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Nutritional management of the critically ill neonate: A position paper of the ESPGHAN committee on nutrition

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Abstract

Objectives: The nutritional management of critically ill term neonates and preterm infants varies widely, and controversies exist in regard to when to initiate nutrition, mode of feeding, energy requirements, and composition of enteral and parenteral feeds. Recommendations for nutritional support in critical illness are needed.

Methods: The ESPGHAN Committee on Nutrition (ESPGHAN-CoN) conducted a systematic literature search on nutritional support in critically ill neonates, including studies on basic metabolism. The Medline database and the Cochrane Library were used in the search for relevant publications. The quality of evidence was reviewed and discussed before voting on recommendations, and a consensus of 90% or more was required for the final approval. Important research gaps were also identified.

Results: This position paper provides clinical recommendations on nutritional support during different phases of critical illness in preterm and term neonates based on available literature and expert opinion.

Conclusion: Basic research along with adequately powered trials are urgently needed to resolve key uncertainties on metabolism and nutrient requirements in this heterogeneous patient population.

What is known

- *Cumulative energy- and protein deficits are common in preterm and term infants treated for critical illness*
- *Critical illness induces an acute stress response that correlates with the duration and the severity of the injury insult and alters carbohydrate, protein and fat metabolism*
- *Nutritional management in neonatal intensive care units varies widely and there is a lack of consensus in regard to optimal timing of initiating and advancement of nutritional support*

What is new

- *The European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition provides a comprehensive review of the literature on nutritional support in critically ill preterm infants and term neonates*
- *Evidence based recommendation for nutritional support during the different phases of illness are provided and urgent research gaps are highlighted*

Introduction

The nutritional management of critically ill neonates varies widely, and controversies exist in regard to when to initiate nutrition, mode of feeding, energy requirements, and composition of enteral and parenteral feeds. Recommendations for nutritional support in critical illness are needed.

Critical illness may be defined as any life-threatening condition induced by sepsis, major surgery, or other insults associated with tissue injury, such as severe trauma, hypoxia-ischemia, severe cardio-respiratory compromise, or any other acute illness requiring intensive care. Whilst mechanisms of injury vary, there is typically an acute metabolic stress response, characterized by the activation of several cytokines (e.g. IL-1, IL-6, IL-8, IL 10, TNF-α), lipid mediators such as lipoxins, resolvins, protectins, and maresins, and neuro-endocrine hormones including catecholamines, glucagon, insulin-like growth factor 1 (IGF_1) and vasopressin [1,2]. The aim of this metabolic response is to repair tissue damage, regain tissue homeostasis and resolve inflammation. It involves mechanisms to maintain plasma volume, increase cardiac output and mobilize energy reserves [1-3]. A persistent or disrupted host response may result in exacerbated tissue catabolism (proteolysis and lipolysis), dysregulated glucose metabolism, impaired immune function, organ failure and death.

Multi organ dysfunction and mortality rates are higher in neonates compared to older infants, children and adolescents [4] and highlight the need for early identification of critical illness to improve outcomes (Table 1) [5]. Early diagnosis is challenging especially in preterm infants who may already need complex medical support for longer term conditions (for example chronic lung disease) without being acutely unwell. Different scoring systems, that mostly include a combination of physiologic variables and biomarkers, have been developed to help identify infants or neonates with high illness severity and mortality risk, but few of these have been tested in prospective trials [6-14].

The acute metabolic response in critical illness was initially categorized by Cuthbertson into the "ebb" and "flow" phases [1,15] to describe the immediate period of depressed metabolism and the subsequent more prolonged period of increased metabolic activity, characterized by catabolism. The release of cytokines and neuro-endocrine hormones during the early phase of critical illness (6-24 h) tends to be proportionate to illness severity and duration and counteracts the anabolic effects of insulin and IGF-1 [1,16-22]. In this phase, degradation of stored glycogen is activated to cover energy needs (glycogenolysis) [23]. Concurrently, protein and fat are mobilized; protein to provide specific amino acid precursors for gluconeogenesis and the synthesis of acute phase reactants (such as CRP and fibrinogen) in the liver, and fat for the provision of free fatty acids and glycerol. Activated hepatic glucose production and reduced uptake of glucose by skeletal muscle increases the risk of hyperglycemia [1,2,23]. The mobilization of energy through muscle and fat catabolism normally persists for several days, resulting in a temporarily cessation of growth [2,15,24,25]. Hence, during critical illness it is prudent to adapt nutritional care according to the different phases of the metabolic stress response and to recognize the hepatic transition to anabolic protein metabolism when growth reoccurs. This would help avoid inappropriate nutrition, especially overfeeding during the early (catabolic) phase of illness and underfeeding during recovery. Consequently, it may help to consider nutritional support in three different phases [25-28]; early acute phase, late acute phase and recovery phase (Figure 1) [25,29,30]. Precisely defining these phases in clinical practice may be challenging, but the early acute phase usually ends when

clinical symptoms stabilize and acute cardio-respiratory support can be reduced, whereas in the recovery phase, intensive cardio-respiratory care is typically no longer required.

Ideally, the nutritional care of critically ill neonates should be based on true measurements of energy expenditure (EE) to avoid the complications associated with under- and overfeeding. The gold standard to measure EE in healthy individuals is the stable isotope technique with doubly labelled water [31,32]. However, when estimating energy requirements in clinical practice it is more common to use predictive equations or indirect calorimetry (based on mathematical algorithms and measurements of oxygen consumption and carbon dioxide production), because they are practical and provide results bedside [33-35]. Nevertheless, predictive equations are often inaccurate in critical illness, especially in preterm infants, and indirect calorimetry is not easily and routinely used in most neonatal intensive care units (NICUs) [36-39].

A large number of observational studies [40-51] and surveys [38,52-56] on nutritional practices in preterm and term infants treated for critical illness show that prescribed and actual delivered intakes are generally below recommendations, and that cumulative protein- and energy deficits may account for as much as 40-45% of the variation in weight for age z-scores during hospitalization [40,49]. Adequate nutrient supply is complicated by carbohydrate and lipid intolerance that frequently results in hyperglycemia or lipemia, and this is often exacerbated by fluid restriction, concomitant medical infusions, interruption or intolerance to enteral feeding or lack of adequate access for enteral and parenteral nutritional support [50,51,57,58]. More proactive nutritional approaches during the first week of life in extreme preterm infants and during the acute phase of critical illness overall have been instigated [59-65], and some observational studies show positive associations between improved nutrient intakes and certain short-term clinical outcomes [46-49,66]. However, this may be explained by reversed causality and the effect of confounders, and several randomized trials have failed to show long term clinical benefits from early, enhanced nutritional support [67,68]. On the contrary, based on studies in adults, it has been suggested that active nutritional support during the acute phase of illness may be harmful and that permissive underfeeding or even starvation improves outcomes, possibly by avoiding the induction of "nutri-traumas" such as hyperglycemia, suppressed autophagy, mitochondrial dysfunction, and refeeding syndrome [69,70].

A large randomized trial, the Early versus Late Parenteral Nutrition in the Pediatric Intensive Care Unit (PEPaNIC) trial, showed that withholding parenteral nutrition (PN) during the first week of acute illness improved early outcomes as compared to PN initiated during the first 24 hours after admission in children [71]. Effects were similar in the subgroup of 209 term-born neonates recruited to the trial [72]. Despite this finding, many clinicians appear reluctant to limit early nutritional support due to 1) concerns about possibly harm by not providing adequate nutrients during the first week of critical illness, particularly in neonates and undernourished children [73], and 2) the belief that exogenous dietary protein provision is essential during critical illness [73].

The results of the PEPaNIC trial require confirmation in other settings, especially by conducting studies focusing on nutritional support in critically ill preterm and term neonates, before firm recommendations for nutritional practice can be made.

Scope of the manuscript and definition of the target patient populations

The scope of this position paper was to conduct a search of published literature on nutritional support during the first week of illness in critically ill neonates to provide practical recommendations for nutrient supply. By considering how critical illness affects energy needs and the metabolic utilization of carbohydrates, protein and lipids, and by evaluating the evidence base for nutritional support in critically ill preterm infants and term neonates, we aimed to answer four key questions related to the topic:

1. How does critical illness affect energy needs and the metabolic utilization of carbohydrates, protein and fat?
2. What is the evidence for mode of feeding (enteral/parenteral)?
3. What is the evidence for the timing of initiation and the advancement of nutritional support?
4. What recommendations can be made based on the current body of evidence?

In cases of limited evidence, we considered data from other paediatric or adult trials to see if the results could be extrapolated to critically ill neonates. Important research gaps were highlighted.

The target patient population for the nutritional management recommendations for this position paper includes 1) preterm infants and term neonates (less than 4 weeks of age) requiring major surgical care e.g. congenital heart disorders, gastrointestinal malformations, necrotizing enterocolitis (NEC) or spontaneous intestinal perforation (SIP), 2) term neonates undergoing therapeutic hypothermia due to hypoxic-ischaemic encephalopathy and 3) preterm infants and term neonates with critical medical illnesses (e.g. sepsis and multi organ failure). Since neonatal illness severity scores predict time-dependent mortality and short-term morbidities better than birth weight and gestational age (GA) in very preterm infants (birth weight < 1500g or GA < 32 weeks) [7,13,14], we further define preterm infants with high illness severity scores as being critically ill, e.g. clinical risk index for babies (CRIB II) > 11 points or a score for neonatal acute physiology II (SNAP-II) ≥ 30.

In the context of this paper nutritional support is regarded as the provision of either enteral nutrition (EN) through a gastric tube or PN and does not specifically address the amount and delivery of intravenous fluids or glucose infusions. This is keeping with the recently published guidelines for nutritional support in the pediatric critically ill patient [74].

Of note, this position paper does not discuss nutritional support in neonates with chronic inflammatory diseases or conditions, such as bronchopulmonary dysplasia (BPD) or patent ductus arteriosus (PDA).

Methods

For this systematic literature review, the Medline database and the Cochrane Library were searched for relevant publications in English up to July 2020. Due to the limited number of randomized controlled trials, we also included cohort studies, case studies and surveys

addressing the topic. Medline search terms included "critical illness" [MeSH Terms], “intensive care unit/or intensive care units”, “pediatric/or intensive care units”, neonatal, exp critical care, OR "parenteral nutrition, total" [Mesh:noexp], “parenteral nutrition”, OR “enteral nutrition” OR “amino acids/ or fat emulsions, intravenous”. These terms were combined with MeSH terms and the key words “therapeutic hypothermia”, “hypoxic ischemic encephalopathy”, and “resting energy expenditure”. The searches were restricted to the "newborn infant (birth to 1 month)", but included "premature infant" or "premature infants" or "very low birth weight" or "very low birth weight infants" or preterm or "preterm infants" or "preterm infant". The primary search retrieved 1113 publications. After screening titles and/or abstracts 115 publications were evaluated and additional studies from the reference list of relevant publications were selected to complete the search. In total 152 studies were included in this position paper to help provide evidence based answers about nutritional management of the critically ill neonate. Based on available data, recommendations were proposed and discussed before anonymous online voting. Any recommendation that did not reach a consensus of 90% or more was rephrased until all authors agreed for publication.

Energy needs in healthy and critically ill neonates

Energy needs in healthy preterm and term neonates

The main objective for feeding is to enable infants to fulfil their genetic potential for growth in order to optimise lifelong health and wellbeing [75,76]. Energy requirements should cover I) the energy needed to maintain basal metabolic functions (basal metabolic rate; BMR), II) energy expended for physical activity, which is usually minimal, III) diet-induced thermogenesis, which includes postprandial nutrient metabolism and the energy required for synthesis and organization of new tissue, IV) energy stored in new tissue (tissue growth) and V) energy lost in stool and urine [27,77]. Because measurement of the basal metabolic rate requires a 12-18 hour fast, a thermo-neutral environment, and the patient being asleep, basal energy requirements are usually estimated by measuring resting energy expenditure (REE), i.e. the energy expended by a person at rest, and includes thermoregulation and resting muscular activity [78]. In neonates, measured REE (or resting metabolic rate; RMR) also includes diet-induced thermogenesis as they are never strictly in a fasting state (Figure 2A and B).

Studies of REE during the first few weeks of life in healthy preterm and term infants show that REE increases with increasing energy supply during the first weeks of life and that REE is directly proportional to growth rate [79,80]. Measured values for REE in healthy preterm infants are around 35-55 kcal/kg/d during the first 2 weeks of life when nutrient intakes are low, and increase to about 70 kcal/kg/d at 1 month of age [80-82]. In healthy term neonates REE increases from 45-50 kcal/kg/d to about 60 kcal/kg/d during the same time interval [79,80]. Since the average energy requirements for growth are 3-5 kcal/g/d [77], depending on the ratio of fat and protein deposition, very premature infants require an additional 50-70 kcal/kg/d of metabolizable energy to approximate intrauterine growth rates [77,83], whereas the energy needed for growth is around 30-40 kcal/kg/d in term neonates. In older children and adults, the energy fraction needed for growth in relation to the total energy expenditure is negligible [19,84]. This means that the change in energy needs during critical illness is much larger in preterm and term neonates, putting them at extra risk of both over and underfeeding.

Energy needs in critically ill neonates

Our literature search identified several small studies of EE during critical illness in different neonatal settings [85-93], but we did not find any studies of EE in neonates with HIE and/or receiving therapeutic hypothermia. Most studies reported REE during the initial acute phase [85,86,89-93], but few studies included exclusively preterm infants or neonates < 28 d of age. Studies in neonates after uncomplicated surgery show a significant brief increase in REE [85], followed by REE in the range of the BMR (40-50 kcal/kg/d) for 4-7 days postoperatively [85,89]. Major surgery, surgery associated with other inflammatory insults, and sepsis provoke a greater metabolic challenge with a higher average postoperative peak in REE (50-60 kcal/kg/d) and a slower resolution of the injury response [86,90,91]. Data indicate that the metabolic stress response after major surgery is shorter in neonates and children than in adults [94], and that premature infants (mean GA 29 ± 2.9 weeks, n=18) exhibit an earlier anabolic recovery after acute illness compared to infants born nearer to term (GA 38.2 ± 1.8 weeks, n=55) [95]. Figure 2B and 2C illustrate the difference in energy expenditure between healthy growing and critically ill neonates.

The respiratory quotient (RQ) obtained from indirect calorimetry has been proposed as a tool to adapt nutritional care during critical illness in neonates and children because the ratio of CO_2 production to oxygen consumption is dependent on the relative contributions of carbohydrate, protein and fat to the EE [19,78,96,97]. The RQ for carbohydrate is 1.0, for protein ~ 0.85, for fat ~ 0.7, and for the conversion of carbohydrate to fat (*de novo* lipogenesis) > 1.0. In other words, overfeeding or high glucose intakes resulting in high lipogenic activity is energy demanding and increases RQ, whereas the use of endogenous fat stores to meet energy requirements decreases RQ. An observational study in 98 neonates and children showed that despite low sensitivity, RQ values > 0.85 excluded underfeeding and RQ-values > 1.0 identified overfeeding or excess carbohydrate intakes [97]. Targeting 64-70 kcal/kg/d provided as 2.5 g/kg/d of protein, 1-2 g/kg/d of fat and 10 g/kg/d of carbohydrate in the early postoperative phase resulted in a RQ > 1, suggestive of some overfeeding in an observational study of 10 surgical neonates [19]. Along with the resolution of the early acute phase, RQ values dropped and caloric support could be increased from the 4th day onwards.

The finding of a change in energy needs during the first week of critical illness is relatively consistent with EE studies in critical ill children, which show that REE values gradually increase with increasing length of ICU stay (< 4 days, 4-7 days, > 7 days) [98], but also that EE is affected by other factors such as weight, temperature, heart rate, diastolic blood pressure, minute ventilation, and drugs [98,99].

Macronutrient utilization in healthy and critically ill neonates

Carbohydrate utilization

Carbohydrate and fat are the main macronutrients for provision of energy [27,75,100]. Metabolic studies on parenteral macronutrient utilization have shown that glucose is the primary determinant for both glucose utilization and the metabolism of fat [101,102]. Minimal and maximal glucose recommendations are normally based on the endogenous glucose production rate (GPR) and the glucose oxidation capacity. The estimated GPRs and glucose oxidation rates in preterm infants are ~ 6 mg/kg/min (8.6 g/kg/d) and ~8 mg/kg/min (11.5 g/kg/d), respectively, compared to 5 mg/kg/min (7.2 g/kg/d) and 12.5 mg/kg/min (18 g/kg/d) in term infants [26,101,103]. If glucose supply exceeds the maximum glucose oxidation rate, glucose is converted to fat and fat oxidation ceases [101,102,104]. However, if the carbohydrate-to-

fat ratio is reduced, the opposite occurs and fat utilization increases [101,102,104]. Nevertheless, these rates are only estimates and both higher and lower glucose intakes may sometimes be indicated and provided as long as the infants remain euglycemic [101,105,106].

The utilization of exogenous glucose supply is however influenced by other factors including stress induced insulin resistance [2], persistent endogenous gluconeogenesis and electrolyte disturbances (e.g. hypophosphatemia) [26,107], all of which often occur during critical illness and are commonly encountered in extremely preterm infants [108-112]. Observational studies show that 50-80% of critically ill children and extremely preterm infants experience hyperglycemia (>8.3 mmol/L) [23,113,114]. Stress induced insulin resistance may develop very rapidly as a response to the increased levels of stress hormones (i.e adrenaline, cortisol, glucagon, growth hormone) and inflammatory cytokines (TNF-α, IL-1, IL-6 and IL-8 and more), resulting in 1) reduced uptake of glucose by the cells and 2) reduced ability to inhibit hepatic gluconeogenesis despite high glucose levels [23].

Preterm infants are particularly susceptible to hyperglycemia due to immature regulatory mechanisms and decreased insulin production by the pancreatic beta-cells [17,115]. Hyperglycemia is associated with increased mortality and a range of morbidities such as multi organ failure, nosocomial infections, intraventricular haemorrhage, NEC, and impaired neurodevelopment [113,114], but studies confirming causal relationships are lacking.

Glycaemic variability, a measure of blood glucose fluctuations over time, has been shown to be associated with mortality in critically ill adult patients, independent of mean glucose concentrations [116,117]. Tian et al studied the effect of high (≥ 70 kcal/kg/d) versus low caloric intake (≤ 70 kcal/kg/d) on serum glucose levels and glycaemic variability in 37 preterm infants less than 30 weeks GA [30]. The infants were grouped into high or low metabolic stress groups based on peak serum CRP concentration within 72 h of the injury insult (postoperative, sepsis, NEC, etc). High metabolic stress was defined as a CRP concentration ≥ 50 mg/L. In this study, the high stress group had higher glucose levels and increased glycaemic variability compared to the low stress group. A caloric intake ≥ 70 kcal/kg/d was also found to worsen the injury-related hyperglycemia. Of interest is also the interaction between glucose concentrations and lactate levels during critical illness (U-shaped curve) [118]. A large retrospective study in critically ill adults showed that high lactate levels combined with low glucose concentrations was associated with the highest risk of organ dysfunction and hospital mortality [118]. In children, lactate resolution has been shown to be associated with a decreased risk of persistent organ dysfunction during critical illness and is used as a marker to predict outcome [119].

The prevention and treatment of hyperglycaemia in preterm infants is controversial in terms of choosing between reducing carbohydrate supply or starting insulin [120,121]. Insulin has been shown to reduce mortality and morbidity in critically ill adults [122], but follow-up RCTs on the effects of prophylactic insulin infusion with tight glycaemic control in adults, children and preterm infants did not show any clear benefit. On the contrary, many demonstrated an increased incidence of hypoglycaemia [121,123-127] and even a higher 28-days mortality risk in a large RCT of very-low-birth weight infants [127]. Interestingly, insulin treatment of established hyperglycemia was associated with significant lower 28- and 70-days mortality in the population-based EXPRESS (extremely preterm infants in Sweden) cohort study [114]. Present PN guidelines recommend to start insulin therapy if neonates in the NICU experience repeated blood glucose levels >10 mmol/L (180 mg/dL) despite reasonable adaptation of the

glucose infusion rate [26]. The target glucose level, < 10 mmol/L (180 mg/dL), is the same as the target glucose level recommended for critically ill children and adults [26,119,128].

Protein utilization

Protein supply should preferably cover protein turnover and tissue growth, because protein synthesis is energy demanding and unlike glucose and fatty acids, amino acids cannot be stored [27,75,100]. Amino acids that are not incorporated into protein are irreversibly oxidized to CO_2 and ammonia before they are converted to urea in the uric acid cycle and excreted in the urine, providing approximately 4 kcal/g [129-131]. Excessive amino acid intakes may result in toxicity, such as hyperammonemia, metabolic acidosis, seizures or coma [130,132,133]. In healthy infants, protein needs are based on the sum of amino acids needed to ensure adequate growth and the amino acids needed to cover obligatory nitrogen losses [131]. Certain non-essential amino acids may be synthesized in sufficient quantities from other amino acids and glucose, whereas others are essential or conditionally essential and need to be provided through the diet [129,131]. The rate of protein synthesis is dependent on sufficient availability of one or more of the essential or conditionally essential amino acids, whereas an energy supply of 30-40 kcal per 1 g protein is recommended for optimal protein utilization (> 25 kcal/g amino acids when administered parenterally) [129,131].

During critical illness protein degradation is increased [24]. The release of cytokines, cortisol, and growth hormone promote proteolysis of skeletal muscle so that specific amino acids can be redirected and used as substrates for hepatic gluconeogenesis (particularly alanine and glutamine), tissue repair, wound healing and positive acute phase reactants, like CRP, haptoglobin, fibrinogen and procalcitonin [19,24,134]. At the same time, the synthesis of constitutive proteins (albumin and transthyretin), IGF_1, retinol-binding protein, and transferrin is reduced [134]. The endogenous protein breakdown does not seem to be attenuated by exogenous protein or carbohydrate supply and may rapid lead to protein-caloric malnutrition [1,24,26,135]. This may play an important role in growth restricted and premature infants with limited protein and energy stores.

Several studies in preterm infants and sick neonates and children show that a minimum intake of 55-58 kcal/kg/d and 1.3-1.5 g protein/kg/d are needed to achieve a positive protein balance [57,136-138], albeit higher intakes may be needed in parenterally fed patients with severe illness [57]. However, since endogenous protein breakdown is relatively unaffected by exogenous protein supply, it is not clear whether a positive protein balance is possible or even desirable during the early, critical illness phase. In fact, autophagy, the recycling of cellular components into amino acids and fatty acids for cellular fuel, is enhanced by fasting [69,70]. Fasting also promotes the down regulation of mitochondrial activity to sustain cell life (theory of adaptive hibernation) [70]. Both mechanisms are considered to play important roles during the inflammatory response and it is hypothesized that high energy and protein intakes may lead to hepatic overload, attenuated autophagy and disrupted mitochondrial function [19,70]. On the other hand, excessive autophagy and malnutrition may worsen mitochondrial dysfunction and trigger cell death [69,139], highlighting the challenge of finding the right balance between meeting energy and nutrient needs while avoiding overfeeding.

When the acute stress phase resolves, urinary output commonly increases and endothelial membrane integrity improves [1]. The accompanying reduction in protein catabolism is reflected by decreased urinary nitrogen excretion, decreased CRP and increased

albumin and transthyretin levels [1,140]. CRP, transferrin and transthyretin concentrations have been shown to correlate with the magnitude and duration of the injury response in neonates and infants, [96,140,141], and CRP and transthyretin concentrations are predictive for length of hospital stay and 30-day mortality [140,142]. Thus, it has been suggested that these markers could be used to establish the shift from catabolism to anabolism. Other biochemical markers commonly used to assess protein tolerance and adapt nutritional care are acid-base status and urea levels [143-145]. However, an increase in urea levels is an unspecific marker, which more often reflects the catabolic state of acute inflammation, intravascular volume depletion, inadequate energy supply, suboptimal amino acid composition, or may simply be a sign of appropriate amino acid oxidation or higher protein intakes [131].

Fat utilization

Lipids provide fatty acids, which are concentrated sources of energy, building blocks of cell membranes and precursors of bioactive eicosanoids; important substrates in the regulation of inflammation, platelet aggregation and tissue repair [146]. During the acute metabolic stress response catecholamines (adrenaline, noradrenaline) and growth hormone induce lipolysis with mobilization of free fatty acids and glycerol [17,19]. Studies in sick preterm neonates and older infants have shown that fatty acids are used as a primary fuel source and that lipid oxidation is proportional to stress severity [147].

As mentioned earlier, fat utilization is dependent on the supply of glucose. If glucose is provided in amounts higher than the upper threshold for oxidation, excess glucose will be redirected to *de novo* lipogenesis and the oxidation of fatty acids ceases [101,104]. The conversion of glucose to fat is an energy demanding process characterized by an increase in CO_2 production relative to oxygen consumption, which may lead to increased respiratory rate and ventilator dependency. Reducing the glucose to lipid ratio during parenteral nutritional support has been shown to promote fat utilization and reduce lipid peroxidation [101,104]. The optimal ratio of glucose to lipids is not defined, but some have suggested limiting the amount of calories provided as glucose to a maximum of 50% caloric intake in critically ill adults [104]. Similarly important, if energy supplies are consistently below energy requirements, endogenous fat stores are needed for fat oxidation. In a study of 26 children who received intravenous carbohydrate exclusively after cardiac surgery, approximately 80% of the macronutrient utilization was from oxidation of endogenous fat [148]. Such an increased fat utilization may be detrimental in preterm and growth restricted infants, who have very limited fat stores and are at risk of essential fatty acid deficiencies [149].

Historical studies suggested that parenteral lipid emulsions may have negative effects on pulmonary function, partly by reducing pulmonary diffusion capacity [150], and by increasing pulmonary blood pressure and vascular resistance [151]. Moreover, high contents of soybean oil and phytosterols are thought to induce inflammation and contribute to PN induced cholestasis (PNALD) [152,153]. Newer composite LE with or without fish oil have been developed, providing fatty acids (oleic acid and fish oil) that may be more immunological inert or even promote anti-inflammatory mechanisms [149,152,154] but the evidence for beneficial effects of these emulsions are low [155-157]. Whether newer composite lipid emulsions with or without fish oil may be more beneficial in critically ill neonates has not been studied and is thus unknown [155]. Several components of PN, in addition to lipids, generate oxidants such as hydrogen peroxide, lipoperoxides and ascorbylperoxides, so it is recommended to shield PN from light to reduce the oxidative load of premature infants and critically ill neonates [149,158].

A recent meta-analysis, which included 800 premature infants from 4 trials, showed that mortality in the light-protected group was half of that in the light-exposed group, but whether this was due to the reduction of peroxides or other factors, such as reduced degradation of antioxidant vitamins, remains unclear [158].

Intravenous lipid emulsions do not seem to affect platelet number or function, but there are conflicting data about lipid clearance during sepsis [149]. Serum triglyceride levels have been shown to correlate with illness severity in critically ill children [96], and more frequent monitoring of triglyceride concentrations may thus be helpful when providing nutritional care. At present, serum triglyceride concentrations < 3.0 mmol/L (265 mg/dL) are generally considered acceptable [149]. During suspected/confirmed sepsis, disseminated intravascular coagulation, thrombocytopenia, impaired liver function, increased triglyceride concentrations or metabolic acidosis, it may be prudent to decrease parenteral lipid supply [49,52,58]. However, both high glucose intake and overfeeding may impair lipid utilization as described earlier, and the need for a reduction in glucose load should be considered before parenteral lipids are reduced [149].

Mode of feeding

The recommended route to administer nutritional support during critical illness is by EN where this is possible [159]. In contrast to critically ill children and adults, in whom early initiation of EN (within 24-48 h) is considered standard of care [28,74,160,161], many critically ill preterm infants and neonates receive nutritional support by the parenteral route because the gastrointestinal tract is immature or full enteral feeding has not been established. Nevertheless, minimal enteral nutrition (MEN), usually defined as the supply of nutritionally insignificant milk volumes of 12-24 ml/kg/d [162-164], is advocated whenever possible to maintain gut integrity [165]

Studies show that very- and extremely preterm infants may reach full enteral feeds by 7-14 days [166-168]. However, in a large randomized, controlled trial of 2804 preterm infants, a faster increment of enteral feeding volumes (target 30 mL/kg/d vs 18 mL/kg/d) did not improve survival without moderate or severe neurodevelopmental disability at 24 months, nor did it affect the risk of late onset septicemia or NEC [166]. Importantly, median (SD) age at randomization was 4 (3-6) days and the actual intake volumes were lower than intended, so that median days to reach full milk feeding volumes were 7 and 10 days in the faster and slower increment groups, respectively.

We did not identify any randomized controlled trials on the role of feeding mode in critically ill term neonates. A secondary analysis of the PEPaNIC trial showed that low mean EN intake was associated with new acquired infections, hypoglycaemia, duration of mechanical ventilation, length of PICU and hospital stay, but also that all these associations, except for hypoglycaemia, disappeared after adjustment for confounders [169]. Two small retrospective observational studies [170,171] and one survey [172] reported feeding practices in infants undergoing therapeutic hypothermia for HIE. Available data suggest that MEN is safe and feasible [170,171]. Unfortunately, none of these studies reported details on the parenteral support given. An ongoing, large retrospective national cohort study aims two give some answers to the optimum enteral and PN strategy for term neonates during and after therapeutic hypothermia [173], but the results have not yet been published.

In sum, there is insufficient data from studies in critically ill preterm infants or term neonates to determine whether EN is more beneficial than PN during the acute phase of illness, or whether higher EN intake is superior to lower EN intake. The use of EN as compared to PN has not been shown to have an effect on overall mortality in critically ill adult patients, but to decrease infectious complications and ICU length of stay, most likely caused by reduced macronutrient intake with EN [174]. Interestingly, data from two large RCTs do not support a preference for early enteral compared with early parenteral nutrition when nutritional support is targeted at similar calorie and protein intakes (n= 4810 critically ill adults) [175,176]. On the contrary, these data suggest that early enteral nutrition may be of more harm; mainly by increasing the risk of digestive complications [175,176] and, as found in the PEPaNIC trial, the risk of hypoglycaemia [176].

Time of initiation of nutritional support

Preterm infants

Historically, it was believed that premature infants tolerated fluid and calorie restriction without negative long term effects [177], but in the late 1950s and early 1960s experimental studies showed that early malnutrition permanently affected growth of organs, including the brain [177,178]. Since then, a myriad of studies have investigated safety and efficacy of the timing of nutrient supply after birth in very preterm infants [143,144,167,179-196]. Based on this body of evidence, current European guidelines for PN in children advocate early initiation of PN in preterm infants, including 1.5-2.5 g/kg/d of amino acids and 1-2 g/kg/d of lipids, with a gradual increase to target within a few days [129,149]. Since most of the studies performed do not include critically ill preterm infants nor discriminate between healthier and sicker neonates at inclusion, we do not know whether the results can be generalized to the critically ill preterm infant. In a large exploratory, secondary study of a randomized trial including 1366 extremely low birth weight infants [48], total daily energy intake during the first week of life was found to mediate the effect of critical illness on later outcomes [48]. However, recent reviews and meta-analyses on the effect of initial higher vs lower intakes of parenteral amino acids supply on clinical outcomes in very preterm and low birth weight infants, did not find clear evidence for long-term benefits with early higher intakes when summarizing data from ~1500 infants [67,68,131]. Apart from modest effects on weight gain, protein balance and glucose control, early and higher AA intakes increased the risk of raised urea levels and metabolic acidosis.

Term neonates

We did not identify any RCT on the clinical effect of the timing of nutritional support in critically ill neonates admitted to a NICU [197,198], but two RCTs and one secondary analysis of a RCT have studied the effect of early vs delayed nutritional support in neonates and children admitted to a pediatric intensive care unit (PICU) [71,199,200].

The multicenter PEPaNIC trial (n=1440) [71], included 209 neonates (mostly admitted due to cardiac and abdominal surgery), and studied the effect of withholding PN for 1 week compared to providing full nutrition up to caloric targets by initiating PN within 24 hours after admission, if enteral nutrition was insufficient to cover 80% of the caloric target. To match fluid intakes between the groups, the late PN group received a mixture of glucose 50 mg/mL and saline (9 mg/mL). All infants received intravenous trace elements, minerals, and vitamins, and glucose concentrations were controlled with insulin according to local target ranges [71]. Even though the median total macronutrient administration up to day 4 were only

50-70% of target in the early PN group, mean total energy intake exceeded 55 kcal/kg/d on day 2, 70 kcal/kg/d on day 3 and 80 kcal/kg/d on day 4 in the infants with a weight < 10 kg [71,201]. In contrast, the mean total energy intake in the late PN group reached 25 kcal/kg/d on day 2 and remained between 40 and 45 kcal/kg/d on day 3 and 4, which is more in line with both estimated energy requirements and current energy recommendations for the acute phase of critical illness (40-50 kcal/kg/) [25,27]. The primary study showed that permissive underfeeding reduced the incidence of new infections, shortened the duration of intensive care dependency, and reduced length of hospital stay [71]. The strongest effect was observed in neonates and undernourished children [72,202]. The PEPaNIC findings are in line with the results of the adult EPaNIC study, which showed that early combined parenteral/enteral nutrition delayed recovery irrespective of critical illness severity [203].

Secondary observational analyses of the PEPaNIC trial indicate that early provision of parenteral amino acids could explain the worse clinical outcomes in the intervention group [201]. The risk of all studied outcomes gradually increased up to a median daily amino acid dose of 1.15 g/kg (IQR 1.10-1.22), representing 40-50% of reference doses for age and weight. However, higher doses did not further increase the risk of harm. The authors discuss whether this negative effect of parenteral amino acids is caused by the suppression of autophagy, an amino acid load above the metabolic capacity of the liver and kidneys or a suboptimal composition of the amino acid formulations used [201]. Interestingly, higher average doses of lipids were associated with a greater likelihood of earlier live discharge and with a greater likelihood of earlier live weaning from mechanical ventilation in the neonates. These findings support the notion that lipids play an important role during critical illness. Higher plasma 3-hydroxybutyrate (3HB) and lower blood glucose concentrations were also associated with earlier weaning from mechanical ventilator support and live discharge [204]. The ketogenic fasting response in the late PN group was however not associated with new infections. Other adjusted analyses revealed that a higher average blood glucose concentration was an independent risk factor for infections, whereas a higher daily glucose dose was protective [201]. This finding is in line with other studies indicating that factors other than glucose intakes have an impact on glucose concentrations [114,188]. The low average glucose intake in the late PN group (2-3 vs 5-6 mg/kg/min) resulted in a significantly higher risk of hypoglycemia [72]. Recent data from follow-ups at 2 and 4 years after PICU admission show that delayed PN did not negatively affect survival, anthropometrics, health status, or neurocognitive development, but reduced emotional and behavioral problems [205,206]. Interestingly, critically ill term neonates appeared less vulnerable to the developmental harm caused by early-PN compared to infants > 29 days, toddlers and children up to 5 years of age [207].

The second study on the effect of timing of nutritional support, was a small trial on the effect of enteral nutrition given within 24 hours compared to after 48 hours in children with burns (n=77, age range 3.1-18.4 years) [199]. This comprehensive study included blood and urine measurements of several endocrine markers of inflammation throughout the study period, and biweekly indirect calorimetry. The incidence of reportable adverse events, including bowel necrosis, multisystem organ and renal failure, was higher in the early feeding group, but this was not significant. Early enteral feeding reduced caloric deficits, stimulated early insulin secretion and first week nitrogen balance, but there was no difference between the groups in regard to endocrine status, morbidity, mortality, hypermetabolism or length of hospital stay.

The third study investigated the effects of different initiation times of PN (within 48h, after 48h to 72h, after 72h to 7 days, and after 7 days) on outcomes in children with severe

traumatic brain injury (n=77+13) [200]. In this observational part of a RCT (Cool Kids), initiating nutritional support before 72 hours was associated with favorable outcomes, including improved survival with earlier PN initiation (within 48 hours). Of note, most of the children in this trial were between 3 and 15 years.

It is challenging to make clear recommendation in regard to the best timing of nutritional support in critically ill term neonates based on existing evidence. Strengths and limitations of the PEPaNIC trial have been extensively debated previously [208-212]. Although the trial showed no benefit of early PN in any specific age group and a particularly risk of harm in children aged between 29 days and 11 months [207], it is important to stress that PN was started within 24 h after admission if enteral intakes were not > 80% of target. This is not in line with the nutritional guidelines at that time, which only recommended commencing PN after a few days if patients were not able to reach 60% of caloric intake with EN [213,214]. As presented in this literature review, the risk of overfeeding during the acute phase of the metabolic stress response is high and current evidence support a cautious supply of nutrients at or just below basic energy needs until the resolution of the acute phase. In the early PN infants in weight group 0-10 kg of the PEPaNIC trial, energy supplies exceeded 150% of theoretical basal energy requirements and protein supplies more than 60-70% of the reference dose for age and weight during the early acute phase [201]. Since growing infants are at higher risk of overfeeding compared to older children and adults [71], this may partly explain the larger negative effects found in this group. Moreover, the nutritional interventions tested in the PEPaNIC trial represent two extremes of nutrient intakes, and do thus not answer whether delaying PN for 7 days improves outcomes as compared to providing PN at or just below REE during the early acute phase of critical illness. In addition, the PEPaNIC trial did not include preterm infants and since they have very different nutrient requirements, the results from term neonates and children cannot be generalized to preterm infants.

The latest Cochrane review on early versus late PN for critically ill term and late preterm infants [198], which only identified data from the PEPaNIC trial [72], concluded that there is insufficient evidence from RCTs for recommendations for or against nutritional support during the first week of critical illness. Current available guideline recommendations for nutritional support in critically ill children [74], including term infants [160], advocate the initiation of EN within 24-48 h after admission. A minimal enteral protein intake of 1.5 g/kg/d may be considered to avoid a negative protein balance, but energy targets should not exceed REE during the early acute phase of illness [160]. Moreover, recommendations aim to achieve at least two thirds of the prescribed energy target by the end of the first week [74]. This is based on observational cohort studies, which show positive associations between energy intakes greater than 67-80% of estimated energy targets and improved outcomes [215,216], and that energy intakes above 55 kcal/kg/d are needed to maintain energy equilibrium in young children and infants > 1 month of age [57,136]. Due to the potential harm of early commencement of PN, recommendations regarding initiation of parenteral support differ. However, in general, it is recommended that initiation of PN should be considered on an individual basis and that PN support can be delayed until day 8 in term infants and children with normal nutritional state and low risk of nutritional deterioration [27,74,129].

Summary

The ESPGHAN-CoN reviewed relevant studies on nutritional support in critically ill preterm and term neonates, including studies on basic metabolism. A body of evidence support that measured EE during critical illness is substantially lower than predicted EE of healthy

growing neonates; in the range of 40-50 kcal/kg/d with minimal metabolic stress and 50-60 kcal/kg/d with severe inflammatory stress (sepsis, pre-existing inflammation, etc). Nonetheless, there is insufficient data to make firm recommendations on the optimal composition and timing of nutritional support.

In *preterm infants*, available evidence does not support any significant changes to current guidelines, which recommend that critically ill preterm infants should receive nutritional support started at (or reduced to) the minimal amount needed to cover basal metabolic rate and basic macronutrient needs during the early acute phase [26,27,129,149]. For many preterm infants this means that they will need PN.

In critically ill *term neonates*, initiation of PN within 24 hours is not routinely recommended. However, considering the limitations of the PEPaNIC trial and the observed low risk of long-term harm from early PN in critically ill neonates, the ESPGHAN-CoN does not support a change towards withholding parenteral nutritional support for 7 days as standard nutritional care. This position paper suggests considering careful initiation of nutritional support, including micronutrients, just below or at predicted REE after 48-72 h. Even though recent RCT data in adults implicate that permissive underfeeding with PN is safe [175,176], the ESPGHAN-CON only recommends commencing PN to prevent nutritional deficiencies when adequate enteral nutrition is not feasible.

In both critically ill premature infants and term neonates, the phases of clinical illness should be assessed daily for adjustments of nutritional care. Although only indicative, biomarkers such as CRP, serum-glucose, glycemic variability, lactate, serum triglycerides, , transthyretin and urea may be used along with clinical parameters to help recognize the return of growth anabolism. We estimate that the early acute phase is likely to last between 2-4 days and the late acute phase about 3-6 days. This means that full nutrient intakes (target nutrition) may not be appropriate until between 5-10 days after the acute insult, depending on illness severity and duration. Of note, premature infants may exhibit an earlier return to anabolism after acute illness compared to infants born nearer to term. During the recovery phase, nutritional supply in the upper range of recommendations should be considered to help cover cumulative deficits and to promote tissue repair, and catch-up growth.

Conclusion and Recommendations

This literature review identifies that there are insufficient data to determine the optimal composition and timing of nutritional support in preterm infants and term neonates who are critically ill. Based on the reviewed literature and a thorough evaluation and interpretation of present parenteral and enteral macronutrient guidelines [26,27,76,129,149], the ESPGHAN-CoN makes the following cautious recommendations for nutritional management during different phases of critical illness:

General recommendations

- If critical illness is suspected, establish the diagnosis by assessing clinical and biological markers (Table 1)

- Theoretical energy and macronutrient needs during different phases of critical illness are given in table 2
- Minimal enteral nutrition (MEN) should be initiated within 48 h if feasible
- Gradually advance nutrient intakes (~1.3 – 1.5 times REE) when the clinical state and the inflammatory response are resolving. The transition from the catabolic to the anabolic phase seems to start between 3-7 days after the insult, but may occur earlier (24-48 h) in preterm infants or neonates with less illness severity or be delayed in neonates with severe injury insults
- During the recovery phase, consider to increase target above estimated needs to cover cumulative deficits and promote catch-up growth

Monitoring

- Assess the phase of clinical illness every 24 h. Biomarkers such as CRP, glucose, glycemic variability, lactate, transthyretin and urea may be used along with clinical parameters to recognize the transition from the acute to the stable phase when anabolic protein metabolism reoccurs
- In case of hyperglycemia, start insulin infusion if glucose levels remain > 10 mmol/L (180 mg/dL) despite reasonable adaptation of the glucose infusion rate, i.e. ~ 4 mg/kg/min (6 g/kg/d) in preterm infants and ~ 3 mg/kg/min (4 g/kg/d) in term neonates
- Extremely preterm infants and small for GA infants are at risk of refeeding syndrome, particularly hypophosphatemia. Monitor and replace phosphate and potassium if values are low

The different nutritional objectives between term neonates and preterm infants are highlighted in Figure 3.

Research gaps

This review calls attention to the fact that basic research and adequately powered trials are urgently needed to resolve key uncertainties on metabolism and nutrient requirements in critically ill neonates.

The ESPGHAN-CoN recommends that future research include

- RCTs on the timing and amount of PN in critically ill preterm infants and term neonates
- Studies on permissive underfeeding during the early phase of acute illness followed by a gradual increase to nutritional target compared to delayed PN in critically ill neonates
- The clinical effects of enteral vs parenteral nutritional support at isocaloric intakes in critically ill neonates
- Role of specific amino acids and fatty acids during critical illness
- Studies to determine whether nutritional requirements are sex-specific in critically ill neonates

These trials need to consider differing levels of illness severity, include flexible study designs to account for heterogeneity in the populations studied, and be large enough to determine meaningful differences in functional outcomes, both in the short and long term.

DISCLAIMER

"ESPGHAN is not responsible for the practices of physicians and provides guidelines and position papers as indicators of best practice only. Diagnosis and treatment is at the discretion of physicians".

References

1. Cuthbertson DP. Second annual Jonathan E. Rhoads Lecture. The metabolic response to injury and its nutritional implications: retrospect and prospect. JPEN J Parenter Enteral Nutr 1979;3:108-29.

2. Gillis C, Carli F. Promoting Perioperative Metabolic and Nutritional Care. Anesthesiology 2015;123:1455-72.

3. Kulkarni OP, Lichtnekert J, Anders H-J, et al. The Immune System in Tissue Environments Regaining Homeostasis after Injury: Is "Inflammation" Always Inflammation? Mediators Inflamm 2016;2016:2856213-.

4. Bestati N, Leteurtre S, Duhamel A, et al. Differences in organ dysfunctions between neonates and older children: a prospective, observational, multicenter study. Crit Care 2010;14:R202-R.

5. Systemic inflammatory response syndrome (SIRS) and sepsis in children: Definitions, epidemiology, clinical manifestations, and diagnosis. UpToDate, 2020. at https://www.uptodate.com/contents/systemic-inflammatory-response-syndrome-sirs-and-sepsis-in-children.)

6. Parry G, Tucker J, Tarnow-Mordi W. CRIB II: an update of the clinical risk index for babies score. Lancet 2003;361:1789-91.

7. Lee SM, Lee MH, Chang YS. The Clinical Risk Index for Babies II for Prediction of Time-Dependent Mortality and Short-Term Morbidities in Very Low Birth Weight Infants. Neonatology 2019;116:244-51.

8. Patrick SW, Schumacher RE, Davis MM. Methods of mortality risk adjustment in the NICU: a 20-year review. Pediatrics 2013;131 Suppl 1:S68-74.

9. Leteurtre S, Martinot A, Duhamel A, et al. Validation of the paediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet 2003;362:192-7.

10. Graciano AL, Balko JA, Rahn DS, et al. The Pediatric Multiple Organ Dysfunction Score (P-MODS): development and validation of an objective scale to measure the severity of multiple organ dysfunction in critically ill children. Crit Care Med 2005;33:1484-91.

11. Janota J, Stranák Z, Statecná B, et al. Characterization of multiple organ dysfunction syndrome in very low birthweight infants: a new sequential scoring system. Shock (Augusta, Ga) 2001;15:348-52.

12. Pollack MM, Holubkov R, Funai T, et al. The Pediatric Risk of Mortality Score: Update 2015. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2016;17:2-9.

13. Ezz-Eldin ZM, Hamid TA, Youssef MR, et al. Clinical Risk Index for Babies (CRIB II) Scoring System in Prediction of Mortality in Premature Babies. Journal of clinical and diagnostic research : JCDR 2015;9:Sc08-11.

14. Dammann O, Shah B, Naples M, et al. Interinstitutional variation in prediction of death by SNAP-II and SNAPPE-II among extremely preterm infants. Pediatrics 2009;124:e1001-6.

15. Sharma K, Mogensen KM, Robinson MK. Pathophysiology of Critical Illness and Role of Nutrition. Nutr Clin Pract 2019;34:12-22.

16. Taylor AF, Lally KP, Chwals WJ, et al. Hormonal response of the premature primate to operative stress. J Pediatr Surg 1993;28:844-6.

17. Anand KJ, Brown MJ, Bloom SR, et al. Studies on the hormonal regulation of fuel metabolism in the human newborn infant undergoing anaesthesia and surgery. Horm Res 1985;22:115-28.

18. Anand KJ, Aynsley-Green A. Measuring the severity of surgical stress in newborn infants. J Pediatr Surg 1988;23:297-305.

19. Chwals WJ. Overfeeding the critically ill child: fact or fantasy? New Horiz 1994;2:147-55.

20. Jones MO, Pierro A, Hashim IA, et al. Postoperative changes in resting energy expenditure and interleukin 6 level in infants. The British journal of surgery 1994;81:536-8.

21. Anand KJ, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. Lancet (London, England) 1987;1:62-6.

22. Anand KJ, Hansen DD, Hickey PR. Hormonal-metabolic stress responses in neonates undergoing cardiac surgery. Anesthesiology 1990;73:661-70.

23. Srinivasan V. Stress hyperglycemia in pediatric critical illness: the intensive care unit adds to the stress! J Diabetes Sci Technol 2012;6:37-47.

24. Coss-Bu JA, Hamilton-Reeves J, Patel JJ, et al. Protein Requirements of the Critically Ill Pediatric Patient. Nutr Clin Pract 2017;32:128s-41s.

25. Joosten KF, Kerklaan D, Verbruggen SC. Nutritional support and the role of the stress response in critically ill children. Curr Opin Clin Nutr Metab Care 2016;19:226-33.

26. Mesotten D, Joosten K, van Kempen A, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Carbohydrates. Clin Nutr 2018;37:2337-43.

27. Joosten K, Embleton N, Yan W, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Energy. Clin Nutr 2018;37:2309-14.

28. Lambell KJ, Tatucu-Babet OA, Chapple LA, et al. Nutrition therapy in critical illness: a review of the literature for clinicians. Crit Care 2020;24:35.

29. Oshima T, Heidegger CP, Pichard C. Supplemental Parenteral Nutrition Is the Key to Prevent Energy Deficits in Critically Ill Patients. Nutr Clin Pract 2016;31:432-7.

30. Tian T, Coons J, Chang H, et al. Overfeeding-associated hyperglycemia and injury-response homeostasis in critically ill neonates. J Pediatr Surg 2018;53:1688-91.

31. McClintock R, Lifson N. Determination of the total carbon dioxide outputs of rats by the D2O18 method. Am J Physiol 1958;192:76-8.

32. Wong WW, Roberts SB, Racette SB, et al. The doubly labeled water method produces highly reproducible longitudinal results in nutrition studies. J Nutr 2014;144:777-83.

33. Tissot S, Delafosse B, Bertrand O, et al. Clinical validation of the Deltatrac monitoring system in mechanically ventilated patients. Intensive Care Med 1995;21:149-53.

34. Westerterp KR, Lafeber HN, Sulkers EJ, et al. Comparison of short term indirect calorimetry and doubly labeled water method for the assessment of energy expenditure in preterm infants. Biol Neonate 1991;60:75-82.

35. Bendavid I, Lobo DN, Barazzoni R, et al. The centenary of the Harris-Benedict equations: How to assess energy requirements best? Recommendations from the ESPEN expert group. Clin Nutr 2020.

36. Rehal MS, Fiskaare E, Tjader I, et al. Measuring energy expenditure in the intensive care unit: a comparison of indirect calorimetry by E-sCOVX and Quark RMR with Deltatrac II in mechanically ventilated critically ill patients. Crit Care 2016;20:54.

37. Carpenter A, Pencharz P, Mouzaki M. Accurate estimation of energy requirements of young patients. J Pediatr Gastroenterol Nutr 2015;60:4-10.

38. Kerklaan D, Fivez T, Mehta NM, et al. Worldwide Survey of Nutritional Practices in PICUs. Pediatr Crit Care Med 2016;17:10-8.

39. Kerklaan D, Hulst JM, Verhoeven JJ, et al. Use of Indirect Calorimetry to Detect Overfeeding in Critically Ill Children: Finding the Appropriate Definition. J Pediatr Gastroenterol Nutr 2016;63:445-50.

40. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? Pediatrics 2001;107:270-3.

41. Ehrenkranz RA, Dusick AM, Vohr BR, et al. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics 2006;117:1253-61.

42. Valentine CJ, Fernandez S, Rogers LK, et al. Early amino-acid administration improves preterm infant weight. J Perinatol 2009;29:428-32.

43. Dinerstein A, Nieto RM, Solana CL, et al. Early and aggressive nutritional strategy (parenteral and enteral) decreases postnatal growth failure in very low birth weight infants. J Perinatol 2006;26:436-42.

44. Martin CR, Brown YF, Ehrenkranz RA, et al. Nutritional practices and growth velocity in the first month of life in extremely premature infants. Pediatrics 2009;124:649-57.

45. Stoltz SE, Ohlund I, Ahlsson F, et al. Nutrient intakes independently affect growth in extremely preterm infants: results from a population-based study. Acta Paediatr 2013;102:1067-74.

46. Stephens BE, Walden RV, Gargus RA, et al. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. Pediatrics 2009;123:1337-43.

47. Brandt I, Sticker EJ, Lentze MJ. Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood. J Pediatr 2003;142:463-8.

48. Ehrenkranz RA, Das A, Wrage LA, et al. Early nutrition mediates the influence of severity of illness on extremely LBW infants. Pediatr Res 2011;69:522-9.

49. Hulst JM, van Goudoever JB, Zimmermann LJ, et al. The effect of cumulative energy and protein deficiency on anthropometric parameters in a pediatric ICU population. Clin Nutr 2004;23:1381-9.

50. Ng DVY, Unger S, Asbury M, et al. Neonatal Morbidity Count Is Associated With a Reduced Likelihood of Achieving Recommendations for Protein, Lipid, and Energy in Very Low Birth Weight Infants: A Prospective Cohort Study. JPEN J Parenter Enteral Nutr 2018;42:623-32.

51. Mara J, Gentles E, Alfheeaid HA, et al. An evaluation of enteral nutrition practices and nutritional provision in children during the entire length of stay in critical care. BMC Pediatr 2014;14:186.

52. Lapillonne A, Kermorvant-Duchemin E. A systematic review of practice surveys on parenteral nutrition for preterm infants. J Nutr 2013;143:2061s-5s.

53. Iacobelli S, Viaud M, Lapillonne A, et al. Nutrition practice, compliance to guidelines and postnatal growth in moderately premature babies: the NUTRIQUAL French survey. BMC Pediatr 2015;15:110.

54. Mason DG, Puntis JW, McCormick K, et al. Parenteral nutrition for neonates and children: a mixed bag. ArchDisChild 2011;96:209-10.

55. Lapillonne A, Carnielli VP, Embleton ND, et al. Quality of newborn care: adherence to guidelines for parenteral nutrition in preterm infants in four European countries. BMJ Open 2013;3:e003478.

56. Lapillonne A, Fellous L, Mokthari M, et al. Parenteral nutrition objectives for very low birth weight infants: results of a national survey. J Pediatr Gastroenterol Nutr 2009;48:618-26.

57. Bechard LJ, Parrott JS, Mehta NM. Systematic review of the influence of energy and protein intake on protein balance in critically ill children. The Journal of pediatrics 2012;161:333-9.e1.

58. Westin V, Stoltz Sjostrom E, Ahlsson F, et al. Perioperative nutrition in extremely preterm infants undergoing surgical treatment for patent ductus arteriosus is suboptimal. Acta Paediatr 2014;103:282-8.

59. Westin V, Klevebro S, Domellof M, et al. Improved nutrition for extremely preterm infants - A population based observational study. Clin Nutr ESPEN 2018;23:245-51.

60. Rochow N, Fusch G, Muhlinghaus A, et al. A nutritional program to improve outcome of very low birth weight infants. Clin Nutr 2012;31:124-31.

61. Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very low birthweight infant. Clin Perinatol 2002;29:225-44.

62. Miller M, Donda K, Bhutada A, et al. Transitioning Preterm Infants From Parenteral Nutrition: A Comparison of 2 Protocols. JPEN J Parenter Enteral Nutr 2017;41:1371-9.

63. Brennan AM, Fenton S, Murphy BP, et al. Transition Phase Nutrition Recommendations: A Missing Link in the Nutrition Management of Preterm Infants. JPEN J Parenter Enteral Nutr 2018;42:343-51.

64. Brennan AM, Kiely ME, Fenton S, et al. Standardized Parenteral Nutrition for the Transition Phase in Preterm Infants: A Bag That Fits. Nutrients 2018;10.

65. Gentles E, Mara J, Diamantidi K, et al. Delivery of enteral nutrition after the introduction of practice guidelines and participation of dietitians in pediatric critical care clinical teams. J Acad Nutr Diet 2014;114:1974-80.e3.

66. dit Trolli SE, Kermorvant-Duchemin E, Huon C, et al. Early lipid supply and neurological development at one year in very low birth weight (VLBW) preterm infants. Early Hum Dev 2012;88 Suppl 1:S25-S9.

67. Leenders E, de Waard M, van Goudoever JB. Low- versus High-Dose and Early versus Late Parenteral Amino-Acid Administration in Very-Low-Birth-Weight Infants: A Systematic Review and Meta-Analysis. Neonatology 2018;113:187-205.

68. Osborn DA, Schindler T, Jones LJ, et al. Higher versus lower amino acid intake in parenteral nutrition for newborn infants. Cochrane Database Syst Rev 2018;3:Cd005949.

69. Patel JJ, Martindale RG, McClave SA. Controversies Surrounding Critical Care Nutrition: An Appraisal of Permissive Underfeeding, Protein, and Outcomes. JPEN J Parenter Enteral Nutr 2018;42:508-15.

70. Moonen H, Van Zanten ARH. Mitochondrial dysfunction in critical illness during acute metabolic stress and convalescence: consequences for nutrition therapy. Curr Opin Crit Care 2020.

71. Fivez T, Kerklaan D, Mesotten D, et al. Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016;374:1111-22.

72. van Puffelen E, Vanhorebeek I, Joosten KFM, et al. Early versus late parenteral nutrition in critically ill, term neonates: a preplanned secondary subgroup analysis of the PEPaNIC multicentre, randomised controlled trial. The Lancet Child & adolescent health 2018;2:505-15.

73. van Puffelen E, Jacobs A, Verdoorn CJM, et al. International survey of De-implementation of initiating parenteral nutrition early in Paediatric intensive care units. BMC Health Serv Res 2019;19:379.

74. Mehta NM, Skillman HE, Irving SY, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Pediatric Critically Ill Patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition. Pediatr Crit Care Med 2017;18:675-715.

75. Koletzko B, Goulet O, Hunt J, et al. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41 Suppl 2:S1-87.

76. Agostoni C, Buonocore G, Carnielli VP, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr 2010;50:85-91.

77. Reichman BL, Chessex P, Putet G, et al. Partition of energy metabolism and energy cost of growth in the very low-birth-weight infant. Pediatrics 1982;69:446-51.

78. Kleinman R, ed. Pediatric Nutrition Handbook. 6th ed: American Academy of Pediatrics; 2009.

79. Cai W, Yu L, Lu C, et al. Normal value of resting energy expenditure in healthy neonates. Nutrition 2003;19:133-6.

80. Bauer J, Werner C, Gerss J. Metabolic rate analysis of healthy preterm and full-term infants during the first weeks of life. Am J Clin Nutr 2009;90:1517-24.

81. Abranches AD, Soares FVM, Villela LD, et al. Energy expenditure, growth, and nutritional therapy in appropriate and small for gestational age preterm infants. J Pediatr (Rio J) 2018;94:652-7.

82. Bell EF, Johnson KJ, Dove EL. Effect of Body Position on Energy Expenditure of Preterm Infants as Determined by Simultaneous Direct and Indirect Calorimetry. Am J Perinatol 2017;34:493-8.

83. Roberts SB, Young VR. Energy costs of fat and protein deposition in the human infant. Am J Clin Nutr 1988;48:951-5.

84. Pierro A, Carnielli V, Filler RM, et al. Partition of energy metabolism in the surgical newborn. J Pediatr Surg 1991;26:581-6.

85. Jones MO, Pierro A, Hammond P, et al. The metabolic response to operative stress in infants. J Pediatr Surg 1993;28:1258-62; discussion 62-3.

86. Feferbaum R, Leone C, Siqueira AA, et al. Rest energy expenditure is decreased during the acute as compared to the recovery phase of sepsis in newborns. Nutr Metab (Lond) 2010;7:63.

87. Howell HB, Farkouh-Karoleski C, Weindler M, et al. Resting energy expenditure in infants with congenital diaphragmatic hernia without respiratory support at time of neonatal hospital discharge. J Pediatr Surg 2018;53:2100-4.

88. Haliburton B, Chiang M, Marcon M, et al. Nutritional Intake, Energy Expenditure, and Growth of Infants Following Congenital Diaphragmatic Hernia Repair. J Pediatr Gastroenterol Nutr 2016;62:474-8.

89. Shanbhogue RL, Lloyd DA. Absence of hypermetabolism after operation in the newborn infant. JPEN J Parenter Enteral Nutr 1992;16:333-6.

90. Bauer J, Hentschel R, Linderkamp O. Effect of sepsis syndrome on neonatal oxygen consumption and energy expenditure. Pediatrics 2002;110:e69-e.

91. Chwals WJ, Letton RW, Jamie A, et al. Stratification of injury severity using energy expenditure response in surgical infants. J Pediatr Surg 1995;30:1161-4.

92. Chwals WJ, Lally KP, Woolley MM, et al. Measured energy expenditure in critically ill infants and young children. J Surg Res 1988;44:467-72.

93. Powis MR, Smith K, Rennie M, et al. Effect of major abdominal operations on energy and protein metabolism in infants and children. J Pediatr Surg 1998;33:49-53.

94. Bouwmeester NJ, Anand KJ, van Dijk M, et al. Hormonal and metabolic stress responses after major surgery in children aged 0-3 years: a double-blind, randomized trial

comparing the effects of continuous versus intermittent morphine. Br J Anaesth 2001;87:390-9.

95. Tueting JL, Byerley LO, Chwals WJ. Anabolic recovery relative to degree of prematurity after acute injury in neonates. J Pediatr Surg 1999;34:13-7.

96. Briassoulis G, Venkataraman S, Thompson A. Cytokines and metabolic patterns in pediatric patients with critical illness. Clin Dev Immunol 2010;2010:354047-.

97. Hulst JM, van Goudoever JB, Zimmermann LJ, et al. Adequate feeding and the usefulness of the respiratory quotient in critically ill children. Nutrition (Burbank, Los Angeles County, Calif) 2005;21:192-8.

98. Mtaweh H, Garros C, Ashkin A, et al. An Exploratory Retrospective Study of Factors Affecting Energy Expenditure in Critically Ill Children. JPEN J Parenter Enteral Nutr 2019.

99. Pierro A, Jones MO, Hammond P, et al. A new equation to predict the resting energy expenditure of surgical infants. J Pediatr Surg 1994;29:1103-8.

100. Pierro A. Metabolism and nutritional support in the surgical neonate. J Pediatr Surg 2002;37:811-22.

101. Jones MO, Pierro A, Hammond P, et al. Glucose utilization in the surgical newborn infant receiving total parenteral nutrition. J Pediatr Surg 1993;28:1121-5.

102. Basu R, Muller DP, Eaton S, et al. Lipid peroxidation can be reduced in infants on total parenteral nutrition by promoting fat utilisation. J Pediatr Surg 1999;34:255-9.

103. Denne SC, Kalhan SC. Glucose carbon recycling and oxidation in human newborns. Am J Physiol 1986;251:E71-7.

104. Tappy L, Schwarz JM, Schneiter P, et al. Effects of isoenergetic glucose-based or lipid-based parenteral nutrition on glucose metabolism, de novo lipogenesis, and respiratory gas exchanges in critically ill patients. Crit Care Med 1998;26:860-7.

105. Chacko SK, Ordonez J, Sauer PJ, et al. Gluconeogenesis is not regulated by either glucose or insulin in extremely low birth weight infants receiving total parenteral nutrition. J Pediatr 2011;158:891-6.

106. Rozance PJ. Glucose metabolism in the preterm infant. J Pediatr 2011;158:874-5.

107. Dreyfus L, Fischer Fumeaux CJ, Remontet L, et al. Low phosphatemia in extremely low birth weight neonates: A risk factor for hyperglycemia? Clin Nutr 2016;35:1059-65.

108. Ichikawa G, Watabe Y, Suzumura H, et al. Hypophosphatemia in small for gestational age extremely low birth weight infants receiving parenteral nutrition in the first week after birth. JPediatrEndocrinolMetab 2012;25:317-21.

109. Moltu SJ, Strommen K, Blakstad EW, et al. Enhanced feeding in very-low-birth-weight infants may cause electrolyte disturbances and septicemia--a randomized, controlled trial. Clin Nutr 2013;32:207-12.

110. Bonsante F, Iacobelli S, Latorre G, et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants--it is time to change the composition of the early parenteral nutrition. PLoSOne 2013;8:e72880.

111. El Shazly AN, Soliman DR, Assar EH, et al. Phosphate disturbance in critically ill children: Incidence, associated risk factors and clinical outcomes. Annals of medicine and surgery (2012) 2017;21:118-23.

112. Cormack BE, Jiang Y, Harding JE, et al. Neonatal Refeeding Syndrome and Clinical Outcome in Extremely Low-Birth-Weight Babies: Secondary Cohort Analysis From the ProVIDe Trial. JPEN J Parenter Enteral Nutr 2020.

113. Stensvold HJ, Strommen K, Lang AM, et al. Early Enhanced Parenteral Nutrition, Hyperglycemia, and Death Among Extremely Low-Birth-Weight Infants. JAMA pediatrics 2015;169:1003-10.

114. Zamir I, Tornevi A, Abrahamsson T, et al. Hyperglycemia in Extremely Preterm Infants-Insulin Treatment, Mortality and Nutrient Intakes. J Pediatr 2018;200:104-10.e1.

115. Farrag HM, Cowett RM. Glucose homeostasis in the micropremie. Clin Perinatol 2000;27:1-22, v.

116. Meynaar IA, Eslami S, Abu-Hanna A, et al. Blood glucose amplitude variability as predictor for mortality in surgical and medical intensive care unit patients: a multicenter cohort study. J Crit Care 2012;27:119-24.

117. Brunner R, Adelsmayr G, Herkner H, et al. Glycemic variability and glucose complexity in critically ill patients: a retrospective analysis of continuous glucose monitoring data. Crit Care 2012;16:R175-R.

118. Freire Jorge P, Wieringa N, de Felice E, et al. The association of early combined lactate and glucose levels with subsequent renal and liver dysfunction and hospital mortality in critically ill patients. Crit Care 2017;21:218.

119. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med 2020;46:10-67.

120. Bottino M, Cowett RM, Sinclair JC. Interventions for treatment of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev 2011:Cd007453.

121. Sinclair JC, Bottino M, Cowett RM. Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. Cochrane Database Syst Rev 2011:Cd007615.

122. Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes 2006;55:3151-9.

123. Yamada T, Shojima N, Noma H, et al. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive Care Med 2017;43:1-15.

124. Chen L, Li T, Fang F, et al. Tight glycemic control in critically ill pediatric patients: a systematic review and meta-analysis. Crit Care 2018;22:57.

125. Alsweiler JM, Harding JE, Bloomfield FH. Tight glycemic control with insulin in hyperglycemic preterm babies: a randomized controlled trial. Pediatrics 2012;129:639-47.

126. Tottman AC, Alsweiler JM, Bloomfield FH, et al. Long-Term Outcomes of Hyperglycemic Preterm Infants Randomized to Tight Glycemic Control. J Pediatr 2018;193:68-75.e1.

127. Beardsall K, Vanhaesebrouck S, Ogilvy-Stuart AL, et al. Early insulin therapy in very-low-birth-weight infants. N Engl J Med 2008;359:1873-84.

128. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41:580-637.

129. van Goudoever JB, Carnielli V, Darmaun D, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Amino acids. Clin Nutr 2018;37:2315-23.

130. van Goudoever JB, Vlaardingerbroek H, van den Akker CH, et al. Amino acids and proteins. World Rev Nutr Diet 2014;110:49-63.

131. Embleton ND, van den Akker CHP. Protein intakes to optimize outcomes for preterm infants. Semin Perinatol 2019;43:151154.

132. Verbruggen S, Sy J, Arrivillaga A, et al. Parenteral amino acid intakes in critically ill children: a matter of convenience. JPEN J Parenter Enteral Nutr 2010;34:329-40.

133. Blanco CL, Falck A, Green BK, et al. Metabolic responses to early and high protein supplementation in a randomized trial evaluating the prevention of hyperkalemia in extremely low birth weight infants. J Pediatr 2008;153:535-40.

134. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. The New England journal of medicine 1999;340:448-54.

135. Streat SJ, Beddoe AH, Hill GL. Aggressive nutritional support does not prevent protein loss despite fat gain in septic intensive care patients. J Trauma 1987;27:262-6.

136. Jotterand Chaparro C, Laure Depeyre J, Longchamp D, et al. How much protein and energy are needed to equilibrate nitrogen and energy balances in ventilated critically ill children? Clinical nutrition (Edinburgh, Scotland) 2016;35:460-7.

137. Embleton ND. Optimal protein and energy intakes in preterm infants. Early Hum Dev 2007;83:831-7.

138. Reynolds RM, Bass KD, Thureen PJ. Achieving positive protein balance in the immediate postoperative period in neonates undergoing abdominal surgery. J Pediatr 2008;152:63-7.

139. Wesselink E, Koekkoek WAC, Grefte S, et al. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin Nutr 2019;38:982-95.

140. Chwals WJ, Fernandez ME, Jamie AC, et al. Relationship of metabolic indexes to postoperative mortality in surgical infants. J Pediatr Surg 1993;28:819-22.

141. Pons Leite H, Gilberto Henriques Vieira J, Brunow De Carvalho W, et al. The role of insulin-like growth factor I, growth hormone, and plasma proteins in surgical outcome of children with congenital heart disease. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2001;2:29-35.

142. Alaedeen DI, Queen AL, Leung E, et al. C-Reactive protein-determined injury severity: length of stay predictor in surgical infants. J Pediatr Surg 2004;39:1832-4.

143. Burattini I, Bellagamba MP, Spagnoli C, et al. Targeting 2.5 versus 4 g/kg/day of amino acids for extremely low birth weight infants: a randomized clinical trial. J Pediatr 2013;163:1278-82.

144. Vlaardingerbroek H, Vermeulen MJ, Rook D, et al. Safety and efficacy of early parenteral lipid and high-dose amino Acid administration to very low birth weight infants. J Pediatr 2013;163:638-44.

145. Bonsante F, Gouyon JB, Robillard PY, et al. Early optimal parenteral nutrition and metabolic acidosis in very preterm infants. PLoS One 2017;12:e0186936.

146. Calder PC, Adolph M, Deutz NE, et al. Lipids in the intensive care unit: Recommendations from the ESPEN Expert Group. Clin Nutr 2018;37:1-18.

147. Letton RW, Chwals WJ, Jamie A, et al. Neonatal lipid utilization increases with injury severity: recombinant human growth hormone versus placebo. J Pediatr Surg 1996;31:1068-74.

148. Gebara BM, Gelmini M, Sarnaik A. Oxygen consumption, energy expenditure, and substrate utilization after cardiac surgery in children. Crit Care Med 1992;20:1550-4.

149. Lapillonne A, Fidler Mis N, Goulet O, et al. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Lipids. Clin Nutr 2018;37:2324-36.

150. Piedboeuf B, Chessex P, Hazan J, et al. Total parenteral nutrition in the newborn infant: energy substrates and respiratory gas exchange. J Pediatr 1991;118:97-102.

151. Hasselmann M, Reimund J-M. Lipids in the nutritional support of the critically ill patients. Curr Opin Crit Care 2004;10:449-55.

152. Waitzberg DL, Torrinhas RS. Fish oil lipid emulsions and immune response: what clinicians need to know. Nutr Clin Pract 2009;24:487-99.

153. Gura KM, Lee S, Valim C, et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 2008;121:e678-e86.

154. Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr 2007;85:1171-84.

155. Kapoor V, Malviya MN, Soll R. Lipid emulsions for parenterally fed term and late preterm infants. Cochrane Database of Systematic Reviews 2019.

156. Kapoor V, Malviya MN, Soll R. Lipid emulsions for parenterally fed preterm infants. Cochrane Database of Systematic Reviews 2019.

157. Hojsak I, Colomb V, Braegger C, et al. ESPGHAN Committee on Nutrition Position Paper. Intravenous Lipid Emulsions and Risk of Hepatotoxicity in Infants and Children: a Systematic Review and Meta-analysis. J Pediatr Gastroenterol Nutr 2016;62:776-92.

158. Chessex P, Laborie S, Nasef N, et al. Shielding Parenteral Nutrition From Light Improves Survival Rate in Premature Infants. JPEN Journal of parenteral and enteral nutrition 2017;41:378-83.

159. Eveleens RD, Joosten KFM, de Koning BAE, et al. Definitions, predictors and outcomes of feeding intolerance in critically ill children: A systematic review. Clin Nutr 2020;39:685-93.

160. Tume LN, Valla FV, Joosten K, et al. Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) metabolism, endocrine and nutrition section position statement and clinical recommendations. Intensive Care Med 2020;46:411-25.

161. Puntis J, Hojsak I, Ksiazyk J. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Organisational aspects. Clin Nutr 2018;37:2392-400.

162. McClure RJ. Trophic feeding of the preterm infant. Acta Paediatr Suppl 2001;90:19-21.

163. Oddie SJ, Young L, McGuire W. Slow advancement of enteral feed volumes to prevent necrotising enterocolitis in very low birth weight infants. Cochrane Database Syst Rev 2017;8:Cd001241.

164. Tyson JE, Kennedy KA. Trophic feedings for parenterally fed infants. Cochrane Database Syst Rev 2005:Cd000504.

165. Lucas A, Bloom SR, Aynsley-Green A. Gut hormones and 'minimal enteral feeding'. Acta Paediatr Scand 1986;75:719-23.

166. Dorling J, Abbott J, Berrington J, et al. Controlled Trial of Two Incremental Milk-Feeding Rates in Preterm Infants. N Engl J Med 2019;381:1434-43.

167. Moltu SJ, Blakstad EW, Strommen K, et al. Enhanced feeding and diminished postnatal growth failure in very-low-birth-weight infants. J Pediatr Gastroenterol Nutr 2014;58:344-51.

168. Maas C, Franz AR, von Krogh S, et al. Growth and morbidity of extremely preterm infants after early full enteral nutrition. Arch Dis Child Fetal Neonatal Ed 2018;103:F79-f81.

169. Eveleens RD, Hulst JM, de Koning BAE, et al. Achieving enteral nutrition during the acute phase in critically ill children: Associations with patient characteristics and clinical outcome. Clin Nutr 2020.

170. Thyagarajan B, Tillqvist E, Baral V, et al. Minimal enteral nutrition during neonatal hypothermia treatment for perinatal hypoxic-ischaemic encephalopathy is safe and feasible. Acta Paediatr 2015;104:146-51.

171. Chang LL, Wynn JL, Pacella MJ, et al. Enteral Feeding as an Adjunct to Hypothermia in Neonates with Hypoxic-Ischemic Encephalopathy. Neonatology 2018;113:347-52.

172. Hazeldine B, Thyagarajan B, Grant M, et al. Survey of nutritional practices during therapeutic hypothermia for hypoxic-ischaemic encephalopathy. BMJ paediatrics open 2017;1:e000022.

173. Battersby C, Longford N, Patel M, et al. Study protocol: optimising newborn nutrition during and after neonatal therapeutic hypothermia in the United Kingdom: observational study of routinely collected data using propensity matching. BMJ Open 2018;8:e026739.

174. Elke G, van Zanten ARH, Lemieux M, et al. Enteral versus parenteral nutrition in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials. Crit Care 2016;20:117-.

175. Reignier J, Boisramé-Helms J, Brisard L, et al. Enteral versus parenteral early nutrition in ventilated adults with shock: a randomised, controlled, multicentre, open-label, parallel-group study (NUTRIREA-2). Lancet 2018;391:133-43.

176. Harvey SE, Parrott F, Harrison DA, et al. Trial of the route of early nutritional support in critically ill adults. The New England journal of medicine 2014;371:1673-84.

177. Davies DP. The first feed of low birthweight infants. Changing attitudes in the twentieth century. Arch Dis Child 1978;53:187-92.

178. Widdowson EM, McCance RA. The effect of finite periods of undernutrition at different ages on the composition and subsequent development of the rat. ProcRSocLond B BiolSci 1963;158:329-42.

179. Tan M, Abernethy L, Cooke R. Improving head growth in preterm infants--a randomised controlled trial II: MRI and developmental outcomes in the first year. ArchDisChild Fetal Neonatal Ed 2008;93:F342-F6.

180. Tan MJ, Cooke RW. Improving head growth in very preterm infants--a randomised controlled trial I: neonatal outcomes. ArchDisChild Fetal Neonatal Ed 2008;93:F337-F41.

181. Thureen PJ, Melara D, Fennessey PV, et al. Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period. Pediatr Res 2003;53:24-32.

182. Ibrahim HM, Jeroudi MA, Baier RJ, et al. Aggressive early total parental nutrition in low-birth-weight infants. J Perinatol 2004;24:482-6.

183. te Braake FW, van den Akker CH, Wattimena DJ, et al. Amino acid administration to premature infants directly after birth. J Pediatr 2005;147:457-61.

184. Poindexter BB, Langer JC, Dusick AM, et al. Early provision of parenteral amino acids in extremely low birth weight infants: relation to growth and neurodevelopmental outcome. J Pediatr 2006;148:300-5.

185. Drenckpohl D, McConnell C, Gaffney S, et al. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. Pediatrics 2008;122:743-51.

186. Bulbul A, Okan F, Bulbul L, et al. Effect of low versus high early parenteral nutrition on plasma amino acid profiles in very low birth-weight infants. JMaternFetal Neonatal Med 2012;25:770-6.

187. Clark RH, Chace DH, Spitzer AR. Effects of two different doses of amino acid supplementation on growth and blood amino acid levels in premature neonates admitted to the neonatal intensive care unit: a randomized, controlled trial. Pediatrics 2007;120:1286-96.

188. Blanco CL, Baillargeon JG, Morrison RL, et al. Hyperglycemia in extremely low birth weight infants in a predominantly Hispanic population and related morbidities. J Perinatol 2006;26:737-41.

189. Blanco CL, Gong AK, Green BK, et al. Early changes in plasma amino acid concentrations during aggressive nutritional therapy in extremely low birth weight infants. J Pediatr 2011;158:543-8.

190. Balasubramanian H, Nanavati RN, Kabra NS. Effect of two different doses of parenteral amino acid supplementation on postnatal growth of very low birth weight neonates, a randomized controlled trial. Indian Pediatr 2013;50:1131-6.

191. Scattolin S, Gaio P, Betto M, et al. Parenteral amino acid intakes: possible influences of higher intakes on growth and bone status in preterm infants. J Perinatol 2013;33:33-9.

192. Morgan C, McGowan P, Herwitker S, et al. Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study. Pediatrics 2014;133:e120-8.

193. Bellagamba MP, Carmenati E, D'Ascenzo R, et al. One Extra Gram of Protein to Preterm Infants From Birth to 1800 g: A Single-Blinded Randomized Clinical Trial. J Pediatr Gastroenterol Nutr 2016;62:879-84.

194. Uthaya S, Liu X, Babalis D, et al. Nutritional Evaluation and Optimisation in Neonates: a randomized, double-blind controlled trial of amino acid regimen and intravenous lipid composition in preterm parenteral nutrition. Am J Clin Nutr 2016;103:1443-52.

195. Balakrishnan M, Jennings A, Przystac L, et al. Growth and Neurodevelopmental Outcomes of Early, High-Dose Parenteral Amino Acid Intake in Very Low Birth Weight Infants: A Randomized Controlled Trial. JPEN J Parenter Enteral Nutr 2018;42:597-606.

196. Vlaardingerbroek H, Veldhorst MA, Spronk S, et al. Parenteral lipid administration to very-low-birth-weight infants--early introduction of lipids and use of new lipid emulsions: a systematic review and meta-analysis. Am J Clin Nutr 2012;96:255-68.

197. Joffe A, Anton N, Lequier L, et al. Nutritional support for critically ill children. Cochrane Database Syst Rev 2016:Cd005144.

198. Moon K, Athalye-Jape GK, Rao U, et al. Early versus late parenteral nutrition for critically ill term and late preterm infants. Cochrane Database Syst Rev 2020;4:Cd013141.

199. Gottschlich MM, Jenkins ME, Mayes T, et al. The 2002 Clinical Research Award. An evaluation of the safety of early vs delayed enteral support and effects on clinical, nutritional, and endocrine outcomes after severe burns. J Burn Care Rehabil 2002;23:401-15.

200. Meinert E, Bell MJ, Buttram S, et al. Initiating Nutritional Support Before 72 Hours Is Associated With Favorable Outcome After Severe Traumatic Brain Injury in Children: A Secondary Analysis of a Randomized, Controlled Trial of Therapeutic Hypothermia. Pediatr Crit Care Med 2018;19:345-52.

201. Vanhorebeek I, Verbruggen S, Casaer MP, et al. Effect of early supplemental parenteral nutrition in the paediatric ICU: a preplanned observational study of post-randomisation treatments in the PEPaNIC trial. The Lancet Respiratory medicine 2017;5:475-83.

202. van Puffelen E, Hulst JM, Vanhorebeek I, et al. Outcomes of Delaying Parenteral Nutrition for 1 Week vs Initiation Within 24 Hours Among Undernourished Children in Pediatric Intensive Care: A Subanalysis of the PEPaNIC Randomized Clinical Trial. JAMA network open 2018;1:e182668.

203. Casaer MP, Wilmer A, Hermans G, et al. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 2013;187:247-55.

204. De Bruyn A, Gunst J, Goossens C, et al. Effect of withholding early parenteral nutrition in PICU on ketogenesis as potential mediator of its outcome benefit. Crit Care 2020;24:536.

205. Verstraete S, Verbruggen SC, Hordijk JA, et al. Long-term developmental effects of withholding parenteral nutrition for 1 week in the paediatric intensive care unit: a 2-year follow-up of the PEPaNIC international, randomised, controlled trial. The Lancet Respiratory medicine 2019;7:141-53.

206. Jacobs A, Dulfer K, Eveleens RD, et al. Long-term developmental effect of withholding parenteral nutrition in paediatric intensive care units: a 4-year follow-up of the PEPaNIC randomised controlled trial. The Lancet Child & adolescent health 2020;4:503-14.

207. Verlinden I, Dulfer K, Vanhorebeek I, et al. Role of age of critically ill children at time of exposure to early or late parenteral nutrition in determining the impact hereof on long-term neurocognitive development: A secondary analysis of the PEPaNIC-RCT. Clin Nutr 2020.

208. Mehta NM. Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016;374:1190-2.

209. Koletzko B, Goulet O, Jochum F, et al. Use of parenteral nutrition in the pediatric ICU: should we panic because of PEPaNIC? Curr Opin Clin Nutr Metab Care 2017;20:201-3.

210. Groenendaal F. Early versus Late Parenteral Nutrition in Critically Ill Children. N Engl J Med 2016;375:384.

211. Chwals WJ. Evaluating the Impact of Delaying Parenteral Nutrition in Critically Ill Children. Pediatr Crit Care Med 2018;19:1169-72.

212. Balaguer M, Jordan I. Time of parenteral nutrition in paediatric critical care patients, prior nutritional status probably makes the difference? J Thorac Dis 2016;8:1869-71.

213. Mehta NM, Compher C. Clinical guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr 2009;33.

214. Koletzko B, Goulet O, Hunt J, et al. Guidelines on Paediatric Parenteral Nutrition of the European Society of Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41.

215. Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children--an international multicenter cohort study*. Crit Care Med 2012;40:2204-11.

216. Wong JJ-M, Han WM, Sultana R, et al. Nutrition Delivery Affects Outcomes in Pediatric Acute Respiratory Distress Syndrome. JPEN Journal of parenteral and enteral nutrition 2017;41:1007-13.

Figure 1.
Simplified overview of different phases of critical illness. Note that the timing durations may be extremely variable.

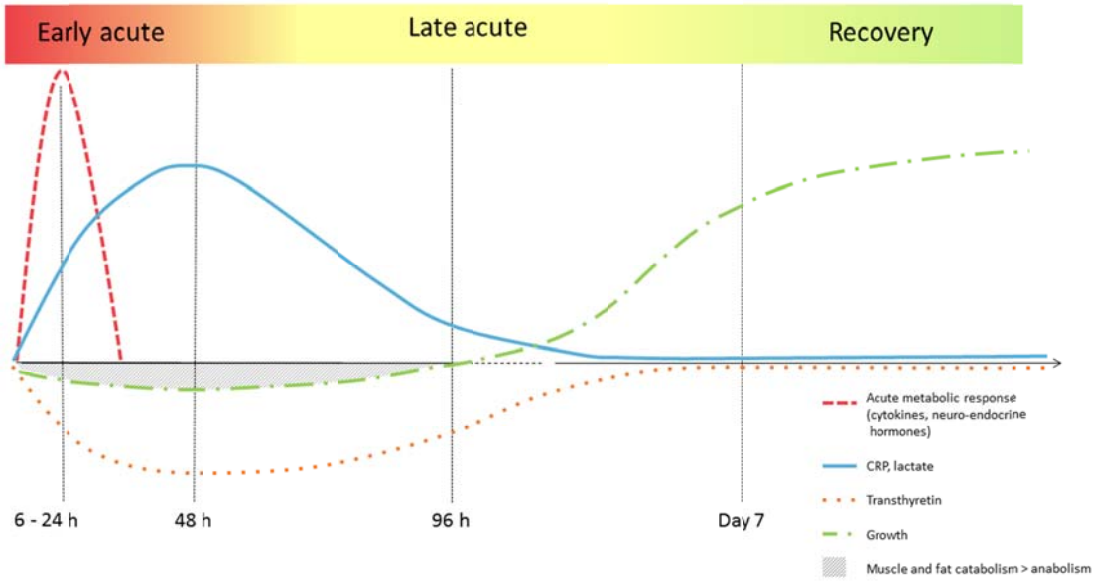
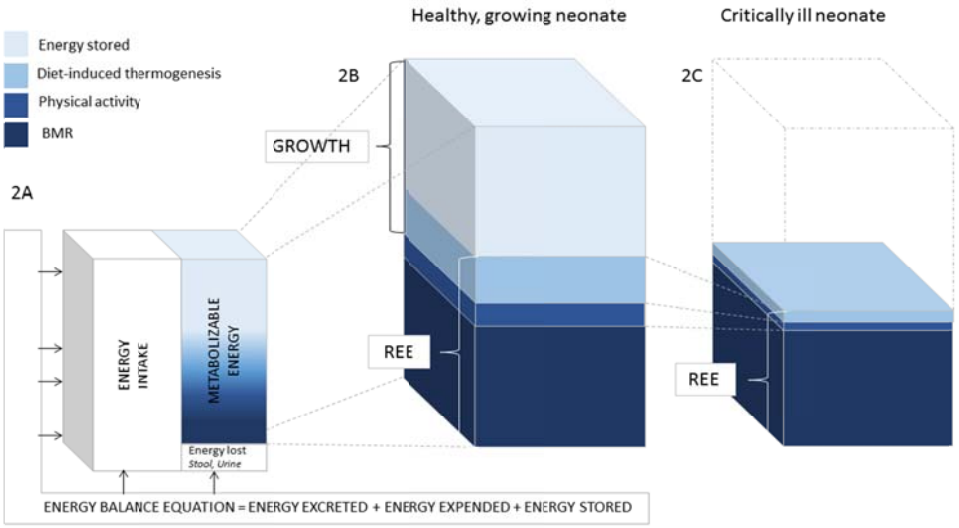


Figure 2. Energy balance in healthy and critically ill neonates



BMR=Basal metabolic rate; REE=Resting energy expenditure

Figure 3.

Recommendation for nutritional management of the critically ill neonate

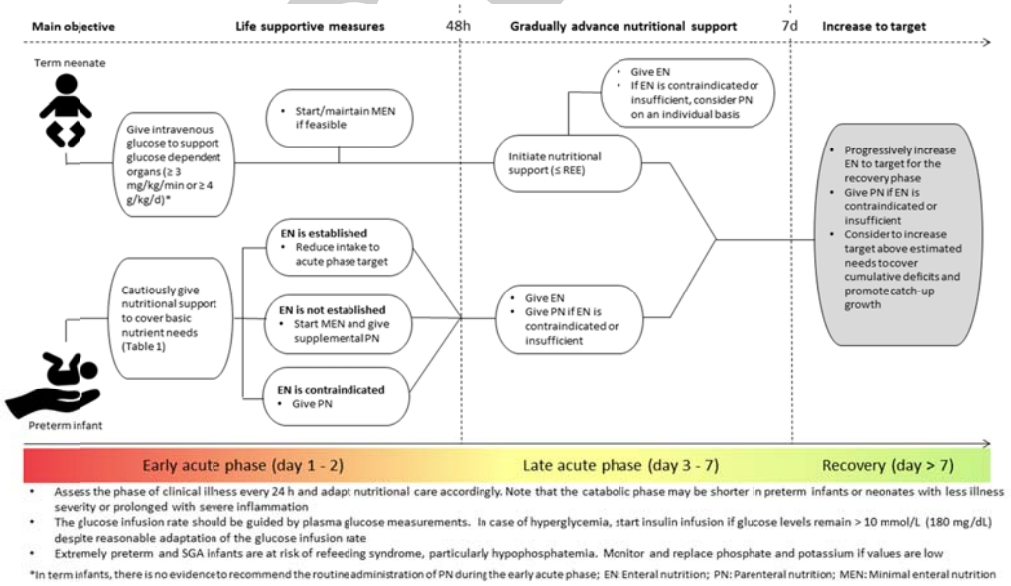


Table 1. Common clinical variables and biomarkers used for the diagnosis and assessment of critical illness. The systemic inflammatory response syndrome (SIRS) refers to any combination of temperature variability (hypothermia, fever), tachycardia, tachypnoea and change in leucocyte count and is referred to as sepsis when it is triggered by an infection. [#]CRIB; Clinical risk index for babies. [$]SNAP; Score for neonatal acute physiology.

Organ specific physiologic variables and biomarkers used for the diagnosis and assessment of critical illness			
Typical underlying conditions for critical illness in preterm and term neonates	Organ system	Physiologic variables	Biomarkers
• Congenital heart defects with hemodynamic instability • Preterm infants with high illness severity score (ie CRIB[#] II-score > 11, SNAP[$]-II ≥ 30) • Major abdominal surgery • Necrotizing enterocolitis (NEC) • Sepsis • Severe asphyxia (hypoxic ischemic encephalopathy) • Severe respiratory distress syndrome (RDS)	Cardiovascular	Skin colour, capillary refill time Hear rate Arterial blood pressure Central venous pressure Pulmonary arterial pressure	Lactate
	Endocrine	Fatigue, muscle weakness, fluid retention, polyuria, and more	Glucose, glucose variability, vasopressin, osmolarity (serum/urine)
	Haematological	Petechiae and ecchymosis, disseminated intravascular coagulopathy	Platelet and leucocyte count, fibrinogen
	Hepatic	Liver size and consistency	Aspartate transaminase (ASAT), bilirubin, C-reactive protein (CRP), procalcitonin, prothrombin time or INR, serum (s)-protein, transthyretin, s-urea
	Neurological	Seizures, pupillary reaction, Glasgow Coma Scale, Core temperature > 38.5 or < 36 °C, Temperature variability	
	Renal	Urine output	s-creatinine, s-urea, s-protein
	Respiratory	Hypocapnia, hypoxemia, mechanical ventilation, respiratory rate	pH, $paCO_2$, PaO_2/FiO_2 ratio
Age specific SIRS criteria for term neonates[$]			
	Newborn (0 -7 days)		Neonate (8 - 28 days)
Heart rate (beats/min)	< 100 or > 180		< 100 or > 180
Respiratory rate (breaths/min)	> 50		> 40
Systolic blood pressure (mmHg)	< 59		< 79
Leucocyte count ($10^3/mm^3$)	< 34		> 19.5 or < 5

Table 2.
Theoretical energy and macronutrient needs during different phases of critical illness in the neonate

	Preterm infants			Term neonates < 28 d		
	Early acute	**Late acute**	**Recovery**	**Early Acute**	**Late acute**	**Recovery**
Energy (kcal/kg/d)						
Enteral	40-55	70-95	110-160	35-50	55-80	90-120
Parenteral[1]	40-55	60-80	90-120	15-40	45-70	75-85
Glucose (g/kg/d)[2]						
Enteral	5-8	7-11	11-15 (18)	4-6	6-10	9-15
Parenteral[1]	5-8 (10)	7-10 (12)	11-14 (17)	4-7 (10)	6-10	8-14
Glucose (~mg/kg/min)						
Enteral	*3.5-5.5*	*5-7.5*	*7.5-10.5 (12.5)*	*3-5*	*4-7*	*6-10.5*
Parenteral[1]	*3.5-5.5 (7.0)*	*5-7 (8.5)*	*7.5-10 (12)*	*3-5 (10)*	*4-7*	*5.5-10*
Protein (g/kg/d)						
Enteral	1.0-2.0	2.0-3.0	3.5-4.5	< 1.5	1.5-2.5	2.0-3.5
Parenteral[1]	1.0-2.0	2.0-3.0	2.5-3.5	0 (-1.0)	1.5-2.5	2.0-3.0
Lipids (g/kg/d)						
Enteral	2.0-3.0	3.0-6.0	5.0-8.0	< 3.0	3.0-4.5	4.0-6.0
Parenteral[1,3]	1.0-2.0	2.0-3.0	3.0-4.0	0 (-1.5)	1.5-2.5	3.0-4.0

[1] When supplementing parenteral nutrition, enteral intakes need to be considered (subtracted from estimated total needs) to optimize nutrient supply and reduce the risk of overfeeding. Note that parenteral energy needs are lower than enteral requirements, and that the maximum ranges of protein (amino acids) and lipids are lower than when given enterally.
[2] The glucose supply should be guided by plasma glucose measurements to avoid hypo- and hyperglycemia
[3] Lipids should be an integral part of PN (30-50% of non-protein calories) and the non-protein energy to protein ratio > 25 kcal/g protein to facilitate protein utilization.