 50–100 % |
| **Growth and anabolism**:<sup>c</sup> | PBMR + 50–100 % |

5a. **Henry’s regression formulae** for estimating REE (kilojoules per day):

| Boy | \(Wt \times 66.9 + 2876\) |
|-----|--------------------------|
| Girl | \(Wt \times 47.9 + 3230\) |

<sup>Ht</sup> Height in cm, <sup>Wt</sup> weight in kilograms, <sup>Age</sup> age in years, °C degree centigrade, <sup>PBMR</sup> predicted basal metabolic rate, <sup>PEE</sup> Predicted Energy Expenditure, <sup>WHO</sup> Food and Agriculture Organization/World Health Organization/United Nations University equation, <sup>MJ</sup> Megajoules, <sup>kj</sup> kilojoules, <sup>kcal</sup> kilocalorie, <sup>ARDS</sup> Acute Respiratory Distress Syndrome, <sup>F</sup> female, <sup>M</sup> male

<sup>a</sup>Includes specific dynamic action and amount of energy needed for equilibrium in the resting but awake state with minimal muscular movements

<sup>b</sup>0 % for comatose state, 25 % for hospitalized child who ambulates two to three times a day, 50 % for active non-hospitalized child

<sup>c</sup>100 % for growth in infancy and adolescence; 50 % for the years in between
and those who have fluid imbalances. For example, hydrodensitometry, which some consider the ‘gold standard’ for body-composition analysis, would be impossible to perform in bedridden patients, as it requires total immersion of the child in water.

**Dual-Energy X-Ray Absorptiometry**

The dual-energy X-ray absorptiometry (DEXA) designed for the diagnosis of osteoporosis provides accurate information about the body compartments (fat, lean mass and bone) and is considered a referential method for this assessment [126]. DEXA has been used in conjunction with gamma in vivo neutron activation analysis, tritiated water dilution, total body potassium and calorimetry to assess body composition and energy expenditure in a small group of patients with blunt trauma [127]. During the first 25 days, a relationship was demonstrated between the changes in body compartments and metabolic requirements.

**Bioelectrical Impedance: Magnetic Resonance Spectroscopy**

Bioelectrical impedance is a simple, noninvasive, easy and low-cost technique; monitoring results of the body composition in adults and children are consistent [128]. Although it has been shown that bioelectrical impedance is good for clinical studies in patients in intensive-care units, it has not been proved very accurate in individual cases [129]. Especially, this method has been studied in patients on dialysis, because of the difficulty to perform anthropometric and laboratorial nutritional assessment of such patients [130]. However, although it was demonstrated that the electrical bioimpedance was more sensitive to body changes than the anthropometric measurements [131], for many PICU patients, bioelectrical impedance may not be useful as a nutritional monitoring tool because of fluctuation in fluid volumes and changing body weight [132].

**Doubly Labeled Water Technique**

Another approach to measure TEE is an isotope dilution, the so-called doubly labeled water (DLW) technique. DLW is based on the differences in turnover rates of $^2$H$_2$O and H$_2^{18}$O in body water. After equilibration, both $^2$H and $^{18}$O are lost as water whereas only $^{18}$O is lost by respiration as carbon dioxide. The difference in the rate of turnover of the two isotopes can be used to calculate the VCO$_2$. Assuming a mean respiratory quotient (i.e. VO$_2$/VCO$_2$) of 0.85, the VO$_2$ and thus energy expenditure can then be calculated from VO$_2$ and VCO$_2$. The DLW technique is validated against indirect calorimetry and is now considered to be a gold standard for measurements of TEE under free-living conditions.

It is clear that $^2$H$_2$O can now be used to address questions related to carbohydrate, lipid, protein and DNA synthesis. Using this novel tracer method, it is thus possible to elucidate new, highly relevant, knowledge regarding health and disease [133]. Especially, the DLW method is most convenient in children because it places low demands on the participant’s performance (only drinking a glass of water and the collection of some urine samples). Sources of error are analytical errors in the mass spectrometric determination of isotopic enrichment, biological variations in the isotope enrichment, isotopic fractionation during formation of carbon dioxide and during vaporization of water, the calculation of total body water and the assumption or calculation of the 24 h respiratory quotient.

**Whole-Body Counting/Neutron Activation**

The elements K, N, P, H, O, C, Na, Cl, and Ca can be measured with a group of techniques referred to as whole-body counting/in vivo neutron activation analysis. Whole-body counting neutron activation methods are important because they provide a means of estimating all major chemical components in vivo. These methods are considered the standard for evaluating the body-composition components of nutritional interest, including body-cell mass, fat, fat-free body mass, skeletal muscle mass, and various fluid volumes [134]. Shielded whole-body counters can count the $\gamma$-ray decay of naturally occurring $^{40}$K, but there is no experience in critically ill settings.

**Miscellaneous Tests Indicating Nutritional Status/Stress Response**

This section covers different tools that have been used to assess nutritional status but which have either had their capacity to monitor malnutrition questioned or have been found to be too difficult to perform routinely in a clinical setting [135].

**Comparison with Recommended Dietary Allowances**

The Recommended Dietary Allowances (RDA) is the most commonly used reference allowances in the pediatric population. These recommended levels for nutrient intake are estimated to meet the nutritional needs of practically all
healthy children. Caloric allowances are estimated using the tables proposed by the Food and Nutrition Board of the Institute of Medicine [136], and Dietary Reference Intakes [137]. Although the upper intake level is the appropriate Dietary Reference Intake to use in assessing the proportion of a group at risk of adverse health effects [137], RDA is inappropriate to assess the nutrient adequacy of groups such as the critically ill [98].

**Routine Laboratory Tests**

The routine electrolyte, mineral (calcium, phosphorus and magnesium) and triglyceride laboratory tests monitoring are not related to anthropometric rates, although they are important to follow nutritional protocols, especially those of parenteral nutrition, and determine specific nutritional deficiencies [138]. Serum cholesterol levels lower than 160 mg/dl have been considered a reflection of low lipoprotein and thus of low visceral protein levels [139]. Hypocholesterolemia, however, seems to occur late in the course of malnutrition, limiting the value of cholesterol as a screening tool. Selenium, Zinc, Chromium, Iodine, Iron, Copper and vitamin (A, B2, B6, B12, E) deficiencies, which are very common in patients belonging to low socioeconomic class in developing countries, may inhibit T4 to T3 conversion and lead to functional hypothyroidism and severe hypometabolism (extremely low REE) [140].

**Glucose Control**

Stress-induced hyperglycemia has been well described in the literature in the acutely ill patient population owing to insulin resistance and increase gluconeogenesis [141]. In fact, insulin resistance is an adaptive mechanism that prioritizes utilization of energy for immune response in the presence of infection or injury [142]. In the presence of fatty acids mitochondrial pathogen associated molecular patterns (PAMPs) and danger associated molecular patterns (DAMPs) receptors, acting as nutrient sensors, may induce an inflammatory cascade that affects insulin signaling with development of insulin resistance [142]. In a prospective, observational cohort study in children with meningococcal sepsis and septic shock [143] hyperglycemia (glucose >8.3 mmol/l) was present in 33% of the children on admission whereas 62% of the hyperglycemic children had overt insulin resistance (glucose >8.3 mmol/l and homeostasis model assessment (HOMA) [β-cell function <50%], 17% had β-cell dysfunction, and 21% had both insulin resistance and β-cell dysfunction. Normalization of blood glucose levels occurred within 48 h, typically with normal glucose intake and without insulin treatment [143].

In the face of stress-induced hyperglycemia, the provision of dextrose infusion in the form of parenteral nutrition (PN) can further exacerbate hyperglycemia, which can lead to increased infectious complications and increased mortality [144]. Landmark trials in adults by Van den Bergehe et al. suggested that targeting normoglycemia (a blood glucose concentration of 80–110 mg/dL [4.4–6.1 mmol/L]) reduced mortality and morbidity [145], but other investigators have not been able to replicate these findings. Recently, the international multicenter Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study reported increased mortality with this approach, and recent meta-analyses do not support intensive glucose control for critically ill patients [146]. Although the initial trials in Leuven produced enthusiasm and recommendations for intensive blood glucose control, the results of the NICE-SUGAR study have resulted in the more moderate recommendation to target a blood glucose concentration between 144 and 180 mg/dL (8–10 mmol/L) [146]. Thus, it was recently shown that the incidence of hypoglycemia was significantly higher with intensive insulin therapy (absolute risk increase 23.5%, number needed to harm 4) [147]. Studies in children also suggest that special consideration should be given to the safety of the youngest patients given their higher risk of hypoglycemia if an investigation of tight glycemic control is performed [148]. Especially high rates of hypo-/hyperglycemia are noted in sicker patients and in those requiring more therapeutic interventions. Adding to this skepticism, it has been recently shown that the current recommended parenteral amino acid intakes are insufficient to maintain protein balance in insulin-resistant patients during tight glucose control [149]. Concerns are raised that high amino acid intakes may exacerbate insulin resistance and favor gluconeogenesis, thereby offsetting their beneficial effects on protein balance by enhancing endogenous glucose production and lipolysis [149].

**Cell-Mediated Immunity and Lymphopenia**

Total lymphocyte counts and impaired cell-mediated immunity have been correlated with nutritional status. These may be difficult to interpret in children, given the variable response of an immature immune system. Additionally, numerous other factors, including sepsis, cancer, collagen vascular diseases, uremia, hepatic dysfunction, and drug administration may impair cell-mediated immunity. Quantification of T-lymphocyte subpopulations, with particular reference to killer cells, may be more specific [150]. However, in the critically ill child, many factors can alter delayed cutaneous hypersensitivity and render it useless in assessing the state of nutrition. Therefore, immunity is neither a specific indicator of malnutrition nor is it easily studied.
Delayed cutaneous hypersensitivity, which results from the inoculation of antigens such as Candida spp., Trichophyton spp., or the mumps virus, has been used to measure immunological competence and, indirectly, nutritional status. These tests are influenced by a number of other situations that cause anergy, such as various drugs (especially steroids and antirejection drugs), the presence of infection, malignancy, and burns, among others [151].

**Functional Tests of Malnutrition**

The use of exercise tolerance by ergometers and measurement of heart rate are useful for population studies but difficult for sick patients with cardiorespiratory impairment and for children in intensive care. Grip strength, respiratory muscle strength, and function by electrical stimulation all demonstrate changes with nutrition. Among them, relaxation rate of single twitches may be a simple, non-invasive, and reproducible way of studying function in sick patients [152].

**Clinical Data Impacting Nutrition and Metabolic Response Monitoring**

**Cytokines**

It is generally accepted that the degree of catabolism of the acutely ill child reflects the degree of stress of the individual, since with more stress there is more neurohumoral activation and more muscle proteolysis [153]. It is known that during stress, interleukin-6 increases plasma arginine vasopressin, indicating that this cytokine has a role in the inappropriate secretion of antidiuretic hormone that can occur in patients with infectious or inflammatory diseases or trauma [154].

**Counter-Regulatory Stress Hormones**

In addition to their short-term effects on the hypothalamus, the inflammatory cytokines can apparently stimulate pituitary corticotrophin and adrenal cortisol secretion directly by interacting with these tissues [155]. Accordingly, it has been shown that hormonal acute stress responses may explain the shift toward fat oxidation and either gluconeogenesis or impaired peripheral carbohydrate uptake, but does not quantitatively affect energy expenditure [156]. Similarly, glucocorticoids may increase nitrogen wasting in head-injured patients without increasing metabolic rate. Although counter-regulatory stress hormones do not cause hypoalbuminemia in healthy volunteers, they do produce protein catabolism [157]. It has been postulated that stress hormones alter the configuration of ribosomes in muscle, decreasing protein synthesis, inducing proteolysis, and fluxing essential amino acids for high priority use in other tissues [158]. Another study has also provided evidence that nutrition intervention may modulate cortisol-binding globulin and the concentration of free circulating cortisol after a severe stress [159]. On the contrary, supplemental insulin may have provided mild improvement in nitrogen utilization, probably related to the insulin effect on the skeletal muscle. This hormone is known to increase protein synthesis in skeletal muscle [160] and decrease degradation in liver and muscle [161].

**Drugs Influencing Monitoring**

Catecholamines are primary mediators of elevated energy expenditure and tissue catabolism in critically ill patients. Systemic corticosteroids also induce a hypermetabolic response and increase protein catabolism. Long-term beta receptor blockade was capable of decreasing REE and tissue catabolism [162]. This effect was associated with an improvement in both muscle protein balance as well as body cell mass conservation. It was also found that propranolol induced an increase in intracellular recycling of free amino acids. Opiates, muscle relaxants, and barbiturates variably significantly reduce energy expenditure [163, 164].

**Critical Illness**

Liver dysfunction is common in critically ill patients, caused by shock or hypodynamic circulatory states, intra and extra-abdominal infections, drugs, infectious hepatitis, as well as metabolic and nutritional causes. The metabolic changes induced by critical illness and inadequate nutritional supply foster the development of fatty liver. The increased release of stress hormones, proinflammatory cytokines and other inflammatory mediators, as well as insulin resistance, are hallmarks of the physiological response to injury. Initial assessment of these critically children would probably show characteristic metabolic changes, such as hyperglycemia, increased hepatic glucose production, increased lipolysis and stimulation of the de novo lipogenesis pathway.

Excessive fluid therapy has emerged as a new mechanism of gastrointestinal failure in critically ill patients during the past few years [165]. While timely administration of fluids is lifesaving, positive fluid balance after hemodynamic stabilization may affect the PICU course in children who do not receive renal replacement therapy by impacting organ function and negatively influencing important outcomes in critically ill patients [166]. More specifically, excessive fluid administration may harm the abdominal organs, because it increases...
intra-abdominal pressure and fosters the development of abdominal compartment syndrome. The latter is characterized by high intraabdominal pressure and decreased abdominal perfusion pressure, and is associated with signs of abdominal organ hypoperfusion, multiple organ failure, and decreased survival. Monitoring of patients with major burns or trauma shows that excessive fluid therapy exerts deleterious effects on the gut, delaying the return of gastrointestinal functions and preventing the use of early enteral feeding [167].

**Nutrition Monitoring**

**Early Nutrition Monitoring**

Among patients who have protein-energy malnutrition at the time of admission to the ICU and enteral feeding is not possible, the American clinical practice guidelines suggest that PN should be initiated without delay [168]. Although the time frame for initiation of PN to supplement patients who are receiving inadequate EN or no EN is not specified by the A.S.P.E.N. pediatric critical care nutrition guidelines [169], the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends PN in 24–48 h if EN will be contraindicated for 3 days, or after 48 h to supplement insufficient EN in critically ill adults [112]. PN infusion protocols, therefore, should always be in place to assure safe administration and close monitoring for the metabolic complications of refeeding syndrome, tolerance of electrolytes and macronutrients, as well as glucose control is necessary; [170] monitoring of specific micronutrients is crucial in long-term PN usage. Since the use of EN as opposed to PN results in an important decrease in the incidence of infectious complications in the critically ill and is less costly, should be the first choice for nutritional support in the critically ill [171]. Fortunately, most critically ill patients who require specialized nutrition (85–90 %) can be fed enterally through gastric or intestinal tubes [166], whereas increases of caloric intake during the acute phase of a critical illness are well tolerated in children and may approach PBMR by the second day and PEE by the fourth day [4].

The refeeding syndrome is of particular importance to critically ill patients, who can be moved from the starved state to the fed state rapidly via enteral or parenteral nutrition, but is often under-appreciated [172]. There are a variety of risk factors for the development of the refeeding syndrome, but all are tied together by starvation physiology. Complications of the refeeding syndrome can include hypophosphatemia, hypokalemia, hypomagnesemia, rapid fluid shifts, peripheral edema, and sometimes thiamine deficiency, heart failure, respiratory failure, and death [173]. The most commonly seen abnormality is hypophosphatemia, which should be monitored very closely and replenished as needed to avoid heart failure, arrhythmia, and life-threatening respiratory failure [174]. An initial phosphate depleted state is further exacerbated by the introduction of dextrose infusion. Insulin leads to an increase in cellular uptake of phosphate, as well as increased synthesis of ATP, 2,3DPG, and creatine phosphokinase, all leading to decreased serum phosphorus levels. In addition, accelerated carbohydrate metabolism increases the body’s use of thiamine and can precipitate symptoms and signs of thiamine deficiency [175].

**The Immunonutrition Question**

It is not known if a low plasma glutamine or selenium concentration is an independent prognostic factor for an unfavorable outcome in the PICU, so that their monitoring is not currently recommended. Recently, a reduced adult ICU mortality was observed during intravenous glutamine supplementation in a broad range of ICU patients [176]. However, no change in the SOFA score was recorded and mortality did not differ at 6 months. Similarly, in a randomized, double blinded, factorial, controlled multicenter trial, the primary (intention to treat) analysis showed no effect on new infections or on mortality when PN was supplemented with glutamine or selenium [177]. Only patients who received PN supplemented with the antioxidant selenium for ≥5 days did show a reduction in new infections.

In a blinded, prospective, randomized, controlled clinical trial, nitrogen balance, nutritional indices, antioxidant catalysts, and outcome were compared in critically ill children given an immune-enhancing formula (IE) or conventional early EN (C) [178]. Although it had a favorable effect on nitrogen balance, nutritional indices and antioxidant catalysts, it did not influence outcome hard endpoints. In group IE nitrogen balance became positive by day 5 compared with group C in which the mean nitrogen balance remained negative (p<0.001). Also, early IE nutrition was shown to modulate cytokines in children with septic shock, but again there was no evidence that this immunomodulation has any impact on short-term outcome [179]. On day 5 IL-6 levels were significantly lower and IL-8 significantly higher in the IE than in the C group, whereas after 5 days of nutritional support a significant decrease in IL-6 levels was recorded only in group IE. In another randomized study in children with severe head injury, nitrogen balance became positive in 30.8 % of patients in the C group and in 69.2 % of patients in the IE group by day 5 [180]. It was also shown however, that although it decreased interleukin-8 and gastric colonization, it was not associated with additional advantage over the one demonstrated by regular early enteral nutrition.
Protocols in the Role of Monitoring

To account for alterations in energy metabolism, caloric amounts equal to the measured REE \[167, 181\] or, if not available, to the PBMR should be provided during the acute metabolic stress period \[4\]. Especially, targeted indirect calorimetry may allow detection of an altered metabolic state energy imbalance in a subset of critically ill children at a high risk of overfeeding, such as those with existing malnutrition on admission, prolonged stay in the ICU, and those who are unable to wean from mechanical ventilatory support, having therefore a role in optimizing energy intake in the PICU \[124\]. On the other hand, inadequate nutritional intake in the PICU, often due to fluid restriction, further leads to protein and energy deficits, especially early after admission \[182\]. Other factors that hinder adequate nutrition are impaired intracellular insulin signaling \[183\], impaired glucose uptake \[184\] and reduced mitochondrial capacity during critical illness \[185\]. These factors are probably the reason why protein-energy malnutrition is observed in 16–24 % of critically ill children and is associated with adverse clinical outcome \[43, 186\].

Mechanically ventilated subjects are at the highest risk of EN interruptions. It was recently shown that avoidable EN interruption was associated with increased reliance on PN and impaired ability to reach caloric goal \[187\]. EN interruption, however, is frequently avoidable in critically ill children; knowledge of existing barriers to EN combined with institution of protocolized feeding approach may allow appropriate interventions to optimize nutrition provision in the PICU \[184\]. In a recent study aimed to assess the impact of enteral feeding protocols on nutritional support practices through a continuous auditing process over a defined period it was found that the time taken to initiate nutrition support was reduced from 15 to 4.5 h \[188\]. Simultaneously, an increase was documented in the percentage of patients receiving a daily energy provision of up to 70 % of the estimated average requirement, whereas the proportion of patients on parenteral feeds was reduced from 11 to 4 %. In a multicenter adult study, on average, protocolized sites used more EN alone (70.4 % of patients vs 63.6 %, \(p=0.0036\)), started EN earlier (41.2 h from admission to ICU vs 57.1, \(p=0.0003\)), and used more motility agents in patients with high gastric residual volumes (64.3 % of patients vs 49.0 %, \(p=0.0028\)) compared with sites that did not use a feeding protocol \[189\]. Importantly, in a 7-day prospective before–after study, early EN without residual gastric volume monitoring in mechanically ventilated adult patients improved the delivery of enteral feeding and did not increase vomiting or ventilator associated pneumonia \[190\]. Awaiting confirmatory studies before removing the residual gastric volume assessment from their ICUs, however, clinicians are advised to take guidance from published evidence-based guidelines \[191\].

Of equal significance of this therapeutic protocols strategy is also to avoid the provision of calories and nutritional substrates which the patient cannot probably handle in order to maintain the metabolic homeostasis of the acute stress response \[2\]. An increase of caloric intake during the acute phase of a stress state has been shown to be feasible and well tolerated in non-cardiac critically ill children \[5\]. Also, increased protein and energy intakes have been recommended in critically ill infants with viral bronchiolitis \[99\]. However, future studies will need to examine the safety of such protocols and the impact of large cumulative energy excess on patient outcomes. In fact, many chronically ill children with malnutrition would be rather overfed (if their daily energy requirements were calculated based on PEE during acute illness) than underfed \[Fig. 42.2 \[192\]\]. Monitoring of energy expenditure, therefore, has been used to characterize alterations in metabolism accompanying critical illness and to provide accurate information necessary for appropriate nutritional repletion, including the type and amount of macronutrient substrates that exactly meets the patient’s energy requirements and avoids the complications of overfeeding \[193\]. Accordingly, it has been shown that when caloric intake was less than REE, mean substrate utilization was 48.6 % from lipid, 37.1 % from carbohydrate but, when it was greater than REE, mean substrate utilization was 83.3 % from carbohydrate and 16.7 % from protein \[60\].
Recent studies have shown that computerized information systems do improve nutritional monitoring (energy delivery and balance, protein and fat delivery), quality of nutrition, glucose control, and reduce nurse workload associated with the multiple balance calculations and ease visualization of events out of planned targets [194]. Overfeeding, particularly carbohydrate overfeeding, increases ventilatory work by increasing CO₂ production, can potentially prolong the need for mechanical ventilation, may increase the risk of infection secondary to hyperglycemia, and can impair liver function by inducing hepatic steatosis and cholestasis [195]. Azotemia can result from overzealous protein infusion, whereas fat-overload syndrome can result from either overall total calorie overfeeding, overfeeding of lipids, or both [196]. Algorithms to control glucose using insulin therapy and alterations in formula administration are intended to prevent hyperglycemia, under close glucose control, and increase synthesis of fatty acids from glucose and other non-lipid precursors in the liver and in peripheral tissues [197]. Parenteral intakes of essential and nonessential amino acids supplied to critically ill children are supplied in lower or higher amounts than the content of mixed muscle proteins or breast milk and are not based on measured requirements to maintain nutrition and functional balance and on knowledge of toxicity [198]. Instead, protocol-driven implementation of nutrition therapy by the third day of admission to the PICU with goal intake achieved by the end of the first week was recently shown to help preserve lean body mass in a group of children with a high prevalence of baseline malnutrition [33].

Monitoring the Metabolic Response

Acute stress may result in a substantial decrease of energy needs. The acute stress may induce a catabolic response that is proportional to the magnitude, nature, and duration of the injury. Increased serum counter-regulatory hormone concentrations induce insulin and growth hormone resistance, resulting in the catabolism of endogenous stores of protein, carbohydrate, and fat to provide essential substrate intermediates and energy necessary to support the ongoing metabolic stress response. During this catabolic response, somatic growth cannot occur and, therefore, the caloric allotment for growth, which is substantial in infancy, should not be administered. The intensive care environment is temperature-controlled, and insensible energy losses are substantially reduced and most patients are ventilated with heated, humidified air, thus reducing insensible energy losses by one third. In addition, children treated in the intensive care setting are frequently sedated and mechanically ventilated, so that their work of breathing and activity level are markedly reduced further lowering energy needs [199]. Similarly, various pharmacologic agents and the capacity of the patient to respond to the metabolic demands imposed by the injury might further alter the metabolic response [200].

Comparing simultaneous REE and PBMR recordings, patients may be classified as hypermetabolic, normometabolic, and hypometabolic when REE is >110, 90–110 % and, <90 % of the PBMR, respectively. Although sustained hypermetabolism has been reported for weeks after burn injury, REE peak returns to baseline within 12 h after some surgical procedures [201]. More studies in children [2, 118] and adults [202] have now verified results of a pioneer indirect calorimetry study reporting lack of hypermetabolic response during critical illness [4]. Using various equations to predict acute phase energy expenditure in mechanically ventilated children whose REE was continuously monitored through an E-COVX metabolic monitor, the mean REE/PBMR ratio was <1 in all but one (Fig. 42.3, G. Briassoulis et al. University of Crete, unpublished work). In a study examining the metabolic patterns in pediatric patients with critical illness, it was shown that the initial predominance of the hypometabolic pattern (48.6 %) declined within 1 week of acute stress (20 %), and the hypermetabolic patterns dominated only after 2 weeks (60 %) [185]. High IL-10 levels and low measured REE were independently associated with mortality (11.7 %), which was higher in the hypometabolic compared to other metabolic patterns. However, although in SIRS or sepsis the cytokine response was reliably reflected by increases in Nutritional Index and triglycerides, it was different from the metabolic (VO₂, VCO₂) or glucose response [201].

The SIRS elicited by peritonitis in mice was accompanied by mitochondrial energetic metabolism deterioration and reduced peroxisome proliferator-activated receptor gamma coactivator (PGC)-1alpha protein expression [203]. Because ATP production by mitochondrial oxidative phosphorylation accounts for more than 90 % of total oxygen consumption, a severe mitochondrial dysfunction implicating bioenergetic failure during stress might explain both: a predominant hypometabolic pattern and the raised tissue oxygen tensions in septic animals and human beings. Performing skeletal muscle biopsies on 28 critically ill septic patients within 24 h of admission to intensive care, Brealey et al. [204] showed that skeletal muscle ATP concentrations were significantly lower in patients with sepsis who subsequently died than in septic patients who survived and in controls and that complex I respiratory-chain activity had a significant inverse correlation with norepinephrine requirements and a significant positive correlation with concentrations of reduced glutathione and ATP. Electron paramagnetic resonance spectra analysis of the paramagnetic centres in the muscle confirmed that a decreased concentration of mitochondrial Complex I iron-sulfur redox centres is linked to mortality [205].
Conclusions

Nutritional monitoring should be an integral part of the care for every pediatric critically ill patient. The nutrition monitoring records the changing nutrition status of the critically ill child and facilitates the development of a nutrition care plan. However, there is little research in the area of pediatric nutrition monitoring upon which to formulate evidence based practice guidelines. A nutrition screen, incorporating objective data such as height, weight, arm circumference, triceps skinfold, primary diagnosis, and presence of co-morbidities should be a component of the initial evaluation of all pediatric patients in an intensive care setting. Following that, repeated anthropometric and laboratory markers must be jointly analyzed, but individually interpreted according to disease and metabolic changes, in order to modify and monitor the nutritional treatment. The recently revised national guidelines for adult and pediatric critical care have emphasized the importance of accurately measured energy expenditure in patients admitted to the intensive care unit. Increases of caloric intake during the acute phase of a critical illness are well tolerated in children and may approach PBMR by the second day and PEE by the fourth day. Over the course of the disease, it seems that the most practical tool is metabolic assessment based on the combination of indirect calorimetry, nitrogen balance, plasma proteins. Since the nutrition monitoring can be viewed as an ongoing process, particularly in the acute care setting, it provides accurate information necessary for appropriate nutritional repletion and helps avoiding the complications of under- and over-feeding. Accordingly, as part of the nutrition care process, the energy expenditure and metabolic monitoring using targeted indirect calorimetry, should be completed and updated at specific intervals, as warranted by metabolic alterations in the patient’s needs or condition.

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