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ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Energy

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Table: Recommendations for energy in parenteral nutrition (PN)

R 2.1	For calculation of resting energy expenditure (REE) the use of Schofield's equation for weight can be recommended (LOE 2+, GPP, conditional recommendation)
R 2.2	Total parenteral energy requirements of stable patients can be calculated from resting energy requirements with adding constants for physical activity, (catch-up) growth and adjusted for disease states that increase or decrease REE (LOE 2+ RG 0, conditional recommendation)
R 2.3	In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using indirect calorimetry is desirable (LOE 3, GPP, conditional recommendation)
R 2.4	On the first day of life of premature neonates, at least 45–55 kcal/kg/day should be provided to meet minimal energy requirements (LOE 2+, RG 0, strong recommendation)
R 2.5	After the initial postnatal nadir of weight loss, aiming for a weight gain of 17–20 g/kg per day in very low birth weight infants is recommended to prevent dropping across weight centiles i.e. growth failure (LOE 2+, RG 0, strong recommendation)
R 2.6	In very low birth weight infants, to approximate intra-uterine lean body mass accretion and growth, energy intakes of 90–120 kcal/kg/day should be provided (LOE 2++, RG B, strong recommendation)
R 2.7	Reasonable parenteral energy requirements after the acute phase of critical illness can be estimated from REE (LOE 2−, RG 0, conditional recommendation)
R 2.8	In the stable phase of critical illness energy requirements can be increased by ~1.3 times REE to enable growth and catch-up growth and further increased in the recovery phase (LOE2−, RG 0, conditional recommendation)
R 2.9	Withholding PN for 1 week in critically ill children while giving micronutrients can be considered (LOE1+, RG B, conditional recommendation)

2. Introduction

Energy supply needs to meet the nutritional needs of the patient which include basal metabolic rate, physical activity, growth, diet induced thermogenesis and correction of pre-existing malnutrition. Excess energy intake may increase the risk of complications both in the short and longer term, such as hyperglycaemia which may increase the risks of complications such as infection, impaired liver function due to steatosis, or abnormal metabolic programming [1]. Inadequate energy supply may result in impaired growth, loss of body tissue including lean mass, sub-optimal motor, cognitive and behavioural development, and impaired immunity, and may also increase the risks of serious morbidity and mortality in infants and children [2].

Protein intake recommendations aim to meet needs for lean mass accretion and not to provide energy for metabolic functioning, however energy intake recommendations presented include energy intake from all sources including proteins, lipids and carbohydrates. Inadequate energy provision may therefore limit growth (or other outcomes) because protein is used as an energy source (through carbon metabolism) and no longer available for accretion into body tissue. Because splanchnic metabolism contributes significantly to whole body energy and protein turnover, and because some nutrients are excreted in the stool, energy requirements are generally 10–20% higher when fed primarily via the enteral compared to the parenteral route.

An adaptation of Atwater factors (energy content of protein, carbohydrate and lipid correspond to 4, 4 and 9 kcal/g respectively) is useful in clinical practice to calculate metabolisable nutritional energy intake. However, the energy available from macronutrients differs between parenteral and enteral sources. The gross energy content of 1 g of amino acid (AA, 4.8 kcal/g) is about 10% lower than that of 1 g of protein (5.4 kcal/g). In addition, the energy provided after oxidation of 1 g of AA into urea is 3.75 kcal whereas the energy of 1 g AA stored in protein is 4.75 kcal, a value identical to gross energy [3–5]. Gross and metabolisable energy content of glucose (3.75 kcal/g) is less than that of more complex carbohydrate (4.2 kcal/g). Lipid metabolisable energy content of intravenous lipid emulsions (ILE) is similar to gross energy (9.3 kcal/g) but could be lower when ILE contain medium chain triglycerides (MCT) and higher for long chain fatty acids (LC-FAs) [3,4]. When glycerol energy content is added to lipid content, energy content of ILE is around 10 kcal/g. These differences are not easy to incorporate into clinical practice. This explains why energy requirements in parenteral nutrition (PN) are close to that in enteral nutrition and Atwater factors are frequently used to calculate energy intakes (4 kcal/g for protein and carbohydrate and 9 kcal/g for lipid) [6,7].

It is not possible to determine precise individual energy needs in clinical practice, because the outcomes of interest are multiple (growth, repair and support for functional outcomes) and cannot be determined in the short term. In clinical practice, it is impossible to determine whether energy intakes may be, for example, 10–20% above or below actual needs.

3. Components of energy needs

Total energy needs of a healthy individual are the sum of different components which can be divided into 4 main subgroups: basal metabolic rate (BMR), diet induced thermogenesis (DIT), physical activity (PA) and growth. Energy needs are affected by several factors including genetics, nutritional status, underlying diseases, energy intake, energy losses, age and gender.

BMR is the amount of energy needed for maintaining the vital processes of the body. It is measured in a recumbent position, in a thermo-neutral environment after 12–18 h fast, just when the individual has awakened before starting daily activities. In practice, this is impossible to measure in infancy and most of childhood, so resting energy expenditure (REE) is usually measured instead of BMR and does not differ by more than 10% from BMR. REE can be measured in a thermo-neutral environment, ideally before feeding or after a period of fasting. REE is increased in conditions such as inflammation, fever and chronic diseases and is decreased in hypothermia.

DIT reflects energy expended during food digestion, absorption and tissue synthesis and is affected by the route of substrate administration (oral, enteral or parenteral). DIT usually accounts for about 10% of daily energy needs [8].

PA requires energy, and whilst this is minimal in preterm infants, in older children it accounts for a large proportion of total energy expenditure (TEE). However, TEE of a hospitalized child lying in bed is reduced by lack of PA. To account for energy needs related to activity, different metabolic constants (physical activity levels, PALs) have been suggested for multiplication of BMR: 1.0 for sleeping, 1.2 for lying awake and for sitting quietly, and 1.4–1.5 for standing quietly or sitting activities [9]. A PAL of 1.7 reflects a moderate level of activity for healthy children and adolescents and PAL levels of 1.5 and 2.0 are estimates for light and vigorous levels of activity [10]. Most children receiving PN will have low PALs.

The energy cost of growth as a percentage of total energy requirements decreases substantially during the first year of life from around 35% at 1 month to 3% at 12 months of age. This is approximately equivalent to 175 kcal/day at 0–3 months to 60 kcal/day at 4–6 months and 20 kcal/day for 6–12 months, and remains low until the pubertal growth spurt, when it increases [9]. The energy cost of growth in healthy children and adolescents is 20 kcal/day increasing to 30 kcal/day at peak growth velocity.

Children recovering from malnutrition need extra calories to correct their growth deficits i.e. weight and height. In such cases the additional energy needs for catch up can be estimated based on the difference in the centile position on a growth chart prior to the onset of illness. Alternatively, calculation may be based on the

actual weight multiplied by 1.2–1.5, or more in severe cases of failure to thrive, although this is rarely the predominant nutritional aim during the period of PN.

4. Estimating and calculating energy needs

R 2.1	For calculation of REE the use of Schofield's equation for weight can be recommended (LOE 2+, GPP, conditional recommendation, strong consensus)
R 2.2	Total parenteral energy requirements of stable patients can be calculated from resting energy requirements with adding constants for physical activity, (catch-up) growth and adjusted for disease states that increase or decrease REE (LOE 2+ RG 0, conditional recommendation, strong consensus)
R 2.3	In a subgroup of patients with suspected metabolic alterations or malnutrition, accurate measurement of energy expenditure using indirect calorimetry is desirable (LOE 3, GPP, conditional recommendation, strong consensus)

Energy needs can be assessed using techniques such as indirect calorimetry and double labelled water, or calculated based on standard equations. The ideal method needs to account for factors such as PAL, disease state, need for catch-up, and ongoing growth. The differences in actual energy need versus calculated need based on general equations arise from additional factors which have to be taken into account such as energy losses from wounds, malabsorption, losses from diarrhoea, and sub-optimal body composition. In addition, the different routes of supplementation, oral/enteral or parenteral influence the total energy need.

Different equations to calculate REE, BMR and TEE have been developed. The main predictor for each component of EE is body weight, but it is important to note that height also accounts for some of the variability in energy needs [11]. Practitioners need to recognise that the estimation of EE using these standard equations can be unreliable but may be useful if indirect calorimetry is not feasible or available. However, in children with suspected metabolic problems or severe malnutrition, accurate measurement of EE using indirect calorimetry is desirable. REE should be measured in young infants and children with moderate to severe failure to thrive when knowledge of caloric needs is required for optimal clinical care. The Schofield-equation using weight and height to calculate REE was least likely to underestimate REE compared to measured REE and is therefore preferred [12]. Total parenteral energy requirements of stable patients can be calculated from resting energy requirements (Table 1) with adding constants for PA, catch-up growth and disease factors or from doubling the resting energy requirements [13].

The energy requirements of infants and children in the previous ESPGHAN guideline of 2005 were derived from the 1985 FAO/WHO/UNU recommendations while current recommendations are derived from the 2004 FAO/WHO/UNU recommendations [9]. On average the energy recommendations were substantially lower and taking into account the fact that no energy has to be added for enteral absorption of feeding (5–10%), the current PN energy recommendations are thus lower compared with these of 2005. Table 2 shows absolute values for energy requirements in the acute, stable and recovery phase for different age groups. The recommendations in the acute and stable phase have to applied in the critical care setting, the recommendations in the recovery phase can be applied for all other patients.

Table 1
Schofield's equations for calculating REE (kcal/d).

Age	Boys	Girls
0–3 year	59.5 × (weight in kg) − 30	58.3 × (weight in kg) − 31
3–10 year	22.7 × (weight in kg) + 504	20.3 × (weight in kg) + 486
10–18 year	17.7 × (weight in kg) + 658	13.4 × (weight in kg) + 692

Table 2
Energy requirements (kcal/kg/day) for parenteral nutrition in different phases of disease.

	2005	2016 Recovery phase	2016 Stable phase	2016 Acute phase
Preterm	110–120	90–120		45–55[a]
0–1	90–100	75–85	60–65	45–50
1–7	75–90	65–75	55–60	40–45
7–12	60–75	55–65	40–55	30–40
12–18	30–60	30–55	25–40	20–30

[a] Recommended energy intake during the first day of life.

5. Special considerations

5.1. Premature infants

R 2.4	On the first day of life of premature neonates, at least 45–55 kcal/kg/day should be provided to meet minimal energy requirements (LOE 2+, RG 0, strong recommendation, strong consensus)
R 2.5	After the initial postnatal nadir of weight loss, aiming for a weight gain of 17–20 g/kg per day in very low birth weight infants is recommended to prevent dropping across weight centiles i.e. growth failure (LOE 2+, RG 0, strong recommendation, strong consensus)
R 2.6	In very low birth weight infants, to approximate intra-uterine lean body mass accretion and growth, energy intakes of 90–120 kcal/kg/day should be provided (LOE 2++, RG B, strong recommendation, strong consensus)

Early nutrition has important short and long-term effects throughout infancy. In preterm infants, inadequate nutrient intakes are associated with impaired growth, increased severity of postnatal diseases, and adverse neurodevelopment, particularly in extremely preterm infants [14–18]. Several recent reports have demonstrated that adequate protein and energy intakes from PN can significantly improve postnatal growth in very preterm infants [19–25]. Nevertheless, a recent survey also demonstrated that PN practices are frequently not compliant with current recommendations, especially during the first days of life [26].

The energy requirements for premature infants correspond to the sum of TEE and the energy stored in new tissue (i.e. growth). EE increases slightly in the first few postnatal days, and corresponds to 45–55 kcal/kg per day in most infants. The energy cost of growth includes the energy stored in new tissues (primarily lean and fat mass), and the cost of tissue synthesis. If the in-utero weight gain of 17–20 g/kg per day is to be matched ex-utero, then total energy requirements for enterally fed premature infants will be approximately 110–135 kcal/kg per day [27,28].

This intake will vary between individuals, and over time, and should be adjusted according to metabolic capacity and postnatal growth during the stable growing period. Given the likelihood of accumulated energy deficits and the potential needs for catch-up growth in preterm infants, most practitioners aim for at least 120 kcal/kg per day to facilitate maximal protein accretion [7,30]. PN energy needs could then be estimated by back calculation from enteral energy needs. Infants receiving PN tend to need lower intakes because splanchnic tissue metabolism and stool losses are much lower than during enteral feeding [31–34]. This would suggest that in preterm infants because up to 30 kcal/kg/d may be used/lost when using the enteral compared to the parenteral route,

energy recommendations using this method might be met with an intake of 90–120 kcal/kg/day. Moreover, estimating energy needs in the common clinical situation where infants are receiving minimal enteral feeds in addition to PN is complex. In such cases, nutrient absorption is likely to be negligible when only low milk volumes (≤25 ml/kg/day) are administered. In such cases, it might be considered prudent to ignore the energy provided by enteral feeds.

In revising this chapter from the 2005 recommendations, we conducted a systematic review aimed at identifying RCTs or other high quality trial designs performed between 2005 and 2016 that examined energy intakes during PN. This failed to identify any such studies in neonates. This is due to multiple reasons but exemplifies the inadequate basis for any firm recommendations. Over the last 10 years whilst there has been a greater understanding of protein and other nutrient needs, the optimal level of energy intake for preterm infants via PN has yet to be determined. In addition, there has been little work that determines the optimal protein:energy ratio, and only a few studies have examined the differing effect on nitrogen retention of lipid intake, or lipid compared to carbohydrate as an energy source [35]. There is also a potential danger in estimating PN energy needs based on estimated enteral requirements, particularly because disease severity is frequently different when comparing infants fed by PN to those able to tolerate full enteral feeds, and because prescribed intakes are frequently not achieved in clinical practice [3]. Several studies show that actual PN intakes maybe 20% less than those prescribed where there is inadequate attention paid to nutritional management in complex clinical environments. The use of concentrated PN formulations may improve this.

Finally, the choice of outcome measures deserves to be highlighted. Typically, macronutrient intakes have been determined by assessing the effect on growth or nitrogen retention, whereas micronutrient requirements more frequently explore the impact on functional outcome, for example iron and anaemia, or minerals and bone density. When considering total energy intake, the potential adverse effects of rapid catch-up growth on later metabolic function must be balanced against potential neuro-cognitive benefit. More recently, data has emerged to show that inadequate energy intake is independently associated with the development of severe retinopathy of prematurity (ROP) [36]. Whilst RCTs are required to determine causality, the strength and potential importance of this data, combined with the clinical situation where actual intakes are lower than prescribed, mean it may be prudent to aim at the upper rather than the lower end of the intake range. Hyperglycaemia is common especially in sick ELBW infants. Clinical management varies between units (either decreasing carbohydrate infusion rates, or using insulin) as does the glucose level at which intervention is deemed appropriate. There are no RCTs exploring these issues and further discussion is beyond the scope of this chapter.

5.2. Pediatric intensive care unit (PICU)

5.2.1. General PICU patients

R 2.7	Reasonable parenteral energy requirements after the acute phase of critical illness can be estimated from REE (LOE 2−, RG 0, conditional recommendation, strong consensus)
R 2.8	In the stable phase of critical illness energy requirements can be increased by ~1.3 times REE to enable growth and catch-up growth and further increased in the recovery phase (LOE2−, RG 0, conditional recommendation, strong consensus)
R 2.9	Withholding PN for 1 week in critically ill children while giving micronutrients can be considered (LOE1+, RG B, conditional recommendation, consensus)

Acute injury, infection or a surgical insult induces a metabolic response that is proportional to the magnitude, nature, and duration of the injury. This response is characterized by a brief hypometabolic and hypermetabolic phase. This hypermetabolic phase is catabolic in nature. The pathways of energy production are altered and alternative substrates are used as a result of the loss of control of energy substrate utilization by their availability. The duration of this catabolic response in most critically ill children however might be short [37]. During the acute phase, endogenous production of energy provides the majority of energy requirements irrespective of the exogenous provided amount of energy. This results in a considerable risk for an energy imbalance which is associated with poor outcomes and energy adequacy is associated with lower mortality [38,39].

During the stable/recovery phase of critical illness REE values are a useful guide for energy intake. In mechanically ventilated children the optimal method for determining energy intake in these phases is measuring EE with indirect calorimetry. Nutritional requirements for critically ill children vary widely between individuals. Studies have shown that within-day variations in EE measurements are small [40–44]. A temporary increase of REE is seen in children after major operations (a REE peak 2–4 h after surgery and a return to baseline levels by 12–24 h [45]), and in septic neonates a 20% increase in REE day 1–3 and a 40% increase in REE during the recovery phase compared to the acute phase compared to normal REE for weight and age [46,47].

A single measurement may serve to assess the energy need of the individual child and guide nutritional therapy. However, in most clinical settings the lack of availability of indirect calorimetry means that prediction equations have to be used. Prediction equations may not reliably predict EE meaning there is a risk for under and overfeeding.

A variety of equations have been developed as a surrogate estimate of REE but all have failed to predict EE with acceptable precision [42,44,48–53]. However, in most infants and children reasonable values for REE can be derived from Schofield's formula for weight but there is no rationale to add stress or activity factors to resting energy requirements [1].

In the acute phase energy intake is equal or lower to measured EE, thereafter energy intake should be increased to account for tissue repair and growth. The optimal nutrition support in the critical ill child, including the optimal route and doses of macronutrient supplementation, and especially the timing of the parenteral macronutrient supplementation is unknown. In previously well-nourished adults, the omission of PN during the first week in ICU lowered the incidence of new infections, enhanced recovery and reduced healthcare costs [54,55]. Omitting PN early during critical illness reduced ICU-acquired weakness in adults, most likely by a more efficient activation of autophagy [56]. On the contrary, the administration of PN in a rabbit model of acute critical illness suppresses autophagy in skeletal muscle and liver [57]. Besides, early PN does not prevent wasting of skeletal muscle in the acute phase of critical illness, but increases adipose tissue deposition in the muscle compartments [58]. In the majority of critically ill children, the acute metabolic stress period typically lasts no more than 1–2 days.

The first evidence with regard to the timing of macronutrient supplementation from PN in critically ill children has been provided by the PEPaNIC trial [59]. This large international multicentre randomized controlled trial in 1440 critically ill term newborns, infants, and children compared early initiation of supplemental PN (initiated within 24 h after admission) with late PN (withholding PN up to day 8) in the PICU, while administering micronutrients [59]. Withholding PN significantly reduced the number of new infections, the time on a ventilator, kidney failure, and the length of

stay in the PICU and the hospital. Children randomized to the late-PN group received a mixture of Glucose 5% and NaCl 0.9% at, respectively, 60% and 40% of the total flow rate that is required to obtain optimal hydration, as prescribed by the attending physician, taking into account the volume of EN and the volume of micronutrients that is being delivered. Late PN increased the incidence of hypoglycaemia (<40 mg/dl) from 4.8% to 9.1%. No refractory hypoglycaemic incidents occurred, and hypoglycaemia did not affect the effect of late PN on any of the outcome measures. Despite these impressive results this study suffers from some limitations, mainly due to the possibility that children in the PN group may not have needed PN provision, may have been overfed with PN and the possibility that ICU findings may not be generalized to children with chronic diseases. Although in this RCT withholding PN was beneficial, the optimum length of time for which long PN should be withheld is unknown.

It is unclear how rapidly enteral energy intake can be increased without the risk of adverse effects. After the acute phase an energy intake of 1.4–1.5 times measured REE has been suggested to be optimal [41,60]. In a systematic review in which 9 studies were included it was concluded that a minimum intake of 57 kcal/kg/day and 1.5 g protein/kg/day were required to achieve a protein anabolic state [61].

5.2.2. *Traumatic brain injury PICU patients*

Patient with traumatic brain injury differ from other critically ill patients because they frequently require drugs (sedatives, analgesics, barbiturates, muscle relaxants) and techniques such as hypothermia that modify metabolic status. The metabolic rate depends on the level of consciousness, presence of infection or other injuries, temperature, and posturing responses.

Both an increased and decreased REE have been measured in children after head trauma [62–67].

However, tailoring of energy intakes is important because studies have shown that the amount of nutrition in the first 5 days was related to death in traumatic brain injury (TBI) patients; every 10-kcal/kg decrease in caloric intake was associated with a 30–40% increase in mortality rates [66]. Early initiation and achieving full caloric intake were both positively correlated with shorter length of ICU stay [67]. It is recommended that without further data for children with TBI the adult guidelines, adjusted for weight, should be considered when providing nutritional support to pediatric patients with TBI [31]. It is recommended that enteral nutritional support should begin by 72 h with full replacement by 7 days [68].

Conflict of interest

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