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ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Amino acids

Johannes B. van Goudoever [a, *], Virgilio Carnielli [b], Dominique Darmaun [c], Miguel Sainz de Pipaon [d], the ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition[1]

[a] Amsterdam UMC, University of Amsterdam, Vrije Universiteit Amsterdam, Emma Children's Hospital, Amsterdam, The Netherlands
[b] Salesi Hospital and Polytechnic University of Marche, Ancona, Italy
[c] IMAD, CHU de Nantes, UMR PHAN, INRA, Université de Nantes, IMAD, CRNH-Ouest, Nantes, France
[d] La Paz University Hospital, Instituto de Salud Carlos III, Red de Salud Materno Infantil y Desarrollo-SAMID, Autonomous University of Madrid, Madrid, Spain

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1. Methods

Search: Searches were performed in three stages. First, all the titles with the relevant key words were retrieved by the Cochrane Collaboration Department from Budapest, who also performed the first reduction. Publications published after the previous guidelines [1] (i.e., from 2004–December 2014), were considered. Members of the Working Group subsequently read all the titles and abstracts, and selected potentially relevant ones. These were retrieved and full articles were assessed. Some studies published in 2015 or 2016

* Corresponding author.
E-mail address: h.vangoudoever@amc.nl (J.B. van Goudoever).

[1] ESPGHAN/ESPEN/ESPR/CSPEN working group on Pediatric Parenteral Nutrition: BRAEGGER Christian, University Children's Hospital, Zurich, Switzerland; BRONSKY Jiri, University Hospital Motol, Prague, Czech Republic; CAI Wei, Shanghai Jiao Tong University, Shanghai, China; CAMPOY Cristina, Department of Paediatrics, School of Medicine, University of Granada, Granada, Spain; CARNIELLI Virgilio, Polytechnic University of Marche, Ancona, Italy; DARMAUN Dominique, Université de Nantes, Nantes, France; DECSI Tamás, Department of Pediatrics, University of Pécs, Pécs, Hungary; DOMELLÖF Magnus, Department of Clinical Sciences, Pediatrics, Umeå University, Sweden; EMBLETON Nicholas, Newcastle University, Newcastle upon Tyne, The United Kingdom; FEWTRELL Mary, UCL Great Ormond Street Institute of Child Health, London, UK; FIDLER MIS Nataša, University Medical Centre Ljubljana, Ljubljana, Slovenia; FRANZ Axel, University Children's Hospital, Tuebingen, Germany; GOULET Olivier, University Sordonne-Paris-Cité; Paris-Descartes Medical School, Paris, France; HARTMAN Corina, Schneider Children's Medical Center of Israel, Petach Tikva, Israel and Carmel Medical Center, Haifa Israel; HILL Susan, Great Ormond Street Hospital for Children, NHS Foundation Trust and UCL Institute of Child Health, London, United Kingdom; HOJSAK Iva, Children's Hospital Zagreb, University of Zagreb School of Medicine, University of J. J. Strossmayer School of Medicine Osijek, Croatia; IACOBELLI Silvia, CHU La Réunion, Saint Pierre, France; JOCHUM Frank, Ev. Waldkrankenhaus Spandau, Berlin, Germany; JOOSTEN, Koen, Department of Pediatrics and Pediatric Surgery, Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; KOLAČEK Sanja, Children's Hospital, University of Zagreb School of Medicine, Zagreb, Croatia; KOLETZKO Berthold, k LMU – Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Munich, Germany; KSIAZYK Janusz, Department of Pediatrics, Nutrition and Metabolic Diseases, The Children's Memorial Health Institute. Warsaw; LAPILLONNE Alexandre, Paris-Descartes University, Paris, France; LOHNER Szimonetta, Department of Pediatrics, University of Pécs, Pécs, Hungary; MESOTTEN Dieter, KU Leuven, Leuven, Belgium; MIHÁLYI Krisztina, Department of Pediatrics, University of Pécs, Pécs, Hungary; MIHATSCH Walter A., Ulm University, Ulm, and Helios Hospital, Pforzheim, Germany; MIMOUNI Francis, Department of Pediatrics, Division of Neonatology, The Wilf Children's Hospital, the Shaare Zedek Medical Center, Jerusalem, and the Tel Aviv University, Tel Aviv, Israel; MØLGAARD Christian, Department of Nutrition, Exercise and Sports, University of Copenhagen, and Paediatric Nutrition Unit, Rigshospitalet, Copenhagen, Denmark; MOLTU Sissel J, Oslo University Hospital, Oslo, Norway; NOMAYO Antonia, Ev. Waldkrankenhaus Spandau, Berlin, Germany; PICAUD Jean Charles, Laboratoire CarMEN, Claude Bernard University Lyon 1, Hopital croix rousse, Lyon, France; PRELL Christine, LMU – Ludwig-Maximilians-Universität Munich, Dr. von Hauner Children's Hospital, Munich, Germany; PUNTIS John, The General Infirmary at Leeds, Leeds, UK; RISKIN Arieh, Bnai Zion Medical Center, Rappaport Faculty of Medicine, Technion, Haifa, Israel; SAENZ DE PIPAON Miguel, Department of Neonatology, La Paz University Hospital, Red de Salud Materno Infantil y Desarrollo – SAMID, Universidad Autónoma de Madrid, Madrid, Spain; SENTERRE Thibault, CHU de Liège, CHR de la Citadelle, Université de Liège, Belgium; SHAMIR Raanan, Schneider Children's Medical Center of Israel, Petach Tikva, Israel; Tel Aviv University, Tel Aviv, Israel; SIMCHOWITZ Venetia, Great Ormond Street NHS Trust, London, The United Kingdom; SZITANYI Peter, General University Hospital, First Faculty of Medicine, Charles University in Prague, Czech Republic; TABBERS Merit M., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN DEN AKKER Chris H.B., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN GOUDOEVER Johannes B., Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands; VAN KEMPEN Anne, OLVG, Amsterdam, the Netherlands; VERBRUGGEN Sascha, Department of Pediatrics and Pediatric Surgery, Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; WU Jiang, Xin Hua Hospital, Shanghai, China; YAN Weihui, Department of Gastroenterology and Nutrition, Xinhua Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China.

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during the revision process have also been considered. The references cited in the previous guidelines are not repeated here, except for some relevant publications; only the previous guidelines will be cited instead.

Type of publications: Original papers, meta-analyses and overviews.

Key words: parenteral nutrition, amino acids, requirements, toxicity, deficiency.

Age: Child, infant, preterm.

Language: English.

Outcome: Recommendations were developed from a standpoint of nutrient adequacy. Depending on age groups, nutrient adequacy was based on intrauterine accretion rate, organ development, factorial estimates of requirements and amino acid interactions. Individual amino acids are discussed. Minimal intakes of specific amino acids are those that meet the specific requirement of children in that age group. Maximal intakes are recommended to prevent excessive and potentially harmful intakes of amino acids.

2. Introduction

Proteins are the major structural and functional components of all cells in the body. They consist of chains of amino acid subunits joined together by peptide bonds. The chain length ranges from two amino acids to thousands, with molecular weights subsequently ranging from hundreds to hundreds of thousands of Daltons. From a nutritional perspective, an important aspect of a protein is its amino acid composition. Some amino acids are classified as essential (indispensable). These are amino acids that cannot be synthesized by humans and hence must be provided in the diet or parenteral solution (Table 1). Non-essential amino acids can be synthesized from other amino acids or from other precursors. Some amino acids are categorized as semi-essential. These amino acids can be synthesized from other amino acids but their synthesis is limited under certain circumstances.

Table 1
Essential, non-essential and conditionally essential amino acids.

Essential	Non-essential	Semi-essential
Histidine	Alanine	Arginine
Isoleucine	Aspartic Acid	Glycine
Leucine	Asparagine	Proline
Lysine	Glutamic Acid	Tyrosine
Methionine	Serine	Cysteine
Phenylalanine		Glutamine
Threonine		
Tryptophan		
Valine		

3. Methods for estimating total and individual amino acid needs

Amino acid requirements are mainly determined by the rate of net protein synthesis, which depends on the availability of rate limiting amino acids. There are several physiological and biochemical ways to determine whether the amino acid intake is sufficient or in excess of the needs of children. Different measurements for assessing adequacy of amino acid intake include anthropometry (weight and length), nitrogen balance, metabolic indices (e.g. amino acid concentrations, albumin, pre-albumin, total protein concentrations, blood urea nitrogen, metabolic acidosis), whole-body nitrogen kinetics, specific amino acid kinetics and the indicator amino acid method. The intake of each essential amino acid required to maintain nitrogen equilibrium in children and infants has been defined as the amount necessary to obtain adequate growth and nitrogen balance. The amino acid indicator method is an accurate and fast way to determine specific amino acid requirements. It has been developed to measure specific amino acid requirements [2–4] and has been validated in animal models of infancy [5,6]. Such an approach has recently been used in the determination of the requirement of several amino acids in parenterally fed neonates (Table 2) [7–10].

Table: Recommendations for amino acids in PN

R 3.1	In preterm infants the amino acid supply should start on the first postnatal day with at least 1.5 g/kg/d to achieve an anabolic state. (LOE 1++, RG A, strong recommendation)
R 3.2	In preterm infants the parenteral amino acid intake from postnatal day 2 onwards should be between 2.5 g/kg/d and 3.5 g/kg/d and should be accompanied by non-protein intakes >65 kcal/kg/d and adequate micronutrient intakes. (LOE 1+, RG A, strong recommendation)
R 3.3	In preterm infants, parenteral amino acid intakes above 3.5 g/kg/d should only be administered as part of clinical trials (LOE 2+, RG 0, conditional recommendation)
R 3.4	A minimum amino acid intake of 1.5 g/kg/d should be administered to stable term infants to avoid a negative nitrogen balance while the maximum amino acid intake should not exceed 3.0 g/kg/d (LOE 1+, RG B, strong recommendation)
R 3.5	Withholding parenteral nutrition, including amino acids, for 1 week in critically ill term infants while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation)
R 3.6	A minimum amino acid intake of 1.0 g/kg/d should be administered in stable infants and children to avoid negative balance (LOE 1−, moderate quality, RG B, strong recommendation)
R 3.7	Withholding parenteral nutrition, including amino acids, for 1 week in critically ill infants and children from 1 month to 3 years while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation)
R 3.8	In stable children aged 3–12 years an amino acid intake of 1.0–2.0 g/kg per day may be considered. (LOE 4, RG GPP, conditional recommendation)
R 3.9	Withholding parenteral nutrition, including amino acids, for 1 week in critically ill children aged 3–12 years while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation)
R 3.10	An amino acid intake of at least 1.0 with a maximum of 2.0 g/kg/d in stable adolescents may be considered. (LOE 2++, RG 0, conditional recommendation)
R 3.11	Withholding parenteral nutrition, including amino acids, for 1 week in critically ill adolescents while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation)
R 3.12	Bioavailable cysteine (50–75 mg/kg/d) should be administered to preterm neonates. Higher amounts do not improve outcomes (LOE 1+, RG B, conditional recommendation)
R 3.13	The lower limit of tyrosine intake should be at least 18 mg/kg per day in preterm infants. (LOE 2++, RG B, conditional recommendation)
R 3.14	The advisable tyrosine intake in term infants is 94 mg tyrosine/kg per day. (LOE 1+, RG B, conditional recommendation)
R 3.15	Glutamine should not be supplemented additionally in infants and children up to the age of two years. (LOE 1++, RG A, strong recommendation)
R 3.16	Taurine should be part of amino acid solutions for infants and children, although no firm recommendation can be made upon advisable lower or upper limits. (LOE 1−, RG B, conditional recommendation)
R 3.17	Arginine supplementation may be used for prevention of NEC in preterm infants (LOE: 1−, RG B, conditional recommendation)

Table 2
Parenteral requirements in neonates of individual amino acids as determined by the gold standard, the indicator amino acid oxidation method [7–10].

Amino acid	Requirement (mg/kg/d)
Tyrosine	74
Methionine + cysteine	47
Threonine	38
Lysine	105

Most currently used parenteral amino acid mixtures contain amino acid amounts that result in a plasma amino acid pattern resembling the plasma amino acid patterns of normally growing, breast fed infants and children, or cord blood. These paediatric parenteral amino acid mixtures provide more essential and less non-essential amino acids than normally deposited by the infant or child. The utilisation of the amino acid supply depends on a sufficient energy intake, and often an energy supply of 30–40 kcal per 1 g amino acids is recommended.

4. Total amino acid needs during parenteral nutrition

4.1. Differences between enterally fed and parenterally fed children

The amino acid requirement is lower in parenterally fed infants and children than in enterally fed infants because the supply bypasses the intestine. Studies in infants (preceded by studies in piglets) and children show that individual amino acids are utilized by the intestines at varying rates [11–16]. There is a wide variation in the intestinal uptake and utilization of specific amino acids that changes with age. First pass (intestinal and liver) leucine utilisation in older children is 24% [17], while it accounts for approximately 50% of the dietary intake in preterm infants [18]. Intestinal utilisation of lysine accounts for approximately 20% of the intake [12] whereas 50% of glutamine is used [18] in preterm infants. Thus, the total needs for amino acids in parenterally fed children are lower than in enterally fed children, but there are huge differences in intestinal utilization of specific amino acids. Besides utilization by the intestine, a number of amino acids are also metabolized and converted into other amino acids within the intestine and/or liver upon first pass. Bypassing the intestine will lower systemic availability of these amino acids and thus increase the parenteral requirements. In addition, while ingested phenylalanine and methionine appear to be converted to tyrosine and cysteine, respectively, it seems that parenterally administered phenylalanine and methionine are converted to a lower extent. Systemically active peptides are produced within the intestine (e.g. sIgA) and animal studies show that the intestine uses predominantly dietary amino acids (rather than amino acids that are offered to the intestine from the systemic circulation) for specific protein synthesis [19].

4.2. Preterm infants

R 3.1 **In preterm infants the amino acid supply should start on the first postnatal day with at least 1.5 g/kg/d to achieve an anabolic state. (LOE 1++, RG A, strong recommendation, strong consensus)**

R 3.2 **In preterm infants the parenteral amino acid intake from postnatal day 2 onwards should be between 2.5 g/kg/d to 3.5 g/kg/d and should be accompanied by non-protein intakes >65 kcal/kg/d and adequate micronutrient intakes. (LOE 1+, RG A, strong recommendation, strong consensus)**

R 3.3 **In preterm infants, parenteral amino acid intakes above 3.5 g/kg/d should only be administered as part of clinical trials (LOE 2+, RG 0, conditional recommendation, consensus)**

A minimum of 30–40 Kcal per 1 g amino acids is usually recommended to guarantee amino acid utilisation. Optimal glucose and lipid intakes that maximize protein accretion and growth in preterm infants have not been determined at various parenteral amino acid intakes [20,21].

4.2.1. Early amino acid intake

Based on current literature, amino acid intake should be started from the first day of life, or, even better, as soon as possible after birth so as to avoid the “metabolic shock” caused by the interruption of continuous feeding that occurs in utero. Early amino acid administration in preterm infants results in increased protein synthesis without a decrease in proteolysis [22]. Several studies evaluating amino acid administration directly after birth have found a positive nitrogen balance, calculated as the difference between nitrogen intake and estimated urinary nitrogen loss [23–26]. Consistent with these findings were those of a positive correlation between an increased amount of amino acid intake and an improved nitrogen balance [26–29]. Few studies have looked at the effect of early amino acid administration on short-term growth [30–33] and in some of the previously mentioned studies growth was recorded as a secondary outcome [25–27]. Overall, early amino acids, when compared to glucose administration alone, are associated with improved short-term growth. Much less is known about the effects on longer-term outcomes such as growth and neurodevelopment. Poindexter and colleagues, in a cohort study [33] found significant improvement in growth parameters at 36 weeks postmenstrual age in favour of the infants who received early amino acids, but no differences were found in growth or in neurodevelopment at 18 months corrected age. Stephens and colleagues [34] reported a retrospective analysis of 150 ELBW infants and found a positive association between protein intake in the first week of life and scores on the Bayley Mental Developmental Index at 18 months corrected age. Van den Akker and co-workers found no difference in growth but a neurodevelopmental advantage at 2 years corrected age for boys that received amino acids from the first day of life compared to the ones who received glucose alone [35].

No detrimental metabolic effects of commencing amino acid administration from birth onwards have been reported [25,27,28,36]. Some researchers did not find higher urea concentrations in the high amino acid supplemented patients [24,29,37,38] while others found a positive correlation between amino acid intake and increased blood urea levels [20,25,39,40], indicating a greater proportion of amino acids being oxidized. This resembles the intrauterine situation in which amino acids are also used as an energy source, and higher blood urea levels should not be interpreted as a sign of intolerance but rather as a reflection of oxidation. Furthermore, the definition of what is a safe blood urea level in preterm infants still has to be determined and indeed the incidence of metabolic acidosis is not related to amino acid intakes [39,41].

4.2.2. High versus low amino acid intakes

The most commonly used method to estimate amino acid requirement is the amount needed to achieve a positive nitrogen balance. Studies show that a mean intake of 0.9–2.65 g/kg/day can result in a positive nitrogen balance, with an energy intake as low as 30 kcal/kg/day. Performing nitrogen balance studies in small, often unstable preterm infants during the first days of life is very challenging. Most of these infant are not in a steady state and nitrogen balance studies often fail to correct for a rapidly expanding urea pool [39].

The 2005 ESPGHAN guidelines on paediatric parenteral nutrition [42] recommended a minimum amino acid intake of 1.5 g/kg/day to prevent a negative nitrogen balance, and a maximum of 4 g/

kg/day, according to the evidence that up to 3.3–3.9 g/kg/day seemed to be well tolerated. There is still limited evidence that increasing amino acid intake above 2.5 g/kg/day is associated with a more favourable outcome. The impact on growth of different amino acid intakes during parenteral nutrition has been studied in non-RCTs [28,31,43] or as secondary analyses of studies designed for other purposes [33,44]. Other studies have evaluated different protein intake schemes with varying non-protein energy, or at different timing of administration [21,27,38,45,46]. To date only a few RCTs were conducted to compare solely the effect of increasing amino acid in parenteral nutrition on growth and neurodevelopment of small preterm infants. In the study by Clark et al. [47], 122 patients were randomised to receive a maximum of 2.5 or 3.5 g/kg/day amino acid supplementation. Growth at 28 days was nearly identical between treatment and controls. In the study by Burattini et al. [39] 114 ELBW infants were randomised to receive standard (2.5 g/kg/day) versus high (4 g/kg/day) amino acid intake. Infants in the intervention group received an extra 8 g/kg of amino acids over the first ten days of life without any significant difference in short and long term growth. Few other studies have looked at the relation between the dose of parenteral amino acids and neurodevelopment. Stephens et al. found [34], in a retrospective study in ELBWI, that increasing first-week protein and energy intakes was associated with significantly higher mental developmental scores at 18 months. Blanco et al. [30,44] in a randomised study found lower mental developmental scores at 18 months in infants who received the higher amino acid intake but the difference was no longer significant at the 2 year follow-up. The study of Blanco et al. was a secondary analysis of a study originally designed with the aim of reducing hyperkalaemia and it was not powered for neurodevelopment. Recent, larger studies did not observe short [48] or long term beneficial effects of increasing amino acid in the early phase [49,50]. Morgan et al. showed an improved head circumference growth by both increasing parenteral amino acid and caloric intake, so no definite conclusion can be drawn on the effect of amino acids alone [21].

It is worth mentioning that some studies reported better glucose control in infants who received amino acids/higher amino acid intakes [25,38,39]. These findings come from studies with small numbers of patients and should be interpreted with caution. High amino acid intakes in small preterm infants have been reported to have an effect on electrolytes and mineral metabolism [51,52].

4.3. Term infants

R 3.4 **A minimum amino acid intake of 1.5 g/kg/d should be administered to stable term infants to avoid a negative nitrogen balance while the maximum amino acid intake should not exceed 3.0 g/kg/d (LOE 1+, RG B, strong recommendation, strong consensus)**

R 3.5 **Withholding parenteral nutrition, including amino acids, for 1 week in critically ill term infants while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation, consensus)**

At a parenteral supply of 2.4 g amino acids/kg per day, urinary nitrogen excretion ranges 0.10–0.12 g N/kg per day in stable, post-surgical term infants [53] corresponding to 0.6–0.8 g protein/kg per day. This results in a positive nitrogen balance of approximately 1.8 g/kg per day. Stable term neonates with a parenteral amino acid intake of 2.5 g/kg per day achieve a moderate but positive protein balance (0.27 g/kg per day) [54]. In a similar age group, Zlotkin recommended a protein intake of 2.3–2.7 g/kg per day to achieve a similar weight gain rate as in full term infants who were fed human milk [55]. Reynolds et al. showed improved nitrogen and leucine balance upon delivery of 2.5 versus 1.5 g/kg/d immediately post-operatively in term neonates [56].

A recent large international multicentre randomised controlled trial in 1440 critically ill children, including term infants, (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) [57]. 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.

4.4. Infants and children from 1 month to 3 years

R 3.6 **A minimum amino acid intake of 1.0 g/kg/d should be administered in stable infants and children from 1 month to 3 years to avoid negative balance (LOE 1−, moderate quality, RG B, strong recommendation, strong consensus)**

R 3.7 **Withholding parenteral nutrition, including amino acids, for 1 week in critically ill children while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation, consensus)**

The administration of 2.4 ± 0.3 g amino acids/kg per day to infants and children up to an age of 43 months (n = 40, median age 2.7 months) resulted in a mean positive nitrogen balance of 242 ± 70 mg/kg per day, with plasma amino acid levels within the reference range except for a low level of tyrosine [58]. A positive nitrogen balance of 242 mg/kg per day corresponds to a positive protein balance of 1.5 g/kg per day. Infants (age 2–12 months) on the first day after cardiac surgery excrete 244 ± 86 mg N/kg per day corresponding to a negative protein balance of 1.5 ± 0.5 g protein/kg per day, whereas the supplementation of 0.8 g amino acids/kg per day resulted in a negative protein balance of −114 ± 81 mg N/kg per day approx. 0.7 ± 0.5 g protein/kg per day [59]. Based upon factorial approach, there is no rational to provide more than 2.5 g/kg/d to stable infants and children.

4.5. Children aged 3–12 years

R 3.8 **In stable children aged 3–12 years an amino acid intake of 1.0–2.0 g/kg per day may be considered. (LOE 4, RG GPP, conditional recommendation, strong consensus)**

R 3.9 **Withholding parenteral nutrition, including amino acids, for 1 week in critically ill children while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation, consensus)**

A study by Coss-Bu shows that critically ill children at a mean age of 5 years have a negative nitrogen balance at a protein intake of 2.1 g/kg per day [60]. The subjects with a positive nitrogen balance had a higher protein intake (2.8 ± 0.9 g/kg per day) than subjects with a negative nitrogen balance (1.7 ± 0.7 g/kg per day). Critically ill children at a mean age of 8 years show a negative protein balance at an intake of 1.7 g protein/kg/d. Regression analysis showed a protein requirement of 2.8 g/kg per day in this study group [61]. However, as discussed previously, a recent trial showed adverse clinical outcomes following immediate parenteral nutrition in critically ill children [57].

There is a paucity of data in the age group 3–12 years of age, insufficient to draw any firm conclusions on the advisable lower and upper limits for protein intake.

4.6. Adolescents

R 3.10	**An amino acid intake of at least 1.0 with a maximum of 2.0 g/kg/d in stable adolescents may be considered. (LOE 2++, RG 0, conditional recommendation, strong consensus)**
R 3.11	**Withholding parenteral nutrition, including amino acids, for 1 week in critically ill adolescents while providing micronutrients can be considered (LOE 1+, RG B, conditional recommendation, consensus)**

Young men, receiving an essentially protein free diet, excrete approximately 24–38 mg N/kg per day which corresponds to 0.15–0.24 g protein/kg per day [62,63]. Goulet et al. administered different amino acid intakes to patients with a compromised gut function [64]. The response of protein turnover to graded levels of amino acid intakes was assessed by using stable isotope technology (leucine kinetics) in approximately 13 years old children in a stable nutritional status receiving home parenteral nutrition. Since the body fat content of adolescents changes very rapidly during this period, the estimates were based on lean body mass rather than body weight alone. Intakes ranged from 0.7 to 2.5 g amino acids/kg lean body mass per day. Positive nitrogen balance was achieved in these children at an intake of 1.5 g amino acids/kg lean body mass per day, whereas this was not the case at an intake 0.7 g amino acids/kg lean body mass per day. There was a significant positive difference in protein balance when the intake increased from 1.5 to 2.5 g/kg lean body mass per day. More recently, Verbruggen et al. showed that critically ill children and adolescents require higher amino acid intakes (3 g/kg/d) to circumvent a catabolic state, although albumin synthesis rates were not affected [65,66]. However, as discussed previously, a recent trial showed adverse clinical outcomes following immediate parenteral nutrition in critically ill children [57].

The recommendations are summarized in Table 3.

5. Specific amino acid requirements during total parenteral nutrition

5.1. Cysteine

R 3.12	**Bioavailable cysteine (50–75 mg/kg/d) should be administered to preterm neonates. Higher amounts do not improve outcomes (LOE 1+, RG B, conditional recommendation, strong consensus)**

Cysteine used to be considered a semi-essential amino acid in the newborn period, indicating that cysteine needed to be administered to circumvent low cysteine synthesis with subsequently low plasma levels and impaired protein synthesis in certain circumstances. It is normally synthesized from methionine (S-donor) and serine (C-donor). The stability of cysteine is low in solution, making it hard to supply enough to the infant. However, it is possible to add cysteine-HCL to the amino acid solution just before the administration to the infant. Cystine (the oxidation product of two cysteine molecules combined) is stable but has a low solubility making it unsuitable as alternative to cysteine. Cysteine is approved for addition to parenteral nutrition in preterm infants.

Table 3
Parenteral amino acid supply considered adequate for stable patients (g/kg/d).

Preterm infants	
First day of life	1.5–2.5
From day 2 onwards	2.5–3.5
Term infants[a]	1.5–3.0
2nd month–3rd year[a]	~2.5
3rd–18th year[a]	~2.0

[a] Critically ill patients may benefit from withholding parenteral nutrition while providing micronutrients during the first week of hospital admission.

A 2006 Cochrane review evaluated five small trials of short-term cysteine supplementation of cysteine-free parenteral nutrition [67]. The authors concluded that growth was not significantly affected by cysteine supplementation (evaluated in one quasi-randomised trial), but that nitrogen retention was significantly increased by cysteine supplementation (studied in four trials); no data were available on clinical outcomes [67]. Riedijk et al. [68] concluded that there was no evidence for limited endogenous cysteine synthesis in 4-week-old low birth weight infants using the indicator amino acid oxidation method, while Courtney-Martin et al. [8] found that the methionine requirement to achieve adequate cysteine plasma levels in postsurgical human neonates requiring parenteral nutrition is lower than the methionine dose currently provided in commercial parenteral nutrition solutions. Indeed, Thomas et al. concluded as well that transsulfuration of methionine is evident in the human newborn in the immediate neonatal period, again suggesting that cysteine may not be considered a “conditionally” essential amino acid for the neonate [69].

Cysteine is a major substrate for glutathione, a tripeptide (glutamic acid/cysteine/glycine) with important antioxidant properties, but also important in maintaining redox potential and calcium homeostasis. Appropriate levels of cysteine are therefore warranted. An intake of 170 μmol/kg per day (approx. 27 mg Cysteine-HCl/kg per day) resulted in plasma cysteine levels below the reference range whereas an intake of 345 μmol/kg per day) (54 mg Cysteine-HCl/kg per day) was enough to reach adequate plasma levels [70]. The supplementation of 462 μmol/kg per day (72 mg/kg per day) resulted in normal plasma amino acid levels [71]. Acetylation of cysteine prevents the instability but the bioavailability is low, approximately 50% [70]. The 2006 Cochrane analysis indicated that Plasma levels of cysteine were significantly increased by cysteine supplementation but not by N-acetylcysteine supplementation. N-acetylcysteine supplementation did not significantly affect the risks of death by 36 postmenstrual weeks, bronchopulmonary dysplasia (BPD), death or BPD, retinopathy of prematurity (ROP), severe ROP, necrotizing enterocolitis requiring surgery, periventricular leukomalacia, intraventricular haemorrhage (IVH), or severe IVH.

In older children (age range 2–8 years) receiving an amino acid solution with varying doses of cysteine-HCl (0–40 mg/g AA, approx. 0–255 μmol/g AA), no changes were noted in free cysteine/cystine or methionine plasma levels were noted. Only plasma taurine levels varied with cysteine supplementation [72].

Te Braake et al. [73] found that administration of high-dose cysteine (81 mg/kg/day) via parenteral nutrition to preterm infants was safe but did not increase plasma cystine or GSH concentrations or synthesis rates when compared to an intake of 45 mg/kg/d). Parenteral cysteine supplementation did not increase erythrocyte GSH in a recent study using tracer methodology in five parenteral nutrition-fed neonates [74]. Calkins et al. did not show that parenteral cysteine when compared with isonitrogenous non-cysteine supplementation increased erythrocyte reduced glutathione (GSH) in neonates at high risk for inflammatory injury, although supplementation for at least 1 week in critically ill neonates resulted in a larger and more positive individual change in GSH [75]. Mager et al. report that addition of N-acetyl-cysteine (NAC) to parenteral nutrition or parenteral hydration fluid at doses

of 20–50 mg/kg/day decreased liver enzyme elevations and tended to increase blood GSH levels in children requiring home parenteral nutrition [76]. RCTs on the clinical and metabolic efficacy of either L-cysteine or NAC added to parenteral nutrition in adults or children requiring this therapy are needed.

5.2. Tyrosine

R 3.13	**The lower limit of tyrosine intake should be at least 18 mg/kg per day in preterm infants. (LOE 2++, RG B, conditional recommendation, strong consensus)**
R 3.14	**The advisable tyrosine intake in term infants is 94 mg tyrosine/kg per day. (LOE 1+, RG B, conditional recommendation, strong consensus)**

Tyrosine is considered a semi-essential amino acid in the neonatal period [77]. The hydroxylation of phenylalanine to tyrosine is argued to be limited although significant hydroxylation takes place in even very preterm infants and human foetuses [78,79]. However, many studies show low plasma concentrations of tyrosine in unsupplemented infants. Supplementation of 55–90 μmol tyrosine/kg per day (10–16 mg/kg per day) resulted in plasma levels below reference range in preterm infants [70]. Acetylation of tyrosine increases the solubility, but the bioavailability is low. In two studies only 60% of N-acetyl-Tyrosine is retained [70,77]. An intake of approximately 700 μmol/kg per day which corresponds to a net intake of 126 mg tyrosine as NAT/kg per day resulted in adequate tyrosine levels. An intake of less than 200 μmol/kg per day (corresponds to a net intake of 36 mg tyrosine as NAT/kg per day) did not. However, plasma levels of N-acetyl tyrosine exceeded the plasma levels of tyrosine. Due to the immaturities in the neonatal tyrosine catabolic enzyme pathway, tolerance of tyrosine intakes at levels greatly over requirement is limited [80]. In addition, due to the known neurologic impairment caused by hypertyrosinemia to the developing brain as assessed by lower IQ and psychologic tests, excess intakes must be avoided [81,82]. There is a paucity of data in preterm infants, insufficient to draw any firm conclusions on the advisable upper limits of tyrosine intake.

The upper and lower requirements of tyrosine in term surgical neonates was determined using a dipeptide, glycyl-L-tyrosine and stable isotope techniques [7]. Based on the mean estimates of whole-body phenylalanine oxidation, the tyrosine mean requirement and safe level of intake were found to be 74 mg/kg/d and 94 mg/kg/d, respectively.

5.3. Glutamine

R 3.15	**Glutamine should not be supplemented additionally in infants and children up to the age of two years. (LOE 1++, RG A, strong recommendation, strong consensus)**

In critically ill adult patients, glutamine supplementation may reduce sepsis and mortality [83]. Systematic reviews state that there is no evidence from randomised trials to support the routine use of glutamine supplementation in infants [84,85]. In 4 day old preterm infants, additional glutamine did not have an effect on leucine balance [86]. Ten days of glutamine supplementation in very-low-birth weight infants resulted in higher plasma glutamine levels but ammonia levels were not increased [87]. No effect of glutamine supplementation on sepsis incidence or mortality was observed. Glutamine also had no effect on tolerance of enteral feeds, necrotizing enterocolitis, or growth [88]. Anecdotal evidence shows that glutamine might reduce some elevated plasma liver enzyme levels [89]. A recent pilot trial showed that a dipeptide containing glutamine did not result in adverse effects [90]. Thus, there is no new evidence indicating that glutamine should be added to parenteral mixtures for preterm infants. Two trials addressing the effect of glutamine supplementation to infants and children up to the age of two years did not report any clinical significant effect [91–93]. No data are available in older children.

5.4. Taurine

R 3.16	**Taurine should be part of amino acid solutions for infants and children, although no firm recommendation can be made upon advisable lower or upper limits. (LOE 1−, RG B, conditional recommendation, strong consensus)**

Taurine is not a typical amino acid because, although it contains an amino group, it does not have the requisite carboxyl group. Despite this, it is discussed here. Taurine deficiency may increase glyco-conjugates of bile acids and result in cholestasis. Although the cause of neonatal cholestasis is probably multifactorial, there are data indicating that adequate taurine may prevent cholestasis in neonates. In addition, taurine deficiency may result in retina dysfunction [94]. Taurine is synthesized from methionine and cysteine and studies show that prolonged parenteral nutrition in children with a cysteine and taurine free parenteral solution resulted in reduced plasma taurine levels [95,96]. Taurine supplementation (3 mg/g AA) maintained plasma taurine concentrations within the reference range in term infants but not in very low birth weight infants [97]. Cysteine supplementation (50–100 mg/kg per day) normalizes taurine concentrations in 7 year old children with short bowel syndrome [72]. One trial studied taurine supplementation (10.8 mg/kg/d) administered with parenteral nutrition for 10 days [98]. Taurine concentrations increased, liver enzyme and ammonia concentrations decreased. Within specific subgroups of neonatal patients, taurine supplementation seem to offer some degree of protection against IFALD [99].

5.5. Arginine

R 3.17	**Arginine supplementation may be used for prevention of NEC in preterm infants (LOE: 1−, RG B, conditional recommendation, strong consensus)**

Arginine is the substrate for the production of nitric oxide (a potent vasodilator), important for glucose homeostasis [100] and there is some speculation that, given the low plasma arginine levels observed in preterm neonates, arginine supplementation may serve to prevent necrotizing enterocolitis (NEC). Furthermore, recent data suggest that arginine depletion is related to the innate immune suppression that occurs in newborn models of bacterial challenge, impairing pathways critical for the immune response [101]. In 2002, a double-blind RCT was published in 152 premature infants randomised to receive either supplemental L-arginine ($n = 75$) or placebo ($n = 77$) with oral feeds (as tolerated) and in any required parenteral nutrition during the first 28 days of life [102]. Arginine supplementation was well tolerated and resulted in a significant decrease in the incidence of NEC (all stages). To our knowledge, no further study of arginine efficacy in paediatrics has subsequently been published, but further study on the issue of NEC is clearly needed [103].

5.6. Other amino acids

No other amino acids are discussed, as there is insufficient data available to recommend any intake ranges.

Conflict of interest

None declared.

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