ESPGLAHN/ESVEN/ESPR guidelines on pediatric parenteral nutrition: Carbohydrates

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Table: Recommendations for carbohydrates

| R 5.1 | The amount of glucose to be provided by PN should be guided by [1] the balance between meeting energy needs and the risks of overfeeding/excess glucose load [2], phase of illness (acute, stable, recovery/growing) [3], macronutrient supply by enteral and parenteral nutrition, and [4] glucose administered outside enteral and parenteral nutrition, e.g. with medication (GPP, conditional recommendation) |
| R 5.2 | Excessive glucose intake should be avoided because it may be responsible for hyperglycemia (LoE 1–, RG A, strong recommendation), causes increased lipogenesis and fat tissue deposition together with subsequent liver steatosis and enhanced production of VLDL triglycerides by the liver (LoE 2+, RG B, strong recommendation), and may cause increased CO₂ production and minute ventilation (LoE 2+, RG B, strong recommendation) |
| R 5.3 | Glucose intake does not lower protein catabolism in the acute phase of critical illness (LoE 1–, RG A, strong recommendation) |
| R 5.4 | Recommended parenteral glucose supply in (pre)term newborns in mg/kg per min (g/kg per day) (LoE 2+, RG B, strong recommendation) |

The amount of glucose to be provided by PN should be guided by [1] the balance between meeting energy needs and the risks of overfeeding/excess glucose load [2], phase of illness (acute, stable, recovery/growing) [3], macronutrient supply by enteral and parenteral nutrition, and [4] glucose administered outside enteral and parenteral nutrition, e.g. with medication (GPP, conditional recommendation, strong consensus).

Carbohydrates are the main source of energy in nutrition and usually provide 40–60% of the energy supply in western diets. The majority of the carbohydrate derived from a normal diet reaches the body’s peripheral tissues as glucose. Glucose is utilised by all cells and serves as metabolic fuel for muscle, liver, heart, kidneys and gut and as the obligate energy source for brain, renal medulla and erythrocytes. Glucose is the main carbohydrate utilized during foetal life; in the last trimester of pregnancy about 5 mg/kg per min (7 g/kg per day) of glucose crosses the placenta. In parenteral nutrition (PN) carbohydrate is provided as dextrose (D-Glucose), in its monohydrate form. Dextrose usually contributes most to the osmolality of the PN-solution.

Repetitive and/or prolonged hypoglycemia should be avoided in all ICU patients (extrapolated LoE 2+, RG 0, strong recommendation).
recommendation in the acute, critically ill neonate or child deserves a separate approach.

Glucose metabolism is influenced by age, acute illness, nutritional state and the concomitant provision of other macronutrients. Hence, the amount of glucose to be provided by PN should be guided by [1] the balance between meeting energy needs and the risks of overfeeding/excess glucose load [2], phase of illness (acute, stable, recovery/growing) [3], macronutrient supply from enteral and parenteral nutrition, and [4] glucose administered outside enteral and parenteral nutrition, e.g. with medication.

The statements and recommendations that follow should be taken into consideration when treating a (critically) ill child or neonate who cannot be enterally fed during the acute and/or stable phase of his illness. Neonates and children with a (suspected) underlying metabolic disorder require specific carbohydrate intakes, which are not covered in this chapter.

3. Consequences of overfeeding with glucose

**R 5.2 Excessive glucose intake should be avoided because it may be responsible for hyperglycaemia (LoE 1 – RG A, strong recommendation), causes increased lipogenesis and fat tissue deposition together with subsequent liver steatosis and enhanced production of VLDL triglycerides by the liver (LoE 2+, RG B, strong recommendation), and may cause increased CO2 production and minute ventilation (LoE 2+, RG B, strong recommendation, strong consensus)**

**R 5.3 Glucose intake does not lower protein catabolism in the acute phase of critical illness (LoE 1 – RG A, strong recommendation, strong consensus)**

When glucose is administered in excess of the amount that can be directly oxidized for energy production and glycogen synthesis, the excess is directed to lipogenesis, thus promoting fat deposition [8,9]. Restoration or accumulation of fat stores may be a nutritional goal in infants and children with (severe) malnutrition or rapid growth, by providing more lipids rather than by excessive carbohydrate administration. Excessive fat deposition and dyslipidaemia may be deleterious, especially during the acute phase of critical illness [10]. The conversion of glucose into lipids partially accounts for the increase in energy expenditure observed with high rates of glucose infusion [11]. Excessive glucose intake as well as total energy delivery and amino acid intake, increases CO2 production and minute ventilation [12–14]. Excessive glucose intake may also impair liver function especially by inducing steatosis, while its contribution to the development of cholestasis is not clearly established [15,16]. Studies in healthy adults suggest that high carbohydrate feeding leads to an increase in total very-low-density lipoprotein (VLDL) triglyceride secretion rate from de novo synthesis, primarily due to stimulation of the secretion of preformed fatty acids (FA) [17]. These results imply that the liver derives its energy from carbohydrate oxidation rather than from FA oxidation. FA taken up by the liver are channelled into VLDL triglycerides. Hepatic steatosis results when export of the VLDL triglycerides does not keep pace with triglyceride production [17,18]. High carbohydrate intake, both in hypercaloric as well as eucaloric conditions, leads to lipogenesis [19,20].

Furthermore, high carbohydrate intake induces insulin resistance through activation of the transcription factor ChREBP (carbohydrate response element binding protein) to protect the liver from glucose overload, which will lead to a counterproductive increase in hepatic glucose production [21]. Critical illness causes dyslipidaemia, characterized by increased triglycerides and VLDL, and hypercholesterolaemia [10,22,23]. Although these pathways have not been thoroughly studied in critically ill neonates or children, dyslipidaemia has been observed in septic children [24]. Therefore, excess glucose intake may exacerbate critical illness related dyslipidaemia in children as in adults.

Another concern of parenteral glucose overfeeding is its association with hyperglycaemia. In critically ill children this is caused by insulin resistance as well as beta-cell dysfunction [25,26]. The consequences and management of hyperglycaemia in critically ill children are discussed in the final paragraph of this chapter.

Adding lipid emulsions and amino acid infusions allow the energy input to be diversified, and glucose intake to be decreased, while maintaining adequate energy intake [27]. In preterm newborns, protein metabolism is influenced by the amount and composition of energy intake [28,29].

The glucose intake recommendations in the former guidelines did not cater for acute critical illness [30]. Under these circumstances, the administration of total caloric and glucose amounts appropriate for healthy, growing infants and children may induce hyperglycaemia and other metabolic derangements [5,31]. Decreased energy recommendations in the acute phase of critical illness (chapter 1) allow the parenteral glucose intake to be lowered. The amount of glucose and/or energy intake does not impact protein metabolism in the acute post-operative phase [6,7]. Reduced glucose intake in these critically ill infants safely lowered high blood glucose levels, despite an increased endogenous glucose production [31,32]. A study in burned children (age 7.3 ± 5.4 y) also showed that judicious use of parenteral nutrition within one week of injury by capping glucose intake at 5–7 mg/kg/min was safe and effective, while minimizing complications of PN [33]. When a patient is recovering, insulin resistance will decrease and glucose metabolism will improve. This will allow a higher glucose supply, necessary for rehabilitation and growth.

4. Rate of endogenous glucose production and rate of glucose oxidation

The efficiency with which glucose is utilised should guide the upper limit of carbohydrate supply, while the lower limit is defined by the risk of hypoglycaemia. The majority of quantitative estimates of production and oxidation of glucose have been performed using stable isotopic tracers and indirect calorimetry (IC) in healthy term or preterm newborns. Stable isotope studies cannot be used at the bedside and IC has several limitations. Furthermore, IC uses a Respiratory Quotient >1 as marker of excessive glucose intake, but this has not been validated. Rate of glucose oxidation (RGO) and endogenous rate of glucose production (RGP) can be measured with stable isotopes. Exogenous glucose delivered in excess of the rate of glucose oxidation (RGO) may enter non-oxidative pathways and is unlikely to improve energy balance. Decreasing or stopping endogenous glucose production would be a normal physiological response. When exogenous glucose is insufficient this would increase the RGP, however this could be insufficient to prevent hypoglycaemia. Again, these responses are affected by age as well by the phase of illness.

4.1. Endogenous glucose production in preterm infants

In preterm infants RGP, gluconeogenesis and glycogenolysis have been studied under different nutritional circumstances, showing that RGP in preterm infants is influenced by IV glucose and PN. RGP increased in preterm infants when the exclusive IV exogenous glucose administration was diminished from 6 to 4 mg/kg per min. Nevertheless, the increased RGP was not enough to
prevent a drop in plasma glucose concentration [39]. Gluconeogenesis is responsible for about 31% of RGP in fasting, healthy full term newborns [40] and for up to 75% in healthy preterm infants receiving IV glucose or PN [39,41]. RGP and gluconeogenesis can be stimulated in preterm infants by administration of glycerol, IV lipids or PN [39,42–44], but not by the administration of alanine [45]. Glucagon increases glucose production from glycogenolysis in preterm infants. Nevertheless, the response is low, especially considering their increased needs [46]. These studies show that preterm infants are capable of glucose production and gluconeogenesis. However, production capacity is limited and therefore they depend both on exogenous glucose and PN components to maintain glucose homeostasis and avoid hypoglycaemia.

On the other hand, several studies showed that in extremely preterm neonates (24–29 weeks) endogenous glucose production and gluconeogenesis on day 3–4 were not affected by the glucose infusion rate or blood glucose levels [41,42,47]. In contrast, in moderately preterm neonates (31 ± 1.5 weeks) the endogenous glucose production on day 8 was suppressed completely by parenteral glucose intake [48]. These studies suggest that the inability to suppress glucose production or gluconeogenesis may contribute to the risk of hyperglycaemia in extremely preterm infants.

4.2. Endogenous glucose production in older infants and children

The basal rate of endogenous glucose production (RGP) varies from 2 mg/kg per min (2.9 g/kg per day) in adults, to 8 mg/kg per min (11.5 g/kg per day) in preterm infants [39,49]. The RGP is maximal during the postnatal period and decreases gradually with age [46]. Few studies are available for infants and children, and even fewer during acute critical illness. In post-surgical critically ill infants (5–10 months of age) reducing parenteral glucose intake in the acute phase to 2.5 mg/kg per min lowered high glycaemic levels and increased the RGP, primarily through increased glycogenolysis [31,32].

4.3. Rate of glucose oxidation

During PN, the rate of parenteral glucose delivery should not exceed the maximum rate of glucose oxidation (RGO). Only three studies have measured RGO in children, showing significant differences among patients according to their age and clinical status. In appropriate for gestational age preterm infants, the RGO is 6–8 mg/kg per min (8.6–11.5 g/kg per day) [50,51]. In term infants after surgery or infants on long-term PN, the maximal RGO is about 12 mg/kg per min (172 g/kg per day) [52,53]. In contrast, a small study in critically burned children (1–11 y) demonstrated the maximal RGO (3.8 mg/kg per min or 5.5 g/kg per day) to be at a glucose intake of 5 mg/kg per min [54].

4.4. General recommendations for parenteral carbohydrate intake

### R 5.5

<table>
<thead>
<tr>
<th>Newborns &lt; 28 days of age, who have an episode of acute illness such as infection or sepsis, should temporarily receive the carbohydrate supply of day 1 (R5.4), guided by the blood glucose levels (GPP, conditional recommendation, strong consensus)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute phase</strong></td>
</tr>
<tr>
<td>28 d–10 kg</td>
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<tr>
<td>11–30 kg</td>
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<tr>
<td>31–45 kg</td>
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<td>&gt; 45 kg</td>
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Acute phase = resuscitation phase when the patient requires vital organ support (sedation, mechanical ventilation, vasopressors, fluid resuscitation). Stable phase = patient is stable on, or can be weaned, from this vital support. Recovery phase = patient who is mobilizing.

The phase of critical illness plays a role in the energy requirement (also see Chapter Energy) and hence also in the carbohydrate supply [55]. A recent large international multicentre randomised controlled trial in 1440 critically ill children, including term neonates, (PEPaNIC study) compared whether a strategy of withholding parenteral nutrition up to day 8 in the PICU (late parenteral nutrition) was clinically superior to early initiation of supplemental PN (initiated within 24 h after admission) [37,38]. It was shown that withholding parenteral nutrition for 1 week while administering micronutrients intravenously was clinically superior to providing early parenteral nutrition to supplement insufficient enteral nutrition. No parenteral nutrition for 1 week significantly reduced the number of new infections, the time on a ventilator, kidney failure and increased the likelihood of earlier live discharge from the PICU and the hospital with decreased direct medical costs [34–36,40]. Based on the above statements we propose that most likely lower amounts of energy/carbohydrate should be given to acutely critically ill children. This acute phase of critical illness (first hours to days) only covers the resuscitation phase when the unstable patient requires vital organ support (sedation, mechanical ventilation, vasopressors, fluid resuscitation). When a patient has been stabilised on, or can be weaned from, this vital support, he/she is in the stable phase. When the child is mobilising, it is called the recovery phase [55]. In the recovery phase more energy/carbohydrates should be provided, which should be further increased in the recovery phase in order to achieve growth.

In (preterm) newborns energy/carbohydrate amounts are gradually increased over the first postnatal days. Carbohydrate intake is determined by energy requirements, blood glucose levels and — after the nadir in postnatal weight loss — growth. The blood glucose level is an important determinant for glucose supply on the first postnatal day. Thereafter the glucose intake is increased stepwise over the next 2–3 days, usually up to 10 mg/kg per min (14.4 g/kg per day) in order to allow growth. Parenteral carbohydrate intake should preferably not exceed 12 mg/kg per min (17.3 g/kg per day) and generally not be lower than 4 mg/kg per min (5.8 g/kg per day) in preterm infants or 2.5 mg/kg per min (3.6 g/kg per day) in term newborns.

Carbohydrate intake must be individualized, especially in newborn infants with specific problems, e.g. hypo- or hyperglycaemia, severe perinatal asphyxia (as concomitant hyperglycaemia may exacerbate brain damage), hyperinsulinaemia, and newborns on (long-term) PN with lipid intolerance or insufficient growth. Finally, as stated before, these statements and recommendations are not applicable to neonates and children with a (suspected) metabolic disorder.
5. Dysglycemia and blood glucose management

5.1. Blood glucose measurements

**R 5.7** Blood glucose measurements should preferably be performed on blood gas analysers (LoE 2+, RG B, strong recommendation, strong consensus)

Blood glucose management starts with measuring blood glucose levels. These measurements should be accurate and accessible for bedside nurses and doctors at the bedside. Due to the use of capillary blood, anaemia and drugs that interfere with the enzymatic reaction of the blood glucose measurement such as ascorbic acid and acetylaminocephin, the accuracy of handheld blood glucose meters is less accurate in critically ill patients [56]. In critically ill patients blood glucose levels can be measured most accurately yet still practically on arterial blood using blood gas analysers [57–59]. In patients who do not need an arterial line, handheld blood glucose meters may be used [58,60].

In newborn infants the accuracy of handheld blood glucose meters is still of great concern [60–63]. Factors that influence glucose measurements are (amongst others) high haemoglobin levels and high bilirubin levels [62–64]. Despite this, handheld blood glucose meters are frequently used in daily clinical practice since they provide very rapid results. Standard laboratory testing is not preferable because of the delay in obtaining a result and the possibility of falsely low results due to ongoing glycolysis in the sample, if appropriate pre-analytical guidelines are neglected [65]. At present, the best method combining quick results and accuracy is delivered by blood gas analysers with glucose modules for blood glucose measurements in newborn infants [66,67].

5.2. Hyperglycaemia

**R 5.8** Hyperglycaemia >8 mmol/L (145 mg/dL) should be avoided in paediatric ICU patients because of increased morbidity and mortality (LoE 1+, RG A, strong recommendation, strong consensus)

**R 5.9** In PICU, repetitive blood glucose levels >10 mmol/L (180 mg/dL) should be treated with continuous insulin infusion (LoE 1+, RG A, strong recommendation, strong consensus)

**R 5.10** Hyperglycaemia >8 mmol/L (145 mg/dL) should be avoided in neonatal ICU patients because it is associated with increased morbidity and mortality (LoE 2+, RG B, strong recommendation, strong consensus)

**R 5.11** In NICU, repetitive blood glucose levels >10 mmol/L (180 mg/dL) should be treated with insulin therapy, when reasonable adaptation of glucose infusion rate has been insufficient (LoE 2+, RG B, conditional recommendation, strong consensus)

In preterm infants, the most common definition of hyperglycaemia is a blood glucose level exceeding 10 mmol/L (180 mg/dL) [68] and this has been associated with increased morbidity [69–73]. Insulin therapy in (preterm) newborns is effective in treating or preventing hyperglycaemia, but also leads to an increased incidence of hypoglycaemia. There is no evidence for recommending tight blood glucose management in the NICU [74]. Hence, insulin therapy at a low starting dose is preferred and only when reasonable adaptation of the glucose infusion rate is insufficient to control neonatal hyperglycaemia [75,76].

In critically ill children, hyperglycaemia has consistently been associated with increased morbidity and mortality [77–81]. Malnourished children with hyperglycaemia have a greater risk of mortality than well-nourished patients [82]. The definitions for hyperglycaemia range from blood glucose levels above 7 mmol/L (126 mg/dL) [83] to levels above 8.3 mmol/L (150 mg/dL) [84]. In a single-centre RCT, tight blood glucose management, to levels between 2.8 and 4.4 mmol/L (50–80 mg/dL) in infants and between 3.9 and 5.6 mmol/L (70–100 mg/dL) in children, reduced the incidence of nosocomial infections, shortened length of stay in the ICU and lowered mortality rate [85]. However, a quarter of the children in the intervention group experienced at least one episode of hypoglycaemia below 2.2 mmol/L (40 mg/dL). Also in severely burned paediatric patients, intensive insulin therapy decreased morbidity [86]. Blood glucose control to a slightly higher target range than the study by Vlasselaers et al. did not result in a better outcome in multicentre trials, in comparison with the control group in which insulin treatment was only started in case of excessive hyperglycaemia [87,88]. A meta-analysis of these four trials revealed that tight blood glucose control in critically ill children does not decrease mortality, but reduces new infections. Yet, tight blood glucose control is strongly associated with a higher incidence of hypoglycaemia [89].

5.3. Hypoglycaemia

**R 5.12** Repetitive and/or prolonged hypoglycaemia ≤2.5 mmol/L (45 mg/dL) should be avoided in all ICU patients (extrapolated LoE 2+, RG B, strong recommendation, strong consensus)

In critically ill children hypoglycaemia is defined as a blood glucose level below 2.8 mmol/L (50 mg/dL) [90] or below 3.3 mmol/L (60 mg/dL) [91]. A recent systematic review and meta-analysis proposed to define hypoglycaemia as 2.2–2.5 mmol/L (<40–45 mg/dL) in newborns and 3.3–3.6 mmol/L (<60–65 mg/dL) in children [90]. The association between hypoglycaemia and mortality risk is less robust in critically ill children, since severity of illness and age may be important confounders [90,92]. Also the long term consequences of a brief period of low glucose levels, that are not associated with clinical signs, remain uncertain. Four years after study inclusion in the trial on tight blood glucose management and being exposed to hypoglycaemia, the children who underwent tight blood glucose control did not show impaired neurocognitive development [92]. Studies on the effect of hypoglycaemia in the postnatal period on subsequent neurodevelopment are mostly of poor methodological quality and so far could not provide a valid estimate [93]. In preterm newborns a large cohort study reported impaired motor and cognitive development at 18 months [94], but found no differences in developmental progress or physical disability 15 years after recurrent low blood glucose levels ≤2.5 mmol/L in the first 10 days after birth [95]. In a more recent cohort study neonatal (>35 weeks) hypoglycaemia was not associated with impaired neurological outcome at two years when treated to maintain blood glucose concentrations of at least 2.6 mmol/L (47 mg/dL) [96]. In (preterm) newborns the suggested blood glucose operational threshold concentrations at which clinicians should consider intervention are: a single measurement of blood glucose <1 mmol/L (18 mg/dL); blood glucose level <2 mmol/L (36 mg/dL) which remains below the same value at the next measurement; or a single measurement of <2.5 mmol/L (45 mg/dL) in a newborn with abnormal clinical signs [97]. Certainly newborns with risk factors for hypoglycaemia, such as premature birth, low birth weight and perinatal asphyxia, require close monitoring and management of their blood glucose levels [98].
Conflict of interest
None declared.

References

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