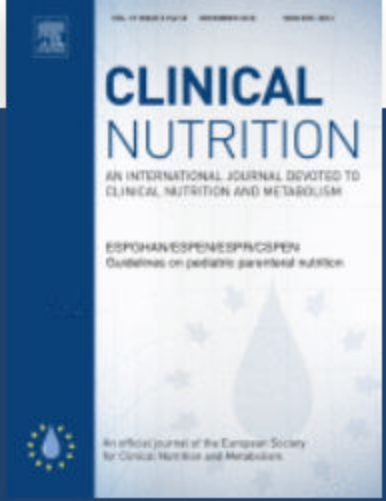

Clinical Nutrition

Supports *open access*

Volume 37, Issue 6, Part B

Pages 2303-2430 (December 2018)

Clinical Nutrition 37 (2018) 2303–2305

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

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

Background: Previous guidelines on Paediatric Parenteral Nutrition (PN) were published in 2010, by 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) were published. The aim of the present paper was to provide up-to-date evidence for health professionals working with infants, children and adolescents receiving PN.

Methods: The current document is a revision of the 2005 guidelines produced by the same 3 organizations (ESPEN, ESPGHAN, ESPR) together with the Chinese Society of Parenteral and Enteral Nutrition (CSPEN).

Experts participating in the guideline updating process were all professionals with extensive experience in managing PN from a wide range of European countries, Israel and China. The guideline development process was coordinated by a guideline steering committee. Each chapter of the guideline was prepared by a separate author group. These author groups were responsible for screening titles and abstracts identified by a systematic literature search for inclusion, for conducting additional expert searches (including secondary sources such as other published valid guidelines), for evaluating the quality of studies included in the given chapter and assigning evidence levels to the literature. Based on the evidence level of included studies experts formulated and graded recommendations.

A consensus conference was held in February 2015. All chapter manuscripts were revised following the recommendations of the consensus conference and then reviewed and edited by the project steering committee. Final consensus on each individual guideline and its individual recommendations was achieved and assessed by online voting. This process lasted until January 2018.

Funding for the consensus conference (including travel expenses for participants) was provided by all participating societies. No other funding was received for the guideline updating process and participants received no payment. Support was provided by the Hungarian Cochrane organization.

Results/conclusions: The present document provides guideline for the use of PN across the wide range of pediatric patients, ranging from extremely premature infants up to teenagers weighing up to and over 100 kg [1]. It covers their individual macro- and micronutrient needs [2–8], fluid requirements [9], venous access [10], organizational aspects [11], home parenteral nutrition [12], standardized vs. individualized PN [13], and last but not least a wide range of safety considerations for prevention and management of complications such central line associated bloodstream infections (CLABSI) [14].

Conflict of interest

None declared.

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https://doi.org/10.1016/j.clnu.2018.05.029
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Clinical Nutrition 37 (2018) 2306–2308

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Guideline development process for the updated guidelines

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Background

In 2005, 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) were published [1]. The current

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https://doi.org/10.1016/j.clnu.2018.06.943
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document is a revision of these guidelines produced by the same 3 organizations (ESPEN, ESPGHAN, ESPR) together with the Chinese Society of Parenteral and Enteral Nutrition (CSPEN). Its primary goal is to provide up-to-date evidence for health professionals working with infants, children and adolescents receiving parenteral nutrition (PN). It is based on literature collected in a systematic way and on expert opinion.

Experts participating in the guideline updating process were all professionals with extensive experience in managing PN. The guideline development process was coordinated by the guideline steering committee: Mihatsch WA (Department of Pediatrics, Ulm University, Ulm, Germany), Shamir R (Schneider Children's Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Israel), van Goudoever JB (VU University Medical Center, Amsterdam, The Netherlands), Fewtrell M (UCL Institute of Child Health, London, UK), and Lapillonne A (APHP Necker-Enfants Malades Hospital, Paris-Descartes University, Paris, France). Each chapter of the guideline was prepared by a separate author group. These author groups were responsible for screening titles and abstracts identified by a systematic search for inclusion, for conducting additional expert searches (including secondary sources such as other published valid guidelines), for evaluating the quality of studies included in the given chapter and assigning evidence levels to the literature. Based on the evidence level of included studies experts formulated and graded recommendations.

A consensus conference was held in February 2015 in Hersching, Germany, where all experts participating in the guideline updating process were invited to participate. At this conference delegates of each author team presented the existing scientific knowledge in the field of PN in the form of a short but focused presentation. Following the presentation, the suggested evidence levels were discussed and final decisions were made by voting. Only 'yes' or 'no' was allowed, to ensure clear majority decisions. Recommendations with more than 75% agreement were accepted, while recommendations with less than 75% agreement were modified according to the feedback of the consensus panel members in order to achieve a higher degree of agreement. Chapter manuscripts were revised accordingly and then reviewed and edited by the Project Steering Committee. There was no final consensus meeting, however, consensus on each individual guideline and its individual recommendations was achieved and assessed by online voting. This process lasted until January 2018.

The recommendations were ultimately developed from a combination of the available literature and the opinions of experts representing different disciplines and from a wide range of European countries, Israel and China.

Funding for the consensus conference (including travel expenses for participants) was provided by ESPGHAN, ESPEN, ESPR and CSPEN. No other funding was received for the guideline updating process and participants received no payment. Support was provided by the Hungarian Cochrane organization.

2. Criteria for considering studies for this guideline

Studies had to have direct relevance to the specific issue covered in the given chapter to be included in the guideline. Studies investigating children (aged 0–18 years) were eligible for inclusion (except for chapter 10 where no age limit was imposed). No restriction was made according to study type or the quality of information.

3. Search methods and selection of studies

A systematic literature search was conducted for each chapter. The Ovid Medline database was searched using a search strategy with both MESH terms and text words; the search was in the form [terms for parenteral nutrition] and [terms for the specific topic of the given chapter] limited to Children (aged 0–18 years) and to years "2004-Current". An exception was made in the case of Chapter 10 (terms for PN were not used) and Chapter 14 (a slightly different structure was used because of the broad topic of the chapter). The search strategy for each Chapter can be found at the start of each chapter. Most of the chapters attempted to identify all relevant trials regardless of language. However, in the case of chapters 7, 10 and 11 results were limited to studies written in English. Since this is an update of the PN guideline published in 2005, the electronic search was limited to studies published between 2004 and December 2014, the date when searches were conducted. Studies published before 2004 were included from the previous guideline. In parallel, experts conducted searches independently from the main search, using other, more specific search terms specific to the given chapter. For each individual guideline, the time frame of the individual literature search is given.

Titles and abstracts were screened by at least two authors from each chapter writing group independently to assess their eligibility for inclusion in the chapter. In cases with a large number of titles a preliminary screening was conducted by a single independent reviewer and titles that were obviously irrelevant were removed from the title list. Full-texts of articles that were deemed potentially relevant to the chapter were retrieved for further assessment. Decision on inclusion was reached by consensus among the authors of the chapter.

4. Assessment of quality of evidence [2]

The GRADE approach was used to assess the quality of evidence and to interpret findings. Authors of the individual chapters independently extracted data on methods, types of participants, interventions, and outcomes from the selected trials and then evaluated the level of evidence (LOE) and grade of recommendation (GOR). The SIGN classification was used to assign both the evidence level and the recommendation grade. The scales used to evaluate LOE and GOR are summarized in Tables 1 and 2. Apart from the

Table 1
Rating scheme for the strength of the evidence [2].

Level of Evidence (LOE)	Type of evidence
1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2−	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g., case reports, case series
4	Expert opinion

Table 2
Rating scheme for the strength of the recommendations [2].

Grade of Recommendation (GOR)	Level of evidence
A	At least one meta-analyses, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points: Recommended best practice based on the clinical experience of the guideline development group

Table 3
Forms of recommendation [2].

Judgement	Recommendation
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possibly conditional recommendation for use restricted to trials
Desirable consequences probably outweigh undesirable consequences	Conditional recommendation for
Desirable consequences clearly outweigh undesirable consequences	Strong recommendation for

Table 4
Classification of the strength of consensus [2].

Classification	Definition
Strong consensus	Agreement of >90% of the participants
Consensus	Agreement of >75–90% of the participants
Majority agreement	Agreement of >50–75% of the participants
No consensus	Agreement of <50% of the participants

classical three class grading (A/B/0) the category 'Good practice points' (GPP) was also offered by this grading system (Table 2), enabling authors to make expert recommendations based on their experience for clinically relevant questions which are not covered by appropriate trials. In addition, a text recommendation (Table 3) was also formulated to give a potentially more definitive recommendation for guideline users; experts were instructed to focus on the recommendations 'Conditional recommendation for' and 'Strong recommendation for'.

5. Achievement of consensus

One to three rounds of online voting using the software SurveyMonkey (SurveyMonkey Europe, 2 Shelbourne Buildings, 2nd Floor, Shelbourne Road, Ballsbridge, Dublin 4, Ireland) were performed with each individual guideline to achieve consensus within all participants of the working group. The first round took place after finalization of each individual guideline by the individual group of authors. The feedback from online voting and its corresponding online discussion were used to modify and improve the initial recommendations in order to reach the highest degree of acceptance at the final (second or third) online voting. This process of modification lasted in individual guidelines till the end of 2017. The level of the strength of consensus is given with each individual recommendation (Table 4).

Conflict of interest

None declared.

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Clinical Nutrition 37 (2018) 2309–2314

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

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

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

Medline search, Pub-Med search.

Timeframe: publications from 2004 to 2016 were used to update the previous recommendations from 2005.

Type of publications: original papers, meta-analyses, experts' recommendations, overviews.

Key words: Energy expenditure, total parenteral nutrition, intensive care, critical care, prematurity, equations.

Language: English

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https://doi.org/10.1016/j.clnu.2018.06.944
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Table: Recommendations for energy in parenteral nutrition (PN)

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

2. Introduction

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

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

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

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

3. Components of energy needs

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

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

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

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

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

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

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

4. Estimating and calculating energy needs

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

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

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

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

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

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

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

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

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

5. Special considerations

5.1. Premature infants

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

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

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

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

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

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

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

5.2. Pediatric intensive care unit (PICU)

5.2.1. General PICU patients

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

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

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

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

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

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

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

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

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

5.2.2. *Traumatic brain injury PICU patients*

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

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

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

Conflict of interest

Dr Embleton declares he has received research funding from Danone Early Life Nutrition, Prolacta Bioscience US and the National Institutes for Health Research UK. Dr Embleton also declares travel support or lecture honoraria from Nestle Nutrition Institute, Baxter, Abbot Nutrition and Fresenius-Kabi. Dr Embleton holds no shares or other financial relationships.

Dr Joosten declares he has received research funding from Danone. Dr Joosten holds no shares or other financial relationships.

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Clinical Nutrition 37 (2018) 2315–2323

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

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

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

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

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https://doi.org/10.1016/j.clnu.2018.06.945
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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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Clinical Nutrition 37 (2018) 2324–2336

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

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

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

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https://doi.org/10.1016/j.clnu.2018.06.946
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Table: Recommendations for the use of intravenous lipid emulsions

R 4.1	In paediatric patients, intravenous lipid emulsions (ILE) should be an integral part of parenteral nutrition (PN) either exclusive or complementary to enteral feeding. (LoE 1−, RG A, strong recommendation for)
R 4.2	In preterm infants, lipid emulsions can be started immediately after birth and no later than on day two of life and for those in whom enteral feeding has been withdrawn, they can be started at time of PN initiation. (LoE 1−, RG A, strong recommendation for)
R 4.3	In preterm and term infants, parenteral lipid intake should not exceed 4 g/kg/day. (LoE 4, GPP, conditional recommendation for)
R 4.4	In children, parenteral lipid intake should be limited to a maximum of 3 g/kg/day. (LoE 3−4, RG 0, conditional recommendation for)
R 4.5	In order to prevent essential fatty acids (EFA) deficiency in preterm infants a lipid emulsion dosage providing a minimum linoleic acid (LA) intake of 0.25 g/kg/day can be given. This lipid emulsion dosage ensures an adequate intake of linolenic acid (LNA) with all lipid emulsions currently registered for paediatric use. (LoE 2−, RG 0, strong recommendation for)
R 4.6	In order to prevent EFA deficiency in term infants and in children a lipid emulsion dosage providing a minimum LA intake of 0.1 g/kg/day can be given, which also provides an adequate intake of LNA with all ILEs currently registered for paediatric use. (LoE 3−4, RG 0, conditional recommendation for)
R 4.7	In preterm infants, newborns and older children on short term PN, pure soybean oil (SO) ILEs may provide less balanced nutrition than composite ILEs. For PN lasting longer than a few days, pure SO ILEs should no longer be used and composite ILEs with or without fish oil (FO) should be the first choice treatment (LoE 1−, RG A, conditional recommendation for)
R 4.8	In preterm infants, ILEs should be protected by validated light-protected tubing. (LoE 1−, RG B, strong recommendation for)
R 4.9	In infants and children, 20% ILEs should be the first choice treatment (LoE 1−, RG B, strong recommendation for)
R 4.10	In newborns including preterm infants, routine use of ILEs should be continuous over 24 h (LoE 2++, RG B, conditional recommendation for)
R 4.11	If cyclic PN is used, for example for home PN children, ILEs should usually be given over the same duration as the other PN components. (LoE 4, GPP, strong recommendation for)
R 4.12	In paediatric patients, heparin should not be given with lipid infusion on a routine basis. (LoE 3−4, GPP, conditional recommendation for)
R 4.13	Carnitine supplementation may be considered in paediatric patients expected to receive PN for more than 4 weeks or in premature infants on an individual basis (LoE 3−4, GPP, conditional recommendation for)
R 4.14	In critically ill paediatric patients, ILE should be an integral part of PN. Composite ILEs with or without FO may be used as the first choice treatment. Available evidence raises the important question on the best timing to provide parenteral nutrition support in critically ill children, but do not allow to differentiate potential effects on outcomes of the timing of introducing parenteral lipid supply (LoE 4, GPP, conditional recommendation for)
R 4.15	In paediatric patients with sepsis, more frequent monitoring of plasma triglyceride concentration and dose adjustment in case of hyperlipidaemia are recommended. ILE dosage may be reduced but lipid supply may generally be continued at least in amounts supplying the minimal EFA requirements (LoE 4, GPP, conditional recommendation for)
R 4.16	Case reports have suggested the use of ILEs as a possible antidote for the treatment of drug toxicity in children, which however is not based on well-designed trials (LoE 3−4, GPP, conditional recommendation for)
R 4.17	In patients with severe unexplained thrombocytopaenia, serum triglyceride concentrations should be monitored and a reduction of parenteral lipid dosage may be considered. (LoE 3−4, GPP, conditional recommendation for)
R 4.18	As part of measures to reverse IFALD in paediatric patients, a discontinuation of SO ILE, a reduction of other ILE dosage and/or the use of composite ILE with FO, should be considered along with the treatment and management of other risk factors (LoE 2+, RG B, strong recommendation for)
R 4.19	The use of pure FO ILE is not recommended for general use in paediatric patients but may be used for short-term rescue treatment in patients with progression to severe IFALD, based on case reports. (LoE 3−4, GPP, conditional recommendation for)
R 4.20	Markers of liver integrity and function, and triglyceride concentrations in serum or plasma should be monitored regularly in patients receiving ILEs, and more frequently in cases with a marked risk for hyperlipidaemia (e.g. patients with high lipid or glucose dosage, sepsis, catabolism, extremely low birth weight infants) (LoE 2−, RG B, strong recommendation for)
R 4.21	Reduction of the dosage of ILEs can be considered if serum or plasma triglyceride concentrations during infusion exceed 3 mmol/L (265 mg/dL) in infants or 4.5 mmol/L (400 mg/dL) in older children (LoE 4, GPP, conditional recommendation for)

1. Methods

Literature search timeframe: The references cited in the previous guidelines [1] are not repeated here, except for some relevant publications, and only the previous guidelines are cited instead. All publications published after the previous guidelines (i.e., from January 2004 to December 2014), have been considered for the first draft of this manuscript. Randomized controlled trials (RCTs), review articles, prospective studies and meta-analyses published in 2015 and 2016, during the revision process, have also been considered.

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

R 4.1	**In paediatric patients, intravenous lipid emulsions (ILE) should be an integral part of parenteral nutrition (PN) either exclusive or complementary to enteral feeding. (LoE 1−, RG A, strong recommendation for, strong consensus)**
R 4.2	**In preterm infants, lipid emulsions can be started immediately after birth and no later than on day two of life and for those in whom enteral feeding has been withdrawn, they can be started at time of PN initiation. (LoE 1−, RG A, strong recommendation for, strong consensus)**
R 4.3	**In preterm and term infants, parenteral lipid intake should not exceed 4 g/kg/day. (LoE 4, GPP, conditional recommendation for, strong consensus)**
R 4.4	**In children, parenteral lipid intake should be limited to a maximum of 3 g/kg/day. (LoE 3−4, RG 0, conditional recommendation for, strong consensus)**

Language: English

Key words: Parenteral nutrition, lipid/fat emulsions, paediatric, fatty acids, LC-PUFA, IFALD, PNALD, cholestasis.

2. Introduction

The rate, amount, and type of lipids provided intravenously are important aspects regarding the efficacy and safety in neonates and children [1–3]. Intravenous lipid emulsions (ILEs) are an indispensable part of paediatric parenteral nutrition (PN) as a non-carbohydrate source of energy delivered as an iso-osmolar solution in a low volume (2.0 kcal/mL with 20% ILEs, or 1.1 kcal/mL with 10% ILEs due to the higher relative content of glycerol). Generally a lipid intake of 25–50% of non-protein calories is recommended in fully parenterally fed patients (see also section on “Energy” of these guidelines). Lipids provide essential fatty acids (EFAs) and help with the delivery of the lipid soluble vitamins A, D, E, and K.

The ILE particle is metabolized following the same pathway as a natural chylomicron. The triglyceride portion is hydrolysed by the endothelial lipoprotein lipase (LPL) [4]. In the circulation, ILE particles also exchange apoproteins and cholesterol with endogenous lipoproteins, thus transforming the initial ILE particle into a so-called remnant particle. The liver rapidly removes ILE remnant particles by hydrolysing them with hepatic lipase. The released free fatty acids (FFAs) can be captured by the adjacent tissues or can circulate bound to albumin, for use in other tissues or uptake by the

liver. The rate of hydrolysis varies according to the type of the triglyceride substrate (i.e., length of the FA, degree of saturation, position of the FA on the glycerol). LPL activity is influenced by prematurity, malnutrition, hypoalbuminaemia, metabolic acidosis, high plasma lipid concentrations, and may be reduced in catabolic states. If the ILE is infused at a rate that exceeds the rate of utilisation, plasma triglyceride concentration will rise and may cause adverse effects including reticulo-endothelial system overload. If the rate of hydrolysis exceeds the rate at which the released FFAs are taken up and oxidized, the plasma concentration of FFAs will also increase and in turn may decrease the LPL activity.

3. Type of lipid emulsions

3.1. 20% Lipid emulsions (20% LEs)

Pure soybean oil (SO) based ILEs (SO ILEs) have been widely used for several decades in adults, children, and neonates. More recent ILEs were also vegetable oil-based ILEs until the newest ILEs with fish oil (FO) became available. These ILEs have marked differences in terms of oil source, FA composition, vitamin E (tocopherols) and phytosterol contents.

Pure SO ILEs are frequently studied in comparison with more recently introduced ILEs. The SO ILEs contain high concentrations of EFAs (~60% of total FAs) with a ratio of linoleic acid (LA) (18:2n-6) to alpha-linolenic acid (LNA) (18:3n-3) of approximately 8:1, but they lack appreciable amounts of any of the long-chain polyunsaturated fatty acids (LC-PUFAs) [5]. In addition, pure SO ILEs contain low amounts of α-tocopherol, the form of vitamin E with the highest *in vivo* antioxidant effect [6]. The low α-tocopherol content further enhances deleterious lipid peroxidation of the high parenteral PUFA supply [2].

The only currently available 20% olive oil/soybean oil-based ILE (OO/SO) contains 80% OO and 20% SO. It is rich in the monounsaturated oleic acid (18:1n-9) [7] and has a naturally higher vitamin E/PUFA ratio, resulting in an improved vitamin E status in recipient patients [1].

The 20% medium-chain triglycerides (MCT)/SO-based ILE (also named MCT/LCT) contains equal proportions of MCTs and long-chain triglycerides (LCTs), from coconut oil and SO, respectively. It contains less PUFAs than the pure SO ILEs and also lacks appreciable amounts of LC-PUFAs [3,5].

Two 20% composite ILEs which include FO as well as other oils have been marketed in Europe. They contain 50% MCT, 40% SO, 10% FO (MSF) or 30% SO, 30% MCT, 25% OO and 15% FO (SMOF), respectively [5]. Compared to pure SO ILEs, both of these ILEs also contain higher amounts of vitamin E and less phytosterols [8].

3.2. 10% Lipid emulsions (10% LEs)

A 10% ILE consisting of pure FO is also available. However, this is registered for use only in adult patients with the goal of supplementing n-3 FAs, while it is not intended to be used as the sole lipid source for long-term PN. Because the pure FO ILE is a 10% solution, it requires twice the volume to be infused as compared to standard 20% ILE. This might be problematic in infants who are on volume restriction. Besides, 10% ILEs have a higher phospholipid content, which can potentially increase plasma triglyceride concentrations.

4. Energy supply

Preterm infants have special nutritional needs in early life, and there is now evidence to suggest that lipids administered at this age may determine various outcomes in later life, including both physical growth and intellectual development [9,10]. Recent meta-analyses and RCTs provide evidence that the initiation of lipids within the first two days of life in very preterm infants appears to be safe and well tolerated [10–14]. No signs of increased respiratory impairment, chronic lung disease, sepsis, patent ductus arteriosus, necrotising enterocolitis, intraventricular haemorrhages, retinopathy of prematurity, or mortality could be demonstrated.

In terms of efficacy, most studies investigated a combination of earlier lipid intake along with early or increased amino acid intake, making it difficult to attribute which macronutrient led to a supposed improved growth [14]. However, some studies demonstrated improved neonatal growth after early initiation of ILE alone [15,16]. It appears possible that the amount of early lipids influences later neurodevelopmental outcome as suggested by observational studies [17].

Positive effects of early parenteral lipids on nitrogen balance have been shown in two studies performed in premature infants [11,18]. In the larger one, the efficacy of the introduction of a high dose of parenteral lipids (i.e., 2–3 g/kg/day) combined with 2.4 g/kg/day of amino acids from birth onwards was compared to a group receiving a similar amount of amino acids, but without lipids. In the group with parenteral lipids, the nitrogen balance on day two was significantly more positive, plasma urea concentrations were significantly lower, and albumin synthesis was enhanced [19], suggesting that administration of parenteral lipids combined with amino acids from birth onwards improves protein anabolism. On the other hand, triglycerides and glucose concentrations were significantly higher in the early lipid group compared with the control group and more infants required insulin therapy. Since there were no benefits for growth, hospital clinical outcomes, total duration of hospital stay, and long term neurodevelopment [20], the clinical benefits of such strategy remain to be proven.

To date there is no evidence that gradual increments in the infusion rate of lipids improve fat tolerance. However, starting lipid emulsion the first day of life at a dose of 2–3 g/kg/d may induce a higher occurrence of hyperlipidaemia as indicated above [19].

The maximum amount of lipids that can be safely given in premature infants is currently not known with certainty. Bilirubin displacement from albumin binding sites by FFAs has also been mentioned as a potential risk of early use of ILE, especially in infants ≤28 weeks gestational age [21]. However, significant displacement of bilirubin does not occur until the FFA to albumin molar concentration ratios are greater than five, while infusion rates of up to 3.25 g/kg/day do not result in ratios over four [22]. Therefore, it is unlikely that lipid infusion at rates of 3–4 g/kg/day results in increased incidence of hyperbilirubinemia or kernicterus. Furthermore, questions arise on long term detrimental effects of ILEs since aortic stiffness and myocardial function in young adulthood has been associated with the exposure to SO ILEs during neonatal life [23]. However, this association does not provide evidence for a causal role of SO ILEs, rather than other associated factors, and it also does not allow generalisation of effects with respect to other ILEs. Most studies in preterm infants limit parenteral lipid intake to 3.0–4.0 g/kg/day, notably a lesser lipid supply than what would be achieved with full enteral feeding. Further well-designed and adequately powered studies are necessary to determine the optimal dose of lipid infusion and the long-term effects on morbidity, growth, and neurodevelopment.

The use of lipids as an energy source reduces the glucose infusion rate necessary to cover the total energy requirements. Since glucose infusion rate should not exceed the maximum glucose oxidation rate (17.3 g/kg/day (12 mg/kg/min) in children) (see also section on “carbohydrates”), a significant amount of lipids should be provided to cover the energy requirements. A

study in malnourished infants and young children has shown that the amount of infused lipid must also be adapted to the lipid oxidation capacity [1]. The maximal lipid oxidation rate is about 3 g/kg/day in young children and decreases with age to 1.7–2.5 g/kg/day in adults. Any lipid provided in excess of metabolic utilization will be stored primarily in adipose tissue and increases the risk of fat overload syndrome which may impair the immune response.

5. Essential and long-chain polyunsaturated fatty acid supply

R 4.5	**In order to prevent essential fatty acids (EFA) deficiency in preterm infants a lipid emulsion dosage providing a minimum linoleic acid (LA) intake of 0.25 g/kg/day can be given. This lipid emulsion dosage ensures an adequate intake of linolenic acid (LNA) with all 20% ILEs currently registered for paediatric use. (LoE 2–, RG 0, strong recommendation for, strong consensus)**
R 4.6	**In order to prevent EFA deficiency in term infants and in children a lipid emulsion dosage providing a minimum LA intake of 0.1 g/kg/day can be given, which also provides an adequate intake of LNA with all 20% ILEs currently registered for paediatric use. (LoE 3–4, RG 0, conditional recommendation for, strong consensus)**

Omission of ILEs from PN may lead to biochemical evidence of EFA deficiency within few days in infants [1]. To prevent EFA deficiency, a minimum LA intake of 0.25 g/kg/day in preterm infants and 0.1 g/kg/day in term infants and older children should be given, which also supplies adequate amounts of LNA (in most ILE the LA to LNA ratio is about 8:1). It should be noted that the provision of EFAs varies with the type of ILE used, and therefore the amount of ILE needed to cover the EFA requirements differs. As an example, a supply of 0.5 g/kg/day of a SO ILE will provide the recommended minimum supply of LA to a preterm infant, whereas 1 g/kg/day will be necessary with an MCT/SO ILE or a composite ILE with FO. At maximum infusion rate, all commercially available solutions (except for the pure FO ILE) provide enough LA and LNA.

The supply of LC-PUFAs is important to consider in neonates because these FAs are conditionally essential in this population and have critical roles during early development [3,9,10]. Vegetable oil-based ILEs lack appreciable amounts of n-6 (arachidonic acid (ARA)) and n-3 LC-PUFAs (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)) which are only supplied in very small amounts from the egg phospholipid emulsifier. In preterm infants the use of pure SO ILEs results in high serum concentrations of LA, whereas the formation of the LC-PUFAs appears to be reduced relative to other available ILEs which have lower EFA contents [22,24,25]. Despite a significantly lower EFA content, similar or even slightly higher LC-PUFAs levels than those observed with pure SO are achieved in preterm infants receiving OO/SO ILEs, most likely because of enhanced LA conversion [22,26]. MCTs seems to enhance the incorporation of EFAs and LC-PUFAs into circulating lipids in preterm infants as the latter are probably spared from oxidation due to preferential oxidation of MCTs [2,25]. Overall, in preterm infants, ILEs providing a mixture of vegetable oils result in more favourable metabolic parameters, and a more desirable lower PUFA supply than pure SO ILEs, but LC-PUFA plasma or blood levels comparable to that of term infants cannot be achieve with any of these lipid emulsions.

In older children, all commercially available 20% ILEs contain sufficient amounts of essential LA and LNA to prevent deficiency. As a general rule, any 20% ILE can be prescribed to compose parenteral regimens or in combination with enteral nutrition to normometabolic patients who require intravenous lipids for a short duration [27].

The smaller preterm infants who receive ILEs that do not contain FO develop an early and severe DHA deficit [28]. Those who receive composite ILEs with FO have higher circulating DHA levels in both plasma and red blood cells than those receiving any other ILEs [29]. This does not mean, however, that the DHA supply provided by ILEs containing FO covers the needs. Indeed, when the mean DHA supply by the composite ILE with FO is similar to the foetal accretion rate (i.e., 42 mg/kg/day), a decrease, not an increase, in circulating DHA levels is observed [30]. It is speculated that both oxidation and tissue uptake may occur and that higher DHA supply might be necessary to fulfil requirements.

A marked elevation of EPA in plasma and red blood cells is observed frequently when ILEs containing FO are used [29]. The estimated EPA supply with FO containing mixed LEs is about 44 mg/kg/day, which is ~10 times greater than that of preterm infants fed their mother's milk [30]. The high EPA intake in the FO group is associated with a significantly greater postnatal drop in ARA levels which suggest a reduced ARA synthesis [29]. The provision of any ILEs with FO that provide no ARA raises questions as to their suitability and biological effects particularly in young infants since low ARA blood concentrations is possibility associated with adverse effects on growth and neurocognitive development [31]. Whether or not these changes in FA profiles are beneficial for the short term and the long term requires further careful evaluation. Based on these findings, it appears prudent to provide n-6 and n-3 precursor fatty acids, as well as n-6 and n-3 LC-PUFA, in balanced amounts and ratios.

6. Choice of lipid emulsion and effects on health

The choice of ILEs is influenced by several considerations which include the composition of the ILE (i.e., fatty acid composition, phytosterols, MCTs, α-tocopherol etc.), the duration of PN, the setting (home PN vs. intensive care unit (ICU) or perioperative PN), age, disease conditions, and other factors. When prescribing ILEs, an understanding of the biological properties and of their FA components is mandatory. As the FA compositions of current ILEs cannot address specific individual clinical needs, the metabolic profiles, and the specific requirement of the patients should guide the prescription of the best-available ILEs to improve not only short term outcomes such as healing and recovery, but also long term outcomes such as growth, cognitive development and development of the immune system.

6.1. Risk of sepsis

Lipids directly support microbial growth and depending on their FA composition lipids can modulate immune functions. The effects of intravenous lipids on the immune system of paediatric patients has only be partially explored. *In vitro* studies showed adverse effects of lipids on the survival of monocytes derived from children, and binding of IL-2 to its receptors. Pure SO ILEs promote more IL-6 production than OO/SO ILEs do [32]. On the other hand, clinical studies in paediatric patients did not reveal adverse effects of ILEs on complement factors or leucocyte function [33], and normal levels of monocyte activation and complement factors have been documented in paediatric patients on long term PN [22].

There are concerns that the administration of ILEs may increase the risk of coagulase-negative staphylococcal bacteraemia in premature infants. Decreased whole blood bactericidal activity has been documented in infants on long term PN but it was not possible to differentiate between the effect of ILEs and other influencing factors such as fasting or other components of the PN solution [1]. A recent comparative study found that ILEs were not significantly associated with an increased risk of overall bacterial and

bloodstream infection rates when given in all-in-one bags [34]. Although this issue has not been settled conclusively, it appears that the nutritional benefits of intravenous lipid administration outweigh the potential risks.

A systemic review and meta-analysis in preterm infants showed a weak association of less sepsis episodes in infants receiving non-pure SO based ILEs as compared to SO ILE [13], which indicates that the source of lipids may play an important role in this situation. This result is however based on only 2 studies that compared pure SO ILE with OO/SO or MCT/SO and has not been confirmed by other meta-analyses [35]. This is, however, in accordance with decreasing DHA concentrations over time in preterm infants receiving pure SO ILEs [36] and with the observed association between low DHA and ARA concentrations and the increased incidence of sepsis [37].

In adults, large RCTs and meta-analyses have shown benefits of composite ILEs without and with FO as compared to pure SO ILE with regard to the risk of infection in ICU [38] and surgical patients [39]. Strategies of using ILEs other than SO ILEs for improving *a priori* the outcomes of older children including those admitted in paediatric ICU may be beneficial even if they have not been fully tested yet [40].

6.2. Prevention of intestinal failure associated liver disease

R 4.7	**In preterm infants, newborns and older children on short term PN, pure soybean oil (SO) ILEs may provide less balanced nutrition than composite ILEs. For PN lasting longer than a few days, pure SO ILEs should no longer be used and composite ILEs with or without fish oil (FO) should be the first-choice treatment (LoE 1−, RG A, conditional recommendation for, strong consensus)**

Intestinal failure associated liver disease (IFALD), also called parenteral nutrition associated liver disease (PNALD) or parenteral nutrition related cholestasis or reflects an heterogeneous liver injury consisting of cholestasis, steatosis, fibrosis and even cirrhosis [41,42]. The most common figure in paediatric patients is cholestasis. Cholestatic liver disease may evolve to fibrosis and cirrhosis [41].

Paediatric patients at risk of IFALD should be identified early in order to prevent, as much as possible, the occurrence of cholestasis. Patients at highest risk include premature infants, infants with long term bowel rest, loss of entero-hepatic cycle (ileal resection, enterostomy) or repeated sepsis, and infants with short bowel syndrome. These patients should be managed by promoting oral feeding as much as possible and by limiting the risk of sepsis and small intestinal bacterial overgrowth [43].

The mechanisms by which ILEs can favour IFALD have been reviewed recently by the ESPGHAN Committee on Nutrition [44] and the ESPGHAN Working Group of Intestinal Failure and Intestinal Transplantation [42]. Since ILEs are considered as one of the many risk factors [45–47], a significant reduction of the dose of ILEs (1 g/kg/d) may prevent cholestasis. Despite pilot studies were in favour of this concept [48,49], other studies including a large RCT including preterm infants born before 29 weeks of gestation failed to demonstrate that a reduced intake of ILEs reduces the risk of cholestasis [50,51]. Furthermore, this remains controversial, since it carries an increased risk of developing EFA deficiency and perhaps also altered development [17,52].

Single studies proposed potential benefits of fish oil containing ILE on indicators of disturbed liver function. One RCT performed in children on home PN showed that the mean total bilirubin concentration decreased in the group on SMOF ILE whereas it increased in the group on SO ILE [58]. Similarly, another study performed in infants with early IFALD and a conjugated bilirubin between 17 and 50 μmol/L at inclusion showed that those receiving the SMOF ILE had a lower conjugated bilirubin concentration at the end of the trial and were more likely to have a decrease of conjugated bilirubin to 0 μmol/L than those receiving a SO ILE [59]. However, a meta-analysis including RCTs and non RCTs showed of fish oil containing ILE for prevention of cholestasis [127].

The ESPGHAN Committee on Nutrition recently performed a systematic review with, where appropriate, a meta-analysis on the effect of different types of ILE on cholestasis and IFALD [44]. The objective of this work was to assess the role of different ILEs in the pathogenesis of cholestasis and IFALD in infants and in children. The primary outcome measure was the incidence of cholestasis (serum conjugated bilirubin >2 mg/dL; 34 μmol/L) and the secondary outcomes included levels of conjugated and total bilirubin, liver enzymes, alkaline phosphatase, and ɣ-glutamyl transferase.

In neonates receiving an ILE for a short term, the pooled meta-analysis did not find any significant difference in any composite ILE compared to the pure SO ILE for the primary and secondary outcomes. One RCT not included in the meta-analysis showed that the group of preterm infants receiving an own-made mixture composed of 50% OO/SO ILE and 50% pure FO ILE had a significantly lower incidence of cholestasis than the group receiving solely the OO/SO ILE [53]. Since the literature search of the ESPGHAN systematic review, one large RCT did not show any significant difference in liver function tests between a group of preterm infants receiving SMOF ILE and a group receiving a SO ILE [54].

In children on short term PN, one RCT performed in children after bone marrow transplantation with no cholestasis before the ILE initiation showed no effect of the MCT/SO ILE versus the OO/SO ILE on serum bilirubin and transaminase concentrations [55].

Finally, in neonates and children on long term PN (i.e., more than 4 weeks), there is no significant effect on the appearance of cholestasis in neonates receiving the 10% pure FO ILE vs the SO ILE [56] nor there is a significant difference in liver enzyme tests and bilirubin concentrations in children receiving the OO/SO ILE or the SO ILE [57]. Other health outcomes

The use of pure SO ILE in preterm infants has been linked to increased pulmonary vascular resistance, impaired pulmonary gas exchange, enhanced oxidative stress and adverse immunologic effects such as increased rates of infection and sepsis [1,5,60].

Compared to LCTs, MCTs show faster plasma clearance, more rapid oxidation, and less dependency on carnitine for beta-oxidation [2,22]. Adult and paediatric studies suggested that MCT/LCT emulsions lead to higher net fat oxidation, reduced liver derangement, improved white blood cell function, and less effects on pulmonary haemodynamic and gas exchange than SO ILEs [22].

The effects of the OO/SO ILE on peroxidation and oxidative stress defence remain controversial, but are either positive or neutral [7,22,26,61,62]. Compared to pure SO ILEs, other advantages of the OO/SO ILE include decreased phytosterol load [63,64], a more neutral effect on immunological modulators [32], and beneficial effects on pulmonary artery pressure [65]. A stable isotope study in premature infants reported that the OO/SO ILE also have a beneficial effect on glucose homoeostasis compared to pure SO ILEs [66].

A RCT performed in children after bone marrow transplantation showed that the MCT/SO and the OO/SO ILEs were equally well tolerated, maintained EFA concentrations and did not have adverse effect on peroxidation status. No differences between MCT/SO and OO/SO ILEs were found for haematological parameters, liver

enzymes, vitamins, plasma peroxidation status, percentage and time to engraftment, but cholesterol levels were significantly lower in the OO/SO ILE group [55].

Whether or not recent composite ILEs containing FO may provide specific health benefits has only been partially investigated [60]. The effect on growth is controversial since one study showed higher weight and head circumference z-scores during hospitalization in preterm infants receiving composite ILEs containing FO compared to those receiving pure SO ILE [67] whereas another did not show any significant effects [54]. No effects of composite ILEs with FO could also be demonstrated on fat mass deposition, intrahepatocellular lipid content and insulin sensitivity assessed at expected term [54]. Other possible beneficial effects of ILEs containing FO in preterm infants include a lower incidence and/or severity of retinopathy of prematurity [53,68,69], the reduction of markers of oxidative stress [70], and a decreased risk of bronchopulmonary dysplasia [71,72]. However, recent meta-analyses comparing ILEs containing FO with other ILEs did not show a significant reduction in mortality, in infection rate or any other clinical variables (e.g., bronchopulmonary dysplasia, sepsis, retinopathy of prematurity, growth) and PN associated complications [29,35]. Also various biochemical markers such as hyperbilirubinaemia, hypertriglyceridaemia, elevated C-reactive protein were not better in the group on composite ILE with FO [29,40] nor was the cholesterol synthesis rate [73]. Finally, no effect of SMOF ILE on brain growth [54] and neurodevelopment [20] could be demonstrated.

Few RCTs were published after the meta-analyses cited above. One of them, using a 2-by-2 factorial protocol, assessed the effects of a composite ILE containing FO versus a pure SO ILE on intrahepatocellular lipid content assessed by MRI at expected term [54]. This study did show any significant effect on the primary outcome nor on growth parameters, adipose tissue deposition, triglyceride concentration and liver parameters.

ILE containing FO may modulate markers of the inflammatory response. In infants undergoing cardiopulmonary bypass composite ILEs containing FO provided prior to surgery, result in a lower inflammatory response after surgery [74]. In children after haematopoietic stem cell transplantation, composite ILEs with FO, compared to SO ILE, improve antioxidant profile but did not alter markers of inflammation at day 10 [75]. However, on prolonged PN for more than 21 days, IL-10 and TNF-α levels were reduced by the composite ILE with FO [76]. Finally, preterm infants receiving a composite ILE with FO compared to a SO ILE, had lower IL-6 and IL8 levels at day 30 of life or at the end of intervention [77]. All together these studies show that providing composite ILE with FO alter the inflammatory response and may be beneficial. However, none of these studies reported clinical outcomes and therefore the clinical relevance of these findings need to be further evaluated.

7. Mode of administration of ILEs

7.1. Photoprotection

R 4.8	**In preterm infants, ILEs should be protected by validated light-protected tubing. (LoE 1−, RG B, strong recommendation for, strong consensus)**

ILEs with high PUFA content are particularly prone to peroxidation. These radicals may be harmful, especially to premature infants in whom they have been associated with poor feeding and high serum triglyceride concentrations [78–81]. The exposure of lipid solutions to blue light irradiation (i.e., phototherapy light) may significantly increase lipid peroxidation leading to cellular damage of the retinal pigment epithelial cells or of the photoreceptors [82,83]. In vitro studies have suggested that administering multivitamins containing ascorbic acid together with ILEs via dark delivery tubing, provides the most effective way of preventing lipid peroxidation and also limiting vitamin loss. The formation of triglyceride hydroperoxides may occur even in ambient light [84–87]. A recent meta-analysis including over 800 infants from 4 RCTs showed a significant reduction of 50% in the mortality rate in the light-protected group [88].

7.2. Emulsions with 20% or 10% lipids

R 4.9	**In newborns including preterm infants, routine use of ILEs should be continuous over 24 h (LoE 2++, RG B, conditional recommendation for, strong consensus)**

ILEs consist of a lipid source and an emulsifier (egg yolk derived phospholipids) that envelopes the fat globules and keeps them soluble. Standard 20% emulsions contain a lower ratio of phospholipid (PL) emulsifier/triglycerides than standard 10% ILEs. The 20% ILEs are currently the most frequently used ILEs in neonatal intensive care units [89]. Preterm infants receiving 10% emulsion vs. 20% emulsion demonstrated various alterations in their plasma lipid profiles. Higher amounts of PL (i.e. particles rich in PL) impede the removal of triglycerides from plasma, leading to an increase in plasma triglyceride concentration and accumulation of cholesterol and phospholipids in low-density lipoproteins [22]. Of note, 10% pure FO emulsion has been used in infants and children at a low dosage of 1 g/kg/d, with no adverse observed effects [90] but further studies are needed to fully explore the safety of this ILE when given to infants or children.

7.3. Continuous vs. discontinuous

R 4.10	**In newborns including preterm infants, ILEs should be administered as continuous infusions over 24 h (LoE 2++, RG B, conditional recommendation for, strong consensus)**
R 4.11	**If cyclic PN is used, for example for home PN children, ILEs should usually be given over the same duration as the other PN components. (LoE 4, GPP, strong recommendation for, strong consensus)**

There is no clear evidence that a lipid free interval allows the lipids to 'clear' from the plasma or allows 'hepatic rest' to improve tolerance [22]. Short-term lipid tolerance is best when infused continuously at steady rate, as several plasma lipid concentrations correspond best with the hourly infusion rate. This is especially the case with lower gestational ages or at higher infusion rates. Besides, interruption of PN in neonates could result in higher infection rate, possibly due to increased line handling [91,92]. A retrospective analysis of PN cycling in both preterm and term neonates with gastrointestinal disorders requiring surgical intervention showed that prophylactic daily discontinuous PN infusion could not prevent a rise in conjugated bilirubin concentrations [93]. In another retrospective analysis of PN treated neonates with gastroschisis, prophylactic cycling of all PN components was associated with reduced cholestasis but the association disappeared after adjusting for confounders [92]. In both previous retrospective studies, there was no mention of the total lipid dose in both groups, so that a reduced daily lipid dose could also be responsible for a supposed difference. In a recent RCT in preterm infants comparing cycled or continuous amino acid infusion together with interrupted lipid infusion for 6 h per day in both groups, no effect on cholestasis has

been demonstrated [91]. In adults and children receiving long-term or home PN, there is a favourable risk-benefit profile of cyclic PN infusion [94]. However, infants under age 2 years are at risk for the development of hypoglycaemia after interrupting PN, and thus blood glucose concentrations should be monitored.

The clearance of the ILEs varies according to the FA composition of the ILEs and is longer for LCT infusions than MCT infusions [95]. Therefore, mixing oils of varying chain lengths can favourably influence the plasma clearance of lipid infusions.

In metabolically stressed children, ILEs can be administered safely at a low dosage over a 12–24 h period. The discontinuous administration of ILEs at higher daily doses may contribute to fat overload syndrome and should be avoided in critically ill children.

7.4. Heparin

R 4.12	**In paediatric patients, heparin should not be given with lipid infusion on a routine basis. (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

The stability of the ILEs may be compromised (flocculation and creaming) by adding components that lower the pH or impose ionic stress. The size of the ILE droplets should remain well below the diameter of capillaries to avoid vascular occlusion. The stability of the ILEs is also threatened because of an interaction between heparin and calcium. This destabilization will depend on proportions of amino acids, multivitamins and ILEs [96], and has been described to occur in ternary admixtures for paediatric PN [97]. It is more likely to occur when the heparin is used at high concentrations and when intravenous lipids are used undiluted, and less likely to occur for ranges of lipid-to-nutrient ratios normally administered to premature infants [98].

Clearance of ILEs from the blood depends on the activity of LPL. LPL activity can be increased by relatively high doses of heparin [22]. However, the increase in LPL activity by heparin leads to an increase in FFAs, which may exceed the infant's ability to clear the products of lipolysis and may weaken the binding of LPL to the endothelium [22].

Overall, since heparin does not improve utilization of intravenous lipids and might compromise the stability of ILEs, it should not be given with lipid infusions on a routine basis, unless indicated for other reasons.

7.5. Carnitine

R 4.13	**Carnitine supplementation may be considered in paediatric patients expected to receive PN for more than 4 weeks or in premature infants on an individual basis (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

Carnitine facilitates the transport of long-chain FAs across the mitochondrial membrane, and thus makes them available for beta-oxidation [22,99]. Carnitine is present in human milk and cows' milk formulae, but PN solutions do not usually contain carnitine.

Carnitine is synthesized in the liver and kidney from lysine and methionine. Thus patients with renal or hepatic insufficiency may be at risk of carnitine deficiency [99]. Tissue carnitine stores of infants aged less than 24 h show a positive correlation with gestational age. Infants and preterm infants have much more limited carnitine stores and synthesis rates compared with adults [22]. In clinical practice, it is difficult to assess the carnitine status because the circulating carnitine levels poorly reflect tissue carnitine stores.

Low carnitine concentrations have been reported in patients on carnitine-free PN, especially in infants with body weight less than 5 kg [22,100]. Parenteral carnitine supplementation increases the plasma levels of total, free and acyl-carnitine, but results on metabolic nutrition and clinical outcomes are inconsistent [101–103]. A meta-analysis showed no benefit of parenteral carnitine supplementation on lipid tolerance, ketogenesis or weight gain in neonates requiring PN [22].

Given that some patients have both limited carnitine stores and biosynthesis, monitoring of plasma carnitine concentrations and carnitine supplementation (e.g. 20–30 mg/kg/d) may be considered on an individual basis in premature infants or those on exclusively PN for more than 4 weeks [99,104].

8. Lipid emulsions in special disease conditions

8.1. Critically ill children

R 4.14	**In critically ill paediatric patients, ILE should be an integral part of PN. Composite ILEs with or without FO may be used as the first choice treatment. Available evidence raises the important question on the best timing to provide parenteral nutrition support in critically ill children, but do not allow to differentiate potential effects on outcomes of the timing of introducing parenteral lipid supply (LoE 4, GPP, conditional recommendation for, strong consensus)**
R 4.15	**In paediatric patients with sepsis, more frequent monitoring of plasma triglyceride concentration and dose adjustment in case of hyperlipidaemia are recommended. ILE dosage may be reduced but lipid supply may generally be continued at least in amounts supplying the minimal EFA requirements (LoE 4, GPP, conditional recommendation for, strong consensus)**

Nutritional support in critically ill infants and children has not been fully studied and remains a controversial topic. A Cochrane review did not identify any RCT assessing the best timing for introducing a PN support in paediatric patients [105]. As a consequence, there are no clear recommendations on the best form or timing of nutrition in critically ill children. In one very recent large RCT, 1440 paediatric patients admitted to 3 different PICUs were randomized to receive PN support, in addition to enteral nutrition, either starting within the first 24 h of ICU treatment or on day 8. Both groups, however, received intravenous minerals, trace elements, and vitamins. As a consequence, parenteral and total energy, lipid and amino acid supply during the first week were significantly different between the 2 groups. Compared with the early PN group, the late PN group showed significantly less new infections and a shorter PICU stay, which leads to the conclusion that routine administration of PN in all pediatric ICU patients on the first day of treatment may not be advisable [106]. The study raises the important question on the best timing to provide PN support in critically ill children, but it does not allow to differentiate potential effects of different PN components, or whether the timing of introducing parenteral lipid supply may affect outcomes. Whether or not withholding lipid emulsion during the first week of critical illness in malnourished children or in children risk of becoming malnourished is beneficial or not has also not been extensively studied and is a matter of debate. On one hand, in one large RCT, children with the highest risk of becoming malnourished benefited of withholding PN (and in turn of withholding parenteral lipid) [106], on the other hand, an observational study suggested that withholding PN in malnourished children may further increase mortality and morbidity [107]. A more careful evaluation of the effect of withholding ILEs in critically ill infants and children is therefore needed.

Concerns have been raised regarding the possible adverse effects of intravenous lipids on pulmonary function. ILEs have been considered toxic in acute respiratory failure since they may induce or intensify gas exchange abnormalities. The SO ILEs induce an increase in pulmonary blood pressure and vascular resistance [108]. In neonates, this is of particular importance because respiratory failure is frequently associated with pulmonary hypertension. Previous studies suggested that ILEs (mainly pure SO) may increase the pulmonary artery pressure in newborns with respiratory failure. There is now some evidence from experimental studies that n-3 PUFA may be beneficial in conditions associated with pulmonary hypertension through production of epoxides [109]. The clinical relevance of these findings has however not yet been proven in neonates [110].

There are also conflicting data about lipid clearance during sepsis. Some studies found that lipid clearance is reduced whilst others found no association between hypertriglyceridaemia and infection. In septic premature infants, triglyceride concentrations tend to be higher, because of decreased activity of lipoprotein lipase, and fatty acid oxidation is lower than in non-septic patients but it is difficult to define an upper limit of lipid intake based on these data [22]. In critically ill and in septic patients, close monitoring of plasma triglycerides and adjustment of lipid infusion rate if necessary is recommended.

Composite ILEs could have less pro-inflammatory effects, less immune suppression, and more antioxidant effects than the pure SO ILEs. This would make them more suitable for critically ill patients. Patients receiving composite ILEs with FO have rapid incorporation of EPA and DHA into leucocyte and monocyte cell membranes thereby decreasing their ability to produce TNF-α, IL-1b, IL-6, and IL-8 when stimulated by endotoxin [22]. FAs from FO may attenuate the initial injurious hyperinflammatory state in severe sepsis and in patients with acute lung injury [111]. The bronchoalveolar lavages of adult patients with acute respiratory distress syndrome receiving n-3 FAs and gamma-linoleic acid show an important decrease in global cell count, in polymorphonuclear cell percentage, IL-8 and leukotriene B_4 concentrations which were associated with an improvement of the PaO_2/FiO_2 ratio, a reduction in mechanical ventilation need and duration, a decreased risk of complications, and a decreased length of stay in the ICU [112]. Pretreatment with a composite ILE with FO downregulates TNF-α, leukotrienes B_4, procalcitonin and lymphocyte concentrations after open heart surgery in infants [74,113]. Several recent reviews in adults agreed that there is inadequate evidence to recommend the routine use of FO-containing emulsions in patients with sepsis because a reduction in overall mortality could not be found [108,114,115]. In paediatric patients with sepsis, there is also a lack of data to determine the optimal composition of the parenteral lipid intake and finally, in neonates, the effects of the use of composite LEs, including those containing FO on neonatal morbidity has not yet been confirmed with certainty [35].

There are several reasons to provide intravenous lipids in the critically ill child. Critical illness and the associated inflammation and tissue injury alter metabolism by inducing a catabolic state, which may exacerbate pre-existing malnutrition. Lipid metabolism and turnover are increased in critical illness as fatty acids are used as a primary fuel source [116]. Excessive carbohydrates are converted to lipids but generate carbon dioxide in the process. Administration of lipids to critically ill patients decreases *de novo* lipogenesis from glucose and CO_2 production associated with a high carbohydrate intake [22]. Infants and children generally have limited fat stores and are susceptible to the development of essential fatty acid deficiencies as early as a few days if not receiving sufficient lipids [1].

To date, and although there are no studies in children with acute respiratory failure, it might be prudent to limit lipid intake during the acute phase of respiratory failure especially when pure SO ILEs are used. Despite encouraging results with composite ILEs containing FO, large randomised studies are lacking especially in critically ill children.

8.2. Treatment of drug toxicity

R 4.16	**Case reports have suggested the use of ILEs as a possible antidote for the treatment of drug toxicity in children, which however is not based on well-designed trials (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

ILEs have been proposed as a possible antidote for the treatment of drug toxicity in adults. Initial efficacy of ILEs was shown in the setting of local anaesthetic systemic toxicity, but recent case reports suggest its consideration in a variety of other drug toxicities including beta-blockers, calcium-channel blockers, and tricyclic antidepressants [117,118]. Despite the ever-increasing case report literature of the use of ILE therapy in poisoning, the indications for its use in adults remain limited to severe cardiovascular instability resulting from lipophilic toxin poisoning, in particular if this does not respond to conventional measures [117].

Clinical cases have been reported in paediatric patients despite there are no published recommendations for ILE dosage in children [119]. A review reported the use of ILEs as Pediatric Lipid Rescue in 16 occasions, in 9 cases related to local anaesthetics and 7 cases to other drugs [120]. All of them had a positive response except one, probably due to infra-dosing. One patient developed pancreatitis and another one generated respiratory distress, likely not exclusively related to lipid emulsion but also to cardiac arrest and resuscitation efforts. Given the severity and poor prognosis of cardiac arrest and post cardiac arrest syndrome, as well as the low incidence of fat overload syndrome, one may consider lipid rescue in such severe toxicity cases in the PICU or emergency department.

8.3. Thrombocytopaenia

R 4.17	**In patients with severe unexplained thrombocytopaenia, serum triglyceride concentrations should be monitored and a reduction of parenteral lipid dosage may be considered. (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

ILEs do not seem to affect platelet number or function [22]. However, some concerns were raised regarding the effect of ILEs on platelet aggregation. Long-term administration of PN with pure SO derived ILEs induced hyperactivation of the monocyte-macrophage system with haematological abnormalities, including recurrent thrombocytopaenia due to reduced platelet lifespan and haemophagocytosis in bone marrow [22].

Fat overload syndrome (FOS) is a well-known complication of intravenous ILE therapy in high dosages or excessive rate of infusion [1]. It is characterized by headaches, fever, jaundice, hepatosplenomegaly, respiratory distress, and spontaneous haemorrhage. Other symptoms include anaemia, leukopenia, thrombocytopaenia, low fibrinogen levels, and coagulopathy. Several reports in the literature describe fat overload syndrome caused by rapid infusion of ILE overwhelming LPL capacity and orienting lipid plasma clearance to the reticuloendothelial system

(RES) which becomes overload with fat. In cases of infection this RES fat overload may result in clinical-biological FOS with the symptoms described. FOS has been described mostly with SO ILEs but recently also with ILEs containing FO suggesting that the rate of infusion, not the type of the ILE, is responsible for the syndrome [121].

A supply of EFAs meeting minimal requirements is necessary to maintain normal platelet function [22]. Specifically, in children who have thrombocytopaenia after bone marrow transplantation, it seems logical to provide sufficient amounts of EFA to support cell membrane synthesis.

Nevertheless, it seems advisable to monitor serum triglyceride concentrations, and consider decreasing parenteral lipid intake in conditions of severe thrombocytopenia or coagulopathy (e.g. sepsis, disseminated intravascular coagulopathy).

8.4. Management of intestinal failure associated liver disease

R 4.18	**As part of measures to reverse IFALD in paediatric patients, a discontinuation of SO ILE, a reduction of other ILE dosage and/or the use of composite ILE with FO, should be considered along with the treatment and management of other risk factors (LoE 2+, RG B, strong recommendation for)**
R 4.19	**The use of pure FO ILE is not recommended for general use in paediatric patients but may be used for short-term rescue treatment in patients with progression to severe IFALD, based on case reports. (LoE 3–4, GPP, conditional recommendation for, strong consensus)**

Reversal of IFALD by modulating the dose or the type of ILEs has been assessed by several observational studies but data from RCTs are limited. When switching the historical SO ILE to a composite ILE with or without FO, several changes occur that include a reduction in n-6 FAs, a dramatic reduction of phytosterol supply, and the provision of a large amount of alpha-tocopherol and anti-inflammatory n-3 FAs. All these may affect the course of IFALD.

Several case studies reported the efficacy of the pure FO ILE as monotherapy in the treatment of IFALD in infants and children [44]. In most of these studies, a high dose of pure SO emulsion was replaced by 1 g/kg/d of pure FO ILE. Therefore, it is still not clear whether reversal of cholestasis was due to the effect of stopping the SO load or the effect of FO itself (including the high α-tocopherol load) or both. The largest of these studies, using a before and after study design, reported that a dose of 1 g/kg/d of pure FO ILE appears to be sufficient to significantly reduce the combined risk of death and liver transplantation compared to a dose of 1–4 g/kg/d of SO ILEs. Furthermore, 50% of the patients in the pure FO ILE group and who survived and were not transplanted, reached bilirubin levels ≤2 mg/dL compared to 5.6% in the SO ILE group [122]. Another study using a retrospective design showed that the addition of pure FO ILE to the pure SO ILE (ratio 1:1) combined with a small reduction in the total lipid intake (2 g/kg/d vs. 2–3 g/kg/d) was able to reduce cholestasis in nine of the twelve PN-dependent included children [123]. Finally, a retrospective study of children with cholestasis compared changes in serum bilirubin levels while receiving SMOF ILE or remaining on SO ILE [124]. After 6 months, the median bilirubin level felt by 99 μmol/L in the SMOF ILE group but increased by 79 μmol/L in the SO ILE group ($p = 0.02$). Overall, these observational studies suggest that the use of a low-dose of pure FO ILE or alternatively of a composite ILE with FO over several months in IFALD patients might have benefits.

Beside these observational studies, two RCTs have now been published on the effects of composite ILEs or pure FO ILEs in patients with IFALD in comparison to SO ILE. In children after abdominal or oesophageal surgery who had cholestasis before the intervention the use of the MCT/SO ILE decreased bilirubin levels whereas this was not the case with the use of a SO ILE [125]. In infants less than 2 years on long term PN and who have evidence of early hepatic dysfunction, those receiving the pure FO ILE at 1.5 g/kg/d recovered more frequently from cholestasis during PN than those on the SO ILE also provided at 1.5 g/kg/d [126]. A meta-analysis which included RCTs and non RCTs concluded that the use of ILEs containing FO is effective for reversing cholestasis in neonates, while there was no benefit for prevention [127]. Similar beneficial effects on liver function tests have been reported in adult surgical or ICU patients with cholestasis [128,129].

If there is evidence suggesting that cholestasis, the early stage of IFALD, may be reversed by using ILEs containing FO, although there is also evidence that liver fibrosis or cirrhosis may not [130,131]. A study in adults showed that scores for steatosis, inflammation, and cholestasis improved in serial biopsies taken after switching from pure SO ILE to pure FO ILE, but that quantification of fibrosis was unchanged [132].

If the published studies suggest that short term administration of pure FO ILEs may be attempted as rescue treatment, they do not provide evidence that long term use (e.g., >15 days) of pure FO in fully parenterally fed children is safe. Of note, in the USA, the pure FO ILE is currently only available on a compassionate basis in a maximum dose of 1 g/kg/day for infants and children suffering IFALD to serve as rescue treatment [133,134]. In Europe, pure FO ILE is not registered for paediatric use. Pure FO ILEs provide insufficient n-6 FA supply and thereby increase the risk of EFA deficiency. Besides, decreased ARA and exceedingly increased EPA concentrations in plasma and cell membranes have been found but long term effects of these changes particularly on neurodevelopment is unknown [56,135,136]. There is also a concern that long-term administration of pure FO ILEs as a sole lipid source could alter coagulation [137,138]. A case-report was published on the development of Burr cell anaemia from haemolysis in an infant after receiving pure FO ILE for over 5 months [139]. Finally, it should be noted that the efficacy of composite ILEs with FO and pure FO ILE monotherapy has not yet been directly compared.

9. Monitoring

R 4.20	**Markers of liver integrity and function, and triglyceride concentrations in serum or plasma should be monitored regularly in patients receiving ILEs, and more frequently in cases with a marked risk for hyperlipidaemia (e.g. patients with high lipid or glucose dosage, sepsis, catabolism, extremely low birth weight infants) (LoE 2–, RG B, strong recommendation for, strong consensus)**
R 4.21	**Reduction of the dosage of ILEs can be considered if serum or plasma triglyceride concentrations during infusion exceed 3 mmol/L (265 mg/dL) in infants or 4.5 mmol/L (400 mg/dL) in older children (LoE 4, GPP, conditional recommendation for, strong consensus)**

Tolerance of lipid administration is generally monitored by biochemical parameters. Plasma clearance of infused triglycerides can be assessed by measurement of plasma triglyceride concentrations. However, normal plasma triglyceride concentration does not mean optimal oxidation of lipids and it is unclear at what serum level of triglycerides adverse effects may occur [5]. Besides, results should also be interpreted according to whether samples were taken after concomitant oral feeding, or during intermittent rather than continuous lipid infusions; for example, in home PN children, plasma clearance of infused triglycerides is better assessed 12 h after the discontinuation of ILEs.

Hypertriglyceridaemia might occur because of lipogenesis due to providing too much glucose. In this case, glucose intake rather than lipid infusion should be reduced first. Hypertriglyceridaemia may also occur in patients with sepsis (see above). Preterm infants may be at a higher risk of hypertriglyceridaemia than older infants due to their relatively limited muscle and fat mass and therefore decreased hydrolytic capacity [22]. In infants fed human milk or formula, fasting triglyceride concentrations of 1.7–2.3 mmol/L (150–200 mg/dL) are frequently encountered. However, it seems reasonable to accept slightly higher triglyceride concentrations during lipid infusion as the upper limit in premature and term infants. In a recent study on early lipid administration to VLBW infants, the occurrence of hypertriglyceridaemia defined as >3 mmol/L (265 mg/dL), a level when intake was reduced, was not associated with a higher prevalence of neonatal morbidities such as necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity, and intraventricular haemorrhage [11]. In the absence of other evidence it seems advisable to reduce lipid infusions when concentrations exceed 3.0 mmol/L (265 mg/dL).

For older children, serum triglycerides concentrations of 3.4–4.5 mmol/L (300–400 mg/dL) may be acceptable based on the fact that lipoprotein lipase is saturated at around 4.5 mmol/L (400 mg/dL). Hypertriglyceridaemia is most likely to occur 4 h after an infusion is initiated. In malnourished patients, tolerance of intravenous ILEs might need to be monitored more frequently than suggested since these patients have slower rates of clearance that those who are not malnourished.

Checking serum triglyceride levels may be considered within approximately 1–2 days after initiation or adjustment of lipid infusion. Monitoring of serum triglycerides may thereafter be performed from weekly to monthly depending on the stability and history of the patient. In high risk patients (e.g. patients with high lipid or glucose dosage, sepsis, malnourishment, catabolism, extremely low birth weight infants, malnourished patients) there is a risk of hyperlipidaemia and more frequent monitoring is warranted. If plasma levels of triglycerides are above the limits defined according to age, lowering, not stopping the dosage is recommended.

Abnormal liver function has been reported in patients receiving PN both with and without ILEs. The relationship between cholestasis and ILEs has been described and manipulation of lipid dosages or switching between different lipids types have been among the most frequent strategies used in infants or children on PN with liver dysfunction. To guide treatment strategies, it is recommended to monitor liver enzymes and direct bilirubin concentrations two weeks after initiation of PN and weekly to monthly thereafter.

Conflict of interest

None declared.

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Clinical Nutrition 37 (2018) 2337–2343

Contents lists available at ScienceDirect

Clinical Nutrition

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

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

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http://dx.doi.org/10.1016/j.clnu.2018.06.947
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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 CO_2 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, conditional

	Day 1	Day 2 onwards
	Start with	Increase gradually over 2–3 days to
Preterm newborn	4–8 (5.8–11.5)	Target 8–10 (11.5–14.4) Min 4 (5.8); max 12 (17.3)
Term newborn	2.5–5 (3.6–7.2)	Target 5–10 (7.2–14.4) Min 2.5 (3.6); max 12 (17.3)

R 5.5 Newborns < 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)

R 5.6 Recommended parenteral glucose supply in infants and children according to body weight and phase of illness. The units are mg/kg/min (g/kg per day) (LoE 1+, RG A, strong recommendation)

	Acute phase	Stable phase	Recovery phase
28 d–10 kg	2–4 (2.9–5.8)	4–6 (5.8–8.6)	6–10 (8.6–14)
11–30 kg	1.5–2.5 (2.2–3.6)	2–4 (2.8–5.8)	3–6 (4.3–8.6)
31–45 kg	1–1.5 (1.4–2.2)	1.5–3 (2.2–4.3)	3–4 (4.3–5.8)
>45 kg	0.5–1 (0.7–1.4)	1–2(1.4–2.9)	2–3 (2.9–4.3)

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.

R 5.7 Blood glucose measurements should preferably be performed on equipment validated for use such as blood gas analysers (LoE 2+, RG B, strong recommendation)

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)

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

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)

R 5.11 In neonates in the 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 0, conditional recommendation)

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 0, strong recommendation)

1. Methods

Literature Search

Medline search, Pub-Med search, Embase, expert search

Search conducted on 30.11.2014 and on 17.09.2016

Timeframe: publications from <1946 to *17.09.2016*>.

Type of publications: original papers, meta-analyses and overviews

Key words: children, parenteral nutrition, glucose, carbohydrate, energy-resource, insulin, critical illness

Language: English

2. Introduction

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, 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.

Recommendations were established by considering [1] the consequences of excessive glucose intake during PN [2], the rate of glucose production and oxidation and [3] the risk of hypoglycaemia. Energy provision during PN includes the use of intravenous fat emulsions (IVFE) (see Lipids chapter) and intravenous amino acid administration (see Amino acids chapter). Therefore, the recommendations for these macronutrients need to be taken into account in order to meet the energy requirements.

When establishing the lower and upper glucose intake recommendations two important factors have to be considered; respectively cerebral glucose utilization and the effect of glucose intake on protein catabolism [1]. A recommendation for higher glucose intake in the neonatal or paediatric ICU would decrease the risk of hypoglycaemia and presumably provide more energy for protein anabolism and growth. However, whole body glucose metabolism in neonates and children is highly modified during (acute) critical illness [2–4]. During acute illness protein catabolism is not modified with increasing glucose intake, while hyperglycaemia, which occurs more frequently during this phase, might be as undesirable as hypoglycaemia [5–7]. Therefore, the basis for glucose intake

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 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 CO_2 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 CO_2 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 hypocholesterolaemia [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 preterms 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 (17.2 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 5.4 **Recommended parenteral glucose supply in (pre)term newborns in mg/kg per min (g/kg per day) (LoE 2+, RG B, conditional recommendation, strong consensus)**

	Day 1	Day 2 onwards
	Start with	Increase gradually over 2–3 days to
Preterm newborn	**4–8 (5.8–11.5)**	**Target 8–10 (11.5–14.4)** **Min 4 (5.8); max 12 (17.3)**
Term newborn	**2.5–5 (3.6–7.2)**	**Target 5–10 (7.2–14.4)** **Min 2.5 (3.6); max 12 (17.3)**

R 5.5 **Newborns < 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)**

R 5.6 **Recommended parenteral glucose supply in infants and children according to body weight and phase of illness. The units are mg/kg/min (g/kg per day) (LoE 1+, RG A, strong recommendation, strong consensus)**

	Acute phase	Stable phase	Recovery phase
28 d–10 kg	**2–4 (2.9–5.8)**	**4–6 (5.8–8.6)**	**6–10 (8.6–14)**
11–30 kg	**1.5–2.5 (3.6–2.9)**	**2–4 (2.8–5.8)**	**3–6 (4.3–8.6)**
31–45 kg	**1–1.5 (1.4–2.2)**	**1.5–3 (2.2–4.3)**	**3–4 (4.3–5.8)**
> 45 kg	**0.5–1 (0.7–1.4)**	**1–2(1.4–2.9)**	**2–3 (2.9–4.3)**

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 hypoglycaemia 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 acetaminophen, 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 [60–62]. 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 0, 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 0, 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.

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Clinical Nutrition 37 (2018) 2344–2353

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Fluid and electrolytes

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

The aim of the current revision is to update the previous chapter [1] on basis of the scientific evidence published since 2004. The work of the authors who wrote the previous version of this chapter is gratefully acknowledged and forms the basis of this updated guideline.

The literature search was conducted using the Medline and Cochrane syst. Database covering the period from 2004 until

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https://doi.org/10.1016/j.clnu.2018.06.948
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Table: Recommendations on fluid and electrolytes

Neonates during the transition phase (phase I)	
R 6.1	In term neonates, postnatal weight loss generally occurs during the first 2–5 days of life and should not usually exceed 10% of birth weight (LoE 2++, RG 0, conditional recommendation)
R 6.2	In ELBW and VLBW infants, 7–10% weight loss seems to be adequate taking into account their higher body water content and the adverse complications associated with fluid overload (LoE 2++, RG B, strong recommendation)
R 6.3	A gradual increase of fluid intake is recommended in preterm and term neonates after birth (LoE 3, RG B, strong recommendation)
R 6.4	Electrolytes (Na, Cl and K) should be supplied starting during phase I/contraction of ECF compartment/initial loss of body weight (LoE 3, RG 0, strong recommendation)
R 6.5	Cl intake should be slightly lower than the sum of Na and K intakes (Na + K-Cl = 1–2 mmol/kg/d) to avoid excessive Cl intakes and risk of iatrogenic metabolic acidosis (LoE 3, RG 0, strong recommendation)
R 6.6	In ELBW and VLBW infants, Na and K may be recommended from the first day of life when giving the recommended high amino acids and energy supply, providing that urine output is ascertained, and taking into account the potential for the development of nonoliguric hyperkaemia (LoE 2+, RG 0, conditional recommendation)
R 6.7	It should be recognized that the needs of individual patients may deviate markedly from the ranges of generally recommended intakes depending on clinical circumstances such as fluid retention, dehydration or excessive water losses, or others (GPP, strong recommendation)
Neonates during intermediate phase (phase II)	
R 6.8	After initial postnatal weight loss, birth weight should usually be regained by 7–10 days of life (GPP, conditional recommendation)
Neonates during the phase of stable growth (phase III)	
R 6.9	Fluid and electrolyte homoeostasis should be maintained while the infant is gaining appropriate weight during the phase of stable growth (LoE 3, RG B, strong recommendation)
Children and infants beyond the neonatal period	
R 6.10	Requirements for fluid and electrolytes for infants and children (beyond the neonatal period) on PN are mainly based on empirical evidence and recommendations are presented in Table 5 (LoE 4, RG 0, strong recommendation)
R 6.11	The Holliday and Segar formula for calculating the maintenance water needs in children by determining caloric/water needs from weight (see Table 4) is still regarded appropriate in the clinical setting (GPP, strong recommendation)
R 6.12	Generally, an isotonic fluid should be used as intravenous fluid for "maintenance hydration" in sick children especially during the first 24 h. However, this should not delay the initiation of PN if PN is indicated (LoE 1+, RG A, strong recommendation)
R 6.13	It should be recognized that the needs of individual patients may deviate markedly from the ranges of recommended fluid intakes depending on clinical circumstances such as fluid retention, dehydration or excessive water losses (GPP, conditional recommendation)

December 2014. The systematic literature review was performed by the Hungarian Branch of the German Cochrane Centre/Nutritional Research Unit; Department of Paediatrics, University of Pécs (by Szimonetta Lohner and her team). The search strategy was developed on basis of the strategy and the keywords of the 2005 Guidelines [1]. The language restriction used at the search 2004 (publication in English or German language) was discontinued. Search items used were "neonate", "preterm infants", "infants", "children", "fluids", "sodium", "potassium", and "chloride" as well as some of their boolean combinations. Further literature on "fluid and electrolytes" not covered by the search were included in the updated version if it came to attention of the authors.

2. Introduction

Most published studies on the adaptation processes of water and electrolyte metabolism relate to the preterm neonate who may develop important and deleterious fluid and electrolytes anomalies during the first week of life. Studies on water and electrolyte metabolism in older paediatric patients are limited. Therefore, recommendations for children are often based on extrapolation from data in neonates and adults.

3. Fluid

Water is the major component of the human body at any age and is an essential carrier for nutrients and metabolites. Water and electrolyte requirements are usually proportional to growth rate. Needs per unit body mass are very high in neonates and decrease with age until adulthood [2]. Total body water is divided into two compartments: intracellular fluid (ICF) and extracellular fluid (ECF). The total volume of ICF increases with the number and size of body cells during body growth. ECF is subdivided into intravascular and extravascular components as well as a "third space" which characterises free fluid in preformed body compartments under physiological (urine, cerebral spinal fluid, etc) and pathological conditions (ascites, pleural effusions, etc).

During intrauterine life, particularly during the third trimester of gestation [2–4], body water content decreases along with the relative increase in fat mass. Extremely low birth weight (ELBW, <1000 g) and very low birth weight (VLBW, <1500 g) infants have low body fat content and a higher percentage of lean body mass and body water than older infants, which is related to high water turnover. In premature infants, a daily weight gain of 15 g/kg results in a net storage of about 12 ml of water (~80% of weight gain). Water contributes almost 90% of body weight in the 24 week old foetus, nearly 75% in term infants, and around 50% in adults [2,3]. The proportion of ECF (intra- and extravascular) also decreases during infancy up to adulthood. Blood volume in neonates is 85–100 ml/kg body weight compared to 60–70 ml blood volume/kg body weight in adolescents and adults [5].

Water turnover is high in neonates and decreases with increasing age and the concomitant decrease of metabolic rate and growth velocity [6]. Water turnover, like energy turnover, is related to lean body mass and has no close relationship to body fat mass. In the assessment of fluid balance, metabolic water production may be of particular importance in paediatric patients because of their high metabolic rates. Endogenous water production equals 0.6, 1.0, and 0.4 ml water per gram of carbohydrates, fat and protein oxidised respectively [7]. Evaporation of water from upper respiratory passages accounts for approximately one third of net insensible water loss [8] and reaches the level of 0.8–0.9 ml/kg per hour in premature infants, 0.5 ml/kg per hour in term neonates [9], 0.4 ml/kg per hour in older children and 0.3 ml/kg per hour in adolescents [10].

Many of the regulatory processes involved in fluid and electrolyte balance have limitations in paediatric patients because of immaturity or limited efficacy [11]. The renal glomerular surface area available for filtration is small in preterm and term neonates compared to that in older infants and adults [12]. In neonates, glomerular filtration rate increases significantly during the first week of life [13] and continues to rise over the first two years of life [14]. The velocity of this increase is slower in premature infants and needs to be considered when estimating fluid and electrolyte physiology in these infants [15].

Immaturity of the distal nephron with an anatomically shortened loop of Henle leads to reduced ability to concentrate urine [16]. Maximum urinary concentrations are up to 550 mosm/l in preterm infants, and 700 mosm/l in term infants, compared to 1200 mosm/l in adults [17]. Neonates may be placed at risk for volume depletion when a high renal solute load cannot be compensated for by the ability to produce concentrated urine. Although hormonal factors i.e. the renin-angiotensin-aldosterone system, and the arginine-vasopressin-axis are mature early in gestation, the effects are limited by renal immaturity [18]. Thus, in VLBW infants urine output may frequently increase above 5 ml/kg/h. In preterm infants a lower plasma oncotic pressure and higher permeability of the capillary wall [19] also enhance the shift of water from the intravascular to the interstitial compartment. This puts preterm infants at an increased risk of oedema, especially under pathologic conditions such as sepsis [20].

4. Electrolytes

Sodium (Na) is the principal cation of the ECF and Na concentrations influence intravascular and interstitial volumes. Na excretion occurs primarily through urine, but also through sweat and faeces. Chloride (Cl) is the major anion of the ECF. The exchangeable Cl remains relatively constant per unit of body weight at different ages. Even if chloride balance usually parallels that of sodium, and so it is strictly correlated to the extracellular volume balance, chloride losses and excretion can also occur independently from sodium, mainly in equilibrium with bicarbonate status [21]. The daily turnover of Cl is high. Renal conservation occurs with tubular reabsorption of 60–70% of the filtrated Cl. In addition, Cl is involved in maintaining osmotic pressure, hydration, and ionic neutrality. Na and Cl are also the major ions influencing the 'strong ion difference' (SID), one of the 4 systems acting on blood pH. According to the Stewart's approach, the concept of SID is used to help explain "metabolic" acid base abnormalities associated with changes in chloride concentration [22]. A decrease in the SID will result in an acidifying effect on plasma. The SID is calculated as the charge difference between the sum of measured strong cations (Na^+, K^+, Ca^{2+}, and Mg^{2+}) and measured strong anions (Cl^-, lactate) [23]. As both Na^+ and Cl^- are the major strong ions in plasma, the SID calculated as the simply difference between sodium and chloride represents one independent variable determining the hydrogen ion and the bicarbonate ion concentrations; so, an increase in the plasma Cl^- relative to Na^+ decreases the plasma SID and lowers the pH [24].

Potassium (K) is the major intracellular cation and the K pool correlates well with the lean body mass. The intracellular K concentration is dependent on Na/K-ATPase activity which can be impaired if there are insufficient supplies of oxygen and energy [25]. Ten percent of the K body pools are not exchangeable (bone, connective tissue, cartilage). Extracellular K concentration is not always related to intracellular concentration. In addition, intra- to extracellular K shifts can occur, e.g. in acidotic states through exchange with H ions.

Incidental gastrointestinal and skin electrolyte losses are very low. In neonates Na gastrointestinal losses represent 0.1–0.2 mmol/kg/d in premature infants and around 0.01–0.02 mmol/kg/d in term infants [26]. Electrolyte losses may be increased under pathological conditions like bowel obstruction, ileostomy, pleural effusions, peritoneal drainage, and external cerebrospinal fluid drainage. Under these circumstances the electrolyte losses due to lost fluids can only be estimated and continuous monitoring of serum electrolytes is recommended (see section monitoring below).

On the other hand it may be of importance that considerable amounts of Na and K may be supplied along with drugs (e.g. benzylpenicillin) and minerals that are prepared as Na or K salts (e.g. phosphates). Similarly, sources of Cl are numerous while on parenteral nutrition (PN), e.g. normal saline, amino acid and calcium solutions.

5. The neonatal period

Immediate adaptation processes after birth affect the metabolism of water and electrolytes as a result of discontinuation of placental exchange with a relative immaturity of physiological processes. Birth also implies the onset of thermoregulation and sometimes considerable insensible water losses. Subsequent adaptation includes the onset of autonomic renal regulation of fluids and electrolytes, and intake of fluids and other nutrients.

The time course of adaptation may be divided into three major phases [10]:

- **Phase I: transition.** The immediate postnatal phase is characterised by an initial relative oliguria [27] lasting hours to days, and considerable insensible water losses via the immature skin. It is followed by a diuretic phase lasting some days, and progressive diminished insensible water losses along with increasing cornification of the epidermis. During this transitional phase, body fluid compartments are rearranged by isotonic or hypertonic (i.e. hypernatriemic and hyperchloremic) contraction of the ECF compartment. Continuing natriuresis (as present during foetal life) also occurs during this phase of transition [28]. Phase I usually ends when maximum weight loss has occurred.
- **Phase II: the intermediate phase** corresponds to the period between minimal weight (maximal weight loss) and return to birth weight. In premature neonates – especially in ELBW and VLBW infants – urine output might still be high with high Na excretion during this phase. The duration of the intermediate phase varies in length, but birth weight is usually regained by 7–10 days of life in normal breastfed term infants.
- **Phase III: stable growth** is characterized by continuous weight gain with a positive net balance for water and electrolytes.

5.1. Phase I/transition

R 6.1	**In term neonates, postnatal weight loss generally occurs during the first 2–5 days of life and should not usually exceed 10% of birth weight (LoE 2++, RG 0, conditional recommendation, strong consensus)**
R 6.2	**In ELBW and VLBW infants, 7–10% weight loss seems to be adequate taking into account their higher body water content and the adverse complications associated with fluid overload (LoE 2++, RG B, strong recommendation, strong consensus)**
R 6.3	**A gradual increase of fluid intake is recommended in preterm and term neonates after birth (LoE 3, RG B, strong recommendation, strong consensus)**
R 6.4	**Electrolytes (Na, Cl and K) should be supplied starting during phase I/contraction of ECF compartment/initial loss of body weight (LoE 3, RG 0, strong recommendation, consensus)**
R 6.5	**Cl intake should be slightly lower than the sum of Na and K intakes (Na + K-Cl = 1–2 mmol/kg/d) to avoid excessive Cl intakes and risk of iatrogenic metabolic acidosis (LoE 3, RG 0, strong recommendation, strong consensus)**
R 6.6	**In ELBW and VLBW infants, Na and K may be recommended from the first day of life when giving the recommended high amino acids and energy supply, providing that urine output is ascertained, and taking into account the potential for the development of nonoliguric hyperkalaemia (LoE 2+, RG 0, conditional recommendation, strong consensus)**
R 6.7	**It should be recognized that the needs of individual patients may deviate markedly from the ranges of generally recommended intakes depending on clinical circumstances such as fluid retention, dehydration or excessive water losses, or others (GPP, strong recommendation, strong consensus)**

The goals for fluid and electrolyte administration during this phase are to [11]:

- allow contraction of ECF with negative water and Na balance but without compromising intravascular fluid volume and cardiovascular function and while maintaining normal serum electrolyte concentrations;
- secure a sufficient urinary output without oliguria (<0.5–1.0 ml/kg per hour) for longer than 12 h;
- ensure regulation of body temperature by providing enough fluid for transepidermal evaporation.

During the postnatal transition phase, body fluid compartments are rearranged by isotonic or hypertonic contraction. Normally the phase occurs without oliguria (<0.5–1 ml/kg/h within 12 h), electrolyte disturbances, and/or acidosis. Expected postnatal weight loss depends on hydration status at birth, e.g. intrauterine growth-restricted neonates typically lose less weight than eutrophic neonates. Environmental factors and nutritional intakes also significantly influence postnatal weight loss. Double wall incubators reduce insensible water loss in VLBW neonates by about 30% when a humidity of 90% is used at thermo-neutral temperature. After postnatal maturation of the epidermal barrier and cornification during the first 5 days of life, ambient humidity can be reduced step by step [29]. The use of waterproof coverings (such as plastic films, plastic blankets, and bubble blankets) in addition to treatment in a double wall incubator leads to further reduction of insensible water loss by 30–60% [30]. Endotracheal intubation and mechanical ventilation using warmed and humidified air significantly reduce insensible respiratory water loss [31] and fluid requirements are reduced by 20 ml/kg/d. The use of emollient ointments decreases insensible water loss of up to 50% in open care conditions [32,33] but may also increase infection rates [34,35]. Radiant warmers and single wall incubators significantly increase water loss and impair thermoregulation in VLBW infants [36]. Phototherapy also increases insensible water loss.

Despite some controversies, normal term breastfed neonates usually serve as a reference for all neonates when considering postnatal nutrition, adaptation, and growth. Fluid intakes may significantly vary in normal term breastfed neonates [10]. On average, milk production and infant intakes increase rapidly from less than 100 ml per day on the first day of life to 500–600 ml per day after 4–5 days, then increase more slowly to reach 600–800 ml per day after 1 month and 700–900 ml per day after 6 months [37,38]. On average, the postnatal weight nadir usually occurs after 2–3 days and represents a weight loss of 6–7% in breastfed infants [39]. In formula fed term infants, the timing of loss is similar but weight loss is lower, between 3 and 4% of birth weight. This implies that mean time to regain birth weight is also quicker in formula fed (6–7 days) than in breastfed neonates (8–9 days) [39]. Even though postnatal weight loss exceeding 10% is frequently not wished in term neonates, it is not always linked to an underlying pathology [40]. Because of higher insensible water losses and immature kidneys, premature neonates, especially ELBW infants, require more fluids than term infants during the first week of life [41]. A review of four randomized clinical studies with different levels of fluid intake during the first week of life concluded that fluid restriction reduces the risk of patent ductus arteriosus, necrotising enterocolitis, and death. Fluid restriction also tends to reduce the risk of bronchopulmonary dysplasia but to increase the risk of dehydration [42]. However, tight goals for fluid restriction may interfere with the feasibility of providing sufficient a nutrient supply. Recent investigations regarding enhanced early nutritional support for very preterm infants point to a postnatal weight loss of 7–10% of birth weight in ELBW and VLBW infants receiving higher nutritional supplies starting from birth [43–48]. Loss of body weight higher than generally expected may indicate inadequate fluid, Na, protein and/or energy intakes besides other pathology, and should lead to further investigations. Thus, during the body water contraction of phase I, close clinical monitoring should be performed to avoid inadequate intakes, oliguria (diuresis <1 ml/kg/h for longer than 12 h), electrolytes disturbances and acidosis.

Electrolyte homoeostasis during the first week of life also depends on maturity, birth weight, energy and amino acid intakes [45,49]. In term breastfed neonates, human milk Na content usually decreases from around 40 mmol/L on day 1, to 10–15 mmol/L after day 3. The evolution of Cl content is quite similar to Na content but with 10–20% higher concentrations. Conversely, K content increases from 12 to 16 mmol/L during the first two days of life to 16–20 mmol/L after day 3 [37,38].

In preterm neonates, restricted Na intake has positive effects on oxygen requirements and the risk of later bronchopulmonary dysplasia [50]. However, there is also evidence that Na restriction gives rise to a higher risk of hyponatremia [21,51]. Furthermore, large variations in serum Na concentration may impair later neurocognitive outcome in preterm infants [52]. In addition, restricted supply of Na and K may also affect phosphorus supply if Na- or K-phosphate salts are used.

A restriction of Na intake during the period of ECF contraction should be performed cautiously allowing for a negative net balance for Na of about 2–3 mmol/kg per day during the first 2–3 postnatal days while closely controlling serum concentrations until a weight loss of approximately 5–10% has occurred. Along with the contraction of ECF, Na serum concentrations generally increase during the first 2–5 days, but should remain within the high normal range (<150 mmol/l). Na concentrations <140 mmol/L in combination with significant weight loss around 10% may indicate Na depletion and should always instigate clinical assessment.

Recent studies have demonstrated an increased incidence of hypokalaemia, hypophosphatemia and hypercalcaemia while optimising protein and energy intakes according to current recommendations in VLBW infants [21,43,45,53–58]. It corresponds to a refeeding-like syndrome. In infants with adequate protein and energy intake, especially in growth restricted and ELBW premature infants who have low mineral stores and high requirements, K supplementation may be initiated from the first day of life to reduce the risk of hypokalaemia and to enable the provision of adequate phosphorus supply. However, especially during the oliguric phase and in infants with high risk for nonoliguric hyperkalaemia (i.e. ELBW infants) close monitoring is necessary to ensure normal K serum concentrations. A deferment of K supply might be required in some of these infants to avoid hyperkalaemia. However Na and K supply should start latest before serum concentration of these electrolytes drop below recommended values [21].

A high Cl intake may induce hyperchloraemic metabolic acidosis in VLBW infants and should be avoided. Indeed, these are a causative factor for intraventricular haemorrhage and other morbidities in preterm babies [59].

The use of “Cl-free” Na and K solutions should be considered in preterm infants on PN in order to reduce the risk of metabolic acidosis [21,60–63]. Table 1 shows the recommended parenteral fluid and electrolyte intake of neonates during the first days of life (Phase I of adaptation).

5.2. Phase II: the intermediate phase

R 6.8 **After initial postnatal weight loss, birth weight should usually be regained by 7–10 days of life (GPP, conditional recommendation, strong consensus)**

The goals for fluid and electrolyte management during this intermediate phase are to [11]:

- replete the body for electrolyte losses and replace actual water and electrolytes;
- maintain proper fluid and electrolyte homoeostasis while the infant is regaining birth weight;

The recommended fluid intakes in phase II are based on studies suggesting that a daily fluid intake equal to or higher than 170 ml/kg body weight per day is accompanied by high urinary Na excretion with negative Na balance, even if Na intake is as high as 10 mmol/kg body weight per day [64]. Fluid therapy in ELBW infants in excess of 200 ml/kg/d does not maintain Na balance, regardless of the amount of NaCl provided. There is evidence that fluid intake lower than 140 ml/kg body weight per day, together with Na intake of about 1 mmol/kg body weight per day, is adequate to maintain Na balance in ELBW neonates [65–70].

However, in preterm infants of less than 35 weeks of gestation Na supplementation of 4–5 mmol/kg/day during the first 2 weeks of life led to better neurocognitive performance at the age of 10–13 years compared to a control group of infants with Na intake of only 1–1.5 mmol/kg/d under the study conditions [71]. It seems sensible to increase Na and fluid supply in order to replace electrolyte and fluid losses during the intermediate phase (see Table 2).

Common recommendations suggest an average time to regain birth weight by about 7–10 days after birth. This is supported by evidence from epidemiological studies. Observations from population-based cohorts of healthy neonates point to a median time to recover birth weight in healthy neonates around 8.3 and 6.5 days (in breast-fed and formula-fed infants, respectively), but also suggest a considerable proportion of infants have not regained their birth weight before 12–14 days [39,40]. In those neonates pathology needs to be carefully excluded and the feeding regime checked.

5.3. Phase III: stable growth

R 6.9 **Fluid and electrolyte homoeostasis should be maintained while the infant is gaining appropriate weight during the phase of stable growth (LoE3, RG B, strong recommendation, strong consensus)**

The goals for fluid and electrolyte management during stable growth (phase III) are to

- replace losses of water and electrolytes (maintain water and electrolyte homoeostasis).
- provide enough extra water and electrolytes to reach an adequate rate of growth with adequate fluid and electrolyte homoeostasis

Fluid requirements during stable growth are related to the expected weight gain. Water loss from stool is negligible in early life prior to establishing enteral feeding in premature infants. When full enteral feeding is achieved, faecal losses of 5–10 ml/kg per day are usually assumed to balance metabolic water production [72].

Accretion of body mass during growth periods requires an adequate supply of electrolytes. It has been shown that restricted administration of Na impairs longitudinal growth and weight gain [26]. Plasma Na concentrations were normal in VLBW infants with Na intake of 1.5–2.6 mmol/kg/d and fluid intakes of 140–170 ml/kg/d [73,74]. With more “aggressive” feeding regimes and increased growth rates, additional Na supply in relation to growth rate might be necessary.

Breast-fed term infants need as little as 0.35–0.7 mmol/kg body weight per day of Na during the first 4 months of life to achieve adequate growth [75]. In preterm infants, a higher growth rate explains a higher Na requirement.

The amount of K usually recommended is similar to the amount provided in human milk, about 2–3 mmol/kg per day [76].

Preterm infants also retain about 1.0–1.5 mmol/kg body weight per day of K, which is about the same as foetal accretion [77].

Table 3 shows the recommended parenteral fluid and electrolytes for neonates during the first month of life (phase III/stable growth).

Table 1
Recommended parenteral fluid and electrolyte intake during the first days of life in neonates (Phase I of adaptation).[e]

	Days after birth				
	Day 1	Day 2	Day 3	Day 4	Day 5
Fluid intake[a] (ml/kg/d)					
Term neonate	40–60	50–70	60–80	60–100	100–140
Preterm neonate >1500 g	60–80	80–100	100–120	120–140	140–160
Preterm neonate 1000–1500 g	70–90	90–110	110–130	130–150	160–180
Preterm neonate <1000 g	80–100	100–120	120–140	140–160	160–180
Na[b,d] (mmol/kg/d)					
Term neonate	0–2	0–2	0–2	1–3	1–3
Preterm neonate >1500 g	0–2 (3)	0–2 (3)	0–3	2–5	2–5
Preterm neonate <1500 g	0–2 (3)	0–2 (3)	0–5 (7)	2–5 (7)	2–5 (7)
K[c,d] (mmol/kg/d)	0–3	0–3	0–3	2–3	2–3
Cl (mmol/kg/d)	0–3	0–3	0–3	2–5	2–5

[a] Postnatal fluid requirements are highly dependent on treatment conditions and environmental factors. Certain clinical conditions may afford modifications of daily fluid intakes, e.g. phototherapy (add volume ca. 10–20%), infants with asphyxia/respiratory distress syndrome/mechanical ventilation with humidified respiratory gases (reduce volume by ca. 10–20%).

[b] Careful adjustment of water and electrolyte administration is needed in ELBW infants at onset of diuresis and in polyuric patients. In cases of high urinary Na losses the need for Na supply may exceed 5 mmol/kg/d, especially in neonates <1500 g at the end of phase I.

[c] K administration should regard initial phase of oliguria and the risk of non-oliguric hyperkaliemia in VLBW infants. A deferment of parenteral K supply might be required to avoid hyperkaliemia.

[d] Parenteral Na and K supply should start latest before serum concentrations drop below recommended values.

[e] The recommendations of Table 1 are based on clinical experience, expert opinion, and extrapolated data from different studies in animals and humans.

Table 2
Recommended parenteral fluid and electrolyte intake for neonates during the intermediate phase (phase II) – prior to the establishment of stable growth.[a]

	Fluid (ml/kg/d)	Na (mmol/kg/d)	K (mmol/kg/d)	Cl (mmol/kg/d)
Term neonate	140–170	2–3	1–3	2–3
Preterm neonate >1500 g	140–160	2–5	1–3	2–5
Preterm neonate <1500 g	140–160	2–5 (7)	1–3	2–5

[a] The recommendations of Table 2 are based on clinical experience, expert opinions, and extrapolated data from different studies on animal and men.

6. Children and infants beyond the neonatal period

R 6.10	**Requirements for fluid and electrolytes for infants and children (beyond the neonatal period) on PN are mainly based on empirical evidence and recommendations are presented in Table 5 (LoE 4, RG 0, strong recommendation, strong consensus)**
R 6.11	**The Holliday and Segar formula for calculating the maintenance water needs in children by determining caloric/water needs from weight (see Table 4) is still regarded appropriate in the clinical setting (GPP, strong recommendation, strong consensus)**
R 6.12	**Generally, an isotonic fluid should be used as intravenous fluid for "maintenance hydration" in sick children especially during the first 24 h. However, this should not delay the initiation of PN if PN is indicated (LoE 1+, RG A, strong recommendation, strong consensus)**
R 6.13	**It should be recognized that the needs of individual patients may deviate markedly from the ranges of recommended fluid intakes depending on clinical circumstances such as fluid retention, dehydration or excessive water losses (GPP, conditional recommendation, strong consensus)**

6.1. Fluid

Total water requirements in children and infants beyond the neonatal period mainly consist of maintenance needs, replacement of ongoing losses (urinary and stool losses) and replacement of deficits. Insensible water loss from the skin and lungs is an energy costly process that consumes a quarter of the overall caloric expenditure, 0.5 kcal per 1 ml of water lost.

Urine osmotic load results from protein catabolism and electrolyte excretion, but is little affected by carbohydrate and fat metabolism which produce metabolic water and CO_2. Electrolytes, urea and other substances constitute urine osmotic load. High nitrogen and energy supply with PN require sufficient water supply as the vehicle for nutrient delivery.

Generally, water requirements parallel energy needs with 1 kcal per 1 ml water [78]. With increasing age and decreasing metabolic activity, maintenance water and energy requirements fall. In 1957, Holliday and Segar provided a simple-to-use formula for calculating the maintenance water needs in children by determining caloric/water needs from weight alone. Fluid requirements can be fulfilled by infusing 100 ml/kg//d (4 ml/kg/h) for every kilogram of body weight < 10 kg plus 50 ml/kg/d (2 ml/kg/h) per kg body weight between 10 and 20 kg plus 25 ml//kg/d (1 ml/kg/h) per kg body weight above 20 kg [79,80]; (see Table 4).

However, it is important to emphasize that there will be clinical situations with altered water and energy needs. Water requirements increase with fever, hyperventilation, hypermetabolism and gastrointestinal losses and decrease in renal failure and congestive heart failure. Water and energy requirements are also decreased during critical illness, mechanical ventilation and in temperature-controlled environments. It is beyond the scope of this guideline to cover individual diseases, but it is obvious that parenteral water management should be adjusted according to disease state.

6.2. Electrolytes

Electrolyte requirements for infants and children beyond the neonatal period are mainly based on empirical evidence and are set at the level of 1–3 mmol for Na and 1–3 mmol of K required per intake of 100 kcal [1,78,79,81–86]. This is close to the electrolyte composition of human breast milk or cow milk and is probably appropriate in "healthy", well hydrated children with physiological growth (i.e patients on parenteral nutritional support).

6.3. Maintenance of hydration

Fluid and electrolyte management is an essential part of supportive care in the acutely ill child and in children in the operative setting. Traditionally, maintenance parenteral fluids have been administered as hypotonic saline (Na 35–77 mmol/L in 5% dextrose in water), but a number of publications have addressed the risk of hospital-acquired hyponatremia (<135 mmol/L) and potentially fatal hyponatremic encephalopathy with this fluid and electrolyte regimen if the free water intake is not adapted to individual needs [87,88].

In postoperative and critically ill children a large meta-analyses documented an increased risk of hyponatremia with the administration of hypotonic "maintenance fluids" compared to the use of isotonic (Na 140 mmol/L) fluids [89,90]. This was further underlined in the randomized, double-blind, controlled trial by McNab et al. [91] confirming a lower risk of hyponatremia with the use of isotonic fluid (Na 140 mmol/L) as compared with a hypotonic fluid (Na 77 mmol/L) in a large heterogenous population of hospitalized children [91]. There is substantial evidence supporting the use of isotonic fluid as intravenous fluid for maintenance hydration in hospitalized children in addition to PN if needed.

Table 3
Recommended parenteral fluid and electrolytes intake for neonates during the first month of life with stable growth (phase III).[a]

	Fluid (ml/kg/d)	Na (mmol/kg/d)	K (mmol/kg/d)	Cl (mmol/kg/d)
Term neonate	140–160	2–3	1.5–3	2–3
Preterm neonate >1500 g	140–160	3–5	1–3	3–5
Preterm neonate <1500 g	140–160	3–5 (7)	2–5	3–5

[a] The recommendations of Table 3 are based on clinical experience, expert opinions, and extrapolated data from different studies on animal and men.

Table 4
Maintenance fluid requirements in children and infants beyond neonatal period (Holliday and Segar) [79,80].

Weight	mL/kg/d	mL/kg/h
A: the first 10 kg	100	4
B: weight between 10 and 20 kg	+50 ml/extra kg/d	+2 ml/extra kg/h
C: weight above 20 kg	+25 ml/extra kg/d	+1 ml/extra kg/h
Sum total requirements	A + B + C	A + B + C

Table 5
Recommended parenteral fluid and electrolyte intake for children and infant beyond neonatal period.[b]

	<1 y[a]	1–2 y	3–5 y	6–12 y	13–18 y
Fluid (ml/kg/d)	120–150	80–120	80–100	60–80	50–70
Na (mmol/kg/d)	2–3	1–3	1–3	1–3	1–3
K (mmol/kg/d)	1–3	1–3	1–3	1–3	1–3
Cl (mmol/kg/d)	2–4	2–4	2–4	2–4	2–4

[a] After 1 month of age.
[b] The recommendations of Table 5 are based on clinical experience, expert opinions, and extrapolated data from different studies on animal and men.

Nevertheless, there have been some concerns about the non-physiological nature of normal saline solution as it contains equal concentrations of Na and Cl. The increased Cl load has been associated with hyperchloraemia and acidosis, and there is discussion about whether it would be more appropriate to use intravenous solutions with lower Cl than Na concentrations, so called balanced solutions. At present, there is not enough evidence to strictly recommend balanced solutions over the use of normal saline.

7. Monitoring of parenteral fluid and electrolyte treatment

Postnatal fluid and electrolyte homoeostasis are highly dependent on postnatal environment (humidity, temperature, incubator or open radiant warmer, phototherapy). Premature neonates are vulnerable to both insufficient and excessive intakes, especially ELBW and VLBW infants. Thus in neonates, tight assessment of body water balance, prevention of high insensible water losses, and monitoring of serum electrolyte concentrations should be included in a protocol adapted to the individual condition and clinical presentation of the patient. Monitoring intervals depend on clinical status, underlying pathophysiology, medications and treatment modalities [10].

Indicators of changes of hydration and electrolyte status may include:

- clinical status of the patient
- body weight and estimation of body composition
- blood electrolyte concentrations and acid base status
- fluid and electrolyte balance (it implies the measurement of urine output, urine specific gravity or osmolarity and the measurement of urine electrolyte concentrations).
- haematocrit and blood urea nitrogen

In parenterally fed infants and children, serum electrolyte concentrations and weight are usually monitored daily for the first days of treatment; then the monitoring intervals are adapted depending on the clinical status and the stability of the patient's condition.

8. High fecal output and water/electrolyte losses

High fecal output with subsequent water/electrolyte losses are observed in patients with some types of intestinal failure on long-term parenteral nutrition: i) Short bowel syndrome (SBS), ii) chronic intestinal pseudo-obstruction syndrome (CIPOS) and iii) total or sub-total intestinal aganglionosis (TIA). Both CIPOS and TIA are requiring, most often, an enterostomy [92].

For a safe long-term management, high water-electrolytes losses require sodium supplementation and tools for decreasing gastric hypersecretion and fecal output.

8.1. Sodium supplementation

As discussed above, replacing sodium losses only with sodium chloride solutions exposes to high cumulative Cl intake and risk of metabolic acidosis associated hyperchloraemia. These may lead to neurological morbidities, are a causative factor of growth faltering, and should be avoided not only in premature babies on a short term, but also in older children with high water-electrolyte losses on the long term [59].

In order to reduce the occurrence of these unwanted metabolic consequences, imbalance between electrolytes provided by the PN solution should be detected and corrected and part of sodium intake, in the form of sodium chloride solutions, should be replaced by, for instance, sodium lactate or sodium acetate [61,63].

8.2. Decreasing gastric hypersecretion and fecal output

Cimetidine and ranitidine are histamine H2-receptor antagonist (H2 blockers). Several studies have shown the beneficial effects of H2 blockers in decreasing gastric hypersecretion especially in the setting of SBS [92–100]. Ranitidine has a 7 times more powerful effect than cimetidine [101] and a longer duration of action [102,103]. Intravenous administration of ranitidine is efficient in reducing the water-electrolytes losses in SBS as well as in patients with enterostomy for CIPOS or TIA, and is indicated when enteral administration is impossible or unefficient [104,105]. Side effects are very rare in children [106]. Continuous ranitidine infusion at a lower dosage, is more efficient than intermittent infusion [112]. Stability of ranitidine in PN bags has been established at a dose of 10–15 mg/kg/d [107–111]. One might consider that proton-pump inhibitors (PPI) have the same effects and indications as ranitidine. However, PPIs have a different mechanism of action by decreasing acid secretion rather than gastric hypersecretion as a consequence of extensive small bowel resection. Two studies performed in adults, failed to show any difference between ranitidine and PPI [113,114]. Moreover, there is no data available about the stability of PPIs in PN bags.

9. Electrolyte disturbances

This paragraph summarizes the most frequent electrolyte disturbances which may occur in neonates on PN.

9.1. Hypernatraemia

Hypernatraemia (Na >145 mmol/L) is often 'iatrogenic'. Especially in VLBWI it mostly results from incorrect replacement of transepidermal water loss (TEWL), inadequate water intake, or excessive Na intake (which can be 'inadvertent') during the transition phase. Therapeutic measures should be based on the aetiology. This should be ascertained by assessment of the infant's intravascular volume and hydration status. In case of symptomatic hypovolaemia, plasma volume should be replaced. A rapid correction of hypernatremia may induce cerebral oedema, seizures and neurological injury. A reduction rate of 10–15 mmol/l/24 h is recommended.

9.2. Hyponatraemia

Hyponatraemic states (Na <135 mmol/L) reflect absolute or relative water overload with Na pool reduced, normal or increased. Diagnostic measures for hyponatremia rely on clinical and ECF assessment (intra- and extravascular component) and urinary Na ($_u$Na) measurement. ECF excess with inadequate postnatal weight loss or weight gain suggests water overload (acute renal failure should also be considered in case of oliguria and $_u$Na >20 mmol/l). ECF contraction with adequate weight loss or failure to growth suggests Na depletion: $_u$Na is <20 mmol/l and a clinical history of acute anaemia or postnatal dehydration are usual.

Finally, primary Na depletion is frequent in preterm infants born before 34 weeks gestation due to deficient proximal and distal tubule Na reabsorption (amplified due to drug side effects from e.g. caffeine, diuretics, or others), and should be anticipated.

Treatment of hyponatremia must be based on the underlying causes. Corrections of severe hyponatremia more rapid than 48–72 h have been associated with an increased risk of pontine myelinolysis.

9.3. Hyperkalemia

Hyperkalemia (K > 6 mmol/L) may occur with or without impaired renal K excretion. Early hyperkalemia can develop in the absence of oliguria and potassium intake. Non-oliguric hyperkalemia (NOHK) should be checked for, after birth, in VLBWI at risk (lack of antenatal corticosteroids, systemic acidosis, birth asphyxia, massive haematomas, haemolysis, catabolic state, and other situations). In NOHK diuresis is usually within normal range and K_u > 20 mmol/l. Oliguric hyperkalemia is mostly due to renal failure and exhibits K_u <20 mmol/l. Both conditions need to be identified, in order to avoid excessive K intake in PN. Severe hyperkaemia (K > 7 mmo/l) requires prompt intervention.

9.4. Hypokalemia

Hypokalemia (K <3.5 mmol/L) may develop in cases of enhanced demand (immaturity), electrolyte depletion (growth restriction), inadequate supply (inappropriate parenteral or enteral supply) or due to increased renal losses (f.e. as side effect of medications like caffeine or diuretics, or renal pathology). Early enhanced PN increases endogenous insulin production and promotes the transfer of K (and phosphate) into the cells for protein synthesis. It has been shown that the supply of K (and phosphate) should parallel the supply of amino acids to avoid a refeeding-like syndrome. Thus, when providing early high amino acids and energy from birth according to the revised guidelines, sufficient K intake is also required.

9.5. Severe metabolic acidosis

Severe metabolic acidosis (pH <7.2 with base deficit >10 mmol/L or bicarbonates <12 mmol/L) during PN may be induced by high cumulative Cl intake [>10 mmol/kg during the first 3 days (i.e. 3.3 mmol/kg/day on average) and >45 mmol/kg during the first 10 days (i.e. 4.5 mmol/kg/day on average)]. This could be especially the case for infants at high risk (large PDA, weight loss >15%, ELBW). The use of “Cl-free” Na and K solutions should be considered in preterm infants on PN, in order to reduce the risk of hyperchloraemia and metabolic acidosis.

Conflict of interest

None declared.

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Clinical Nutrition 37 (2018) 2354–2359

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Iron and trace minerals

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

Literature Search

Timeframe: 2004 – 11/2014, in addition relevant earlier publications were considered.

Type of publications: randomized controlled studies; case-control or cohort studies; case reports; case series; expert opinion.

Key words: Parenteral Nutrition; Infusions, Parenteral; Trace Elements; Chromium; Copper; Iodine; Iron; Manganese; Molybdenum; Selenium; Zinc;

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https://doi.org/10.1016/j.clnu.2018.06.949
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Age: Child, infant, preterm

Language: English.

152 abstracts were found. Of these, 69 full text papers were assessed. In addition to the retrieved papers the authors found a few additional papers by hand search.

2. Iron

R 7.1	**In patients receiving PN, iron supplementation should preferentially be given enterally rather than parenterally, if tolerated. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 7.2	**Routine provision of iron in parenteral nutrition should not be given for short term PN (<3 weeks) (LoE 4, RG 0, conditional recommendation, strong consensus)**
R 7.3	**Patients receiving long-term PN, who cannot maintain adequate iron status using enteral iron supplements, should receive parenteral iron supplementation. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 7.4	**Parenteral iron can be given daily added to PN solution or as intermittent, separate infusions. (GPP, conditional recommendation, strong consensus)**
R 7.5	**If given daily, and assuming no enteral iron supplementation, routine parenteral iron supplements should be given at a dose of 200–250 μg/kg/day in preterm infants and 50–100 μg/kg per day up to a maximum dose of 5 mg/day in infants and children. (LoE 4, RG 0, conditional recommendation, strong consensus)**
R 7.6	**Even though currently no intravenous iron preparation is approved for pediatric use in Europe, iron sucrose is the most studied iron preparation in children, severe adverse events are rare and it is approved in the USA for use in children from 2 years of age. It is therefore recommended for intermittent infusions. (LoE 3, RG 0, strong recommendation, strong consensus)**
R 7.7	**Iron status (at least ferritin and hemoglobin) should be monitored regularly in patients on long-term PN in order to prevent iron deficiency and iron overload. (LoE 4, RG 0, strong recommendation, strong consensus)**

Iron is an essential nutrient and iron deficiency results in anemia as well as poor neurodevelopment in children. However, iron is not routinely provided in pediatric parenteral nutrition (PN) mixtures and is usually not a component of commercially available trace element preparations. The major concern is that of iron overload. Parenteral administration of iron bypasses the homeostatic control of gastrointestinal iron absorption, causing loss of protection from iron overload if excessive quantities are provided, since humans have no mechanism for excretion of iron. Iron overload has been reported in children receiving prolonged PN and is associated with increased oxidative stress and increased risk of infections [1].

Thus, the enteral route of iron supplementation should always be preferred in patients receiving PN. Iron status (see below) should be monitored regularly in patients receiving long-term PN (>4 weeks) and parenteral iron supplementation should be initiated in those who cannot maintain adequate iron status on enteral iron supplements. There are two commonly used methods for delivering parenteral iron:

1. Addition of iron (e.g. iron dextran) to daily, fat-free PN solutions.
2. Intermittent iron infusions for iron repletion in anemic patients (e.g. iron sucrose).

A multitude of biomarkers are used to assess iron status, including both hematological (hemoglobin, mean cell volume, reticulocyte hemoglobin, protoporphyrin/heme ratio) and biochemical (ferritin, transferrin saturation, transferrin receptors). When screening for iron deficiency in children, the combination of ferritin and hemoglobin has a reasonably good sensitivity and specificity. In patients with chronic inflammation, transferrin receptors can be a useful addition since ferritin can be falsely elevated. Ferritin and transferrin saturation (the ratio between serum transferrin and serum iron) are useful for detection of iron overload.

Based on factorial calculations, parenteral iron requirements are estimated to be 200–250 μg/kg/day in preterm infants and 50–100 μg/kg per day in term infants and children [1,2] (see Table 1). Ongoing losses (e.g. gastrointestinal bleeding, frequent blood sampling) or increased demand (e.g. erythropoietin therapy) will increase iron requirements.

Adverse drug reactions associated with parenteral iron therapy are common. In various case series in adults, 2–5% of patients experience significant side effects. The processes leading to iron dextran induced symptoms are unclear, but include a type I (IgE-mediated) anaphylactic reaction which is caused by preformed dextran antibodies. Additional mechanisms include a type I anaphylactoid reaction that may be caused by transient overload of the transferrin binding capacity resulting in small amounts of free iron in the circulation (which appears to be dose related) and immune complex activation by specific IgG antibodies. Symptoms include dyspnea, wheezing, hypotension, nausea, vomiting, abdominal pain, arthralgia and myalgia. Most side effects are mild and self-limited with severe reactions occurring in a minority of patients and in conjunction with infusion of larger iron doses. An increased incidence of adverse effects has been reported in patients with collagen diseases. Despite previous episodes of allergic reactions, safe administration of iron dextran is possible following a pre-treatment protocol of methylprednisolone, diphenhydramine and ephedrine. While total dose infusions of iron dextran may be associated with allergic manifestations the administration of the standard maintenance doses may be well tolerated [1]. Low molecular weight dextran has less adverse effects than high molecular weight dextran [3]. More recently introduced iron compounds, e.g. iron sucrose, iron gluconate, iron carboxymaltose are considered to have less adverse effects than iron dextran.

There is a paucity of studies on the effects and complications of intravenous iron in children and, unfortunately, no intravenous iron product is currently approved for use in children in Europe. However, these products are nevertheless used in children. In the USA, iron sucrose is approved from 2 years of age and iron gluconate from 6 years of age for treatment of iron deficiency anemia in children with chronic renal disease. Other products used in children include iron dextran and iron carboxymaltose.

Most recent studies in children have been done using iron sucrose. In 6 studies, a total of 232 children received 1624 doses of iron sucrose and very few serious adverse reactions were observed [4–9]. In a randomized study of three different doses of iron sucrose (0.5 mg/kg, 1 mg/kg and 2 mg/kg) in 145 children, adolescents and young adults, no patient experienced an anaphylactic reaction and only one adverse event (skin rash) in a single patient was considered related to the study drug [4]. In one series of 38 children receiving a total of 510 doses of IV iron sucrose, there were 6 adverse reactions. The only significant reaction occurred in a patient receiving a dose which was greater than the recommended maximum dose of 300 mg [6]. In a case report, systemic iron toxicity with hepatocellular damage was observed in a pediatric patient receiving 16 mg/kg of iron sucrose [10].

There are a few studies on iron gluconate in children [11,12]. In one report, 23 children received a total of 216 doses of iron gluconate (0.75–1.5 mg/kg, maximum dose 125 mg). Only two adverse events were observed which were considered to be related to the treatment: one episode of pain and one episode of hypotension which did not require treatment [12].

There is only one published study of iron carboxymaltose in children [13]. In that study, 72 children with inflammatory bowel disease or other gastrointestinal diseases were given a total of 147 doses of ferric carboxymaltose [13]. The median dose was 500 mg and the maximum was 1000 mg. Only 3 mild adverse reactions were reported in that study.

Due to the higher risk of allergic reactions to iron dextran, it is recommended to give a test dose before the treatment dose. There are a few studies on low molecular weight iron dextran in children [14,15]. In the most recent one, 31 children received iron dextran at doses up to 1000 mg. In 5 patients, the iron dextran was discontinued due to adverse reactions.

Iron dextran at a concentration of 100 mg/L is stable up to 18 h at room temperature, and a concentration of 10 mg/L is stable for 48 h, when added to fat-free PN solutions [3]. Iron dextran cannot be added to lipid emulsions or all-in-one admixtures as it results in destabilisation of the emulsion. Ferrous citrate is also compatible with PN solutions, with no observed precipitation during infusion periods of 18–24 h [1]. Iron sucrose has been shown to be stable in fat-free PN solutions at concentrations up to 2.5 mg/L [16]. Iron chloride added to PN solutions is used in some institutions and may have advantages but studies are lacking.

In conclusion, due to the risk of iron overload and compounding difficulties, iron is not routinely added to pediatric PN solutions. On the other hand, intermittent iron infusions can be associated with adverse events. In long-term PN, iron status should be regularly monitored and if enteral iron supplementation is not sufficient to maintain adequate iron status, parenteral iron should be given, either added to PN (tested for stability) or as intermittent infusions.

3. Zinc

R 7.8	**Zn should be provided with PN at a dose of 400–500 μg/kg/d in preterm infants, 250 μg/kg/d in infants from term to 3 months, 100 μg/kg per day for infants from 3 to 12 months and 50 μg/kg/d in children >12 months of age, up to a maximum of 5 mg/d for routine supplementation. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 7.9	**Zn status (serum Zn, alkaline phosphatase) should be periodically monitored in patients on long-term PN and more often in those with high gastrointestinal fluid output (usually ileostomy losses), who may have significantly higher Zn requirements. (LoE 3, RG 0, strong recommendation, strong consensus)**

Zinc (Zn) is an essential nutrient, involved in the metabolism of energy, proteins, carbohydrates, lipids and nucleic acids and is an essential element for tissue accretion.

Zinc deficiency is commonly reported in children on long term PN and is associated with stunted growth, risk of infections and a typical skin rash [2]. Children with increased enteral fluid losses are at especially high risk.

Urinary Zn excretion and enteral Zn losses occur in the parenterally fed infant [2]. Some amino-acids like histidine, threonine, and lysine have been shown to bind Zn increasing its renal ultrafilterability. Increased urinary losses of Zn and decreased plasma concentrations occur following thermal injury in children [1].

Premature infants need a higher Zn intake than term infants because of their rapid growth: 450–500 μg/kg per day to match in-utero accretion rate. Standard trace element preparations do not supply this amount, and additional Zn has to be added to PN fluid in the preterm infant, or those patients with high Zn losses e.g. from diarrhea, stoma losses or severe skin disease [1].

Current recommendations are to supply 400–500 μg/kg/d in preterm infants, 250 μg/kg/d in infants from term to 3 months, 100 μg/kg per day for infants from 3 to 12 months and 50 μg/kg/d in children >12 months of age (up to a maximum of 5 mg/d for routine supplementation [2,17] (see Table 1).

4. Copper

R 7.10	**Cu should be provided with PN at a dose of 40 μg/kg/day in preterm infants and 20 μg/kg/day in term infants and children up to a maximum dose of 0.5 mg/d for routine supplementation.). (LoE 4, RG 0, strong recommendation, strong consensus)**
R 7.11	**Plasma Cu and ceruloplasmin should be monitored in patients on long term PN, especially if they develop PN associated liver disease or if they have high gastrointestinal fluid losses. (LoE 3, RG 0, conditional recommendation, strong consensus)**

Copper (Cu), is an essential nutrient, and is a functional component of several enzymes, including cytochrome oxidase, superoxide dismutase, monoamine oxidase and lysyl oxidase.

Cu deficiency, which is associated with pancytopenia and osteoporosis, has occasionally been reported in children on long term PN [2].

Cu concentrations in plasma and cells as well as Cu metalloenzymes concentrations are indicative of Cu status [1]. Plasma concentrations of both Cu and ceruloplasmin, the major Cu transport protein, should be monitored during PN [1]. However, Cu-Zn superoxide dismutase (SOD) activity in erythrocytes seems to be a more sensitive indicator of Cu deficiency than plasma concentration of Cu or ceruloplasmin [1]. Other indicators of Cu status include neutrophil count (low in deficiency), SOD activity, platelet cytochrome-c oxidase activity and platelet Cu concentration [1].

Parenteral Cu requirements are estimated to be 40 μg/kg per day Cu for preterm infants and 20 μg/kg per day for term infants and children [2,18] (Table 1).

The high Cu content in gastrointestinal fluid means that losses should be balanced by a higher Cu intake (increased by 10–15 μg/kg) in PN. Plasma concentrations of total Cu and ceruloplasmin are invariably reduced in children with burns, so PN in these patients should be supplemented with more than 20 μg/kg Cu to avoid deficiency [1].

Cu is primarily excreted through bile, so it has previously been recommended to remove Cu from PN in patients with cholestasis. However, some recent data suggests that this is not necessary and may even cause Cu deficiency in children [19–21]. Nevertheless, Cu status should be monitored in patients with cholestasis.

5. Iodine

R 7.12	**Iodine should be provided with PN at a daily dose of 1–10 μg/kg daily in preterms and at least 1 μg/kg/day in infants and children. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 7.13	**Patients on long-term PN should be regularly monitored for iodine status by measuring at least thyroid hormone concentrations (LoE 4, RG 0, conditional recommendation, strong consensus)**

Iodine is an essential component of the thyroid hormones thyroxin (T4) and tri-iodothyronine (T3), which are necessary for cellular metabolism and maintenance of metabolic rate. Thyroid function remained normal and serum iodine levels were not reduced in children receiving long-term PN without iodide supplementation, probably due to iodine contamination of the solutions, use of iodine-containing radiocontrast media, absorption of iodine present in the ingested food, and skin absorption of topical iodinated disinfectants [1].

It is often recommended that iodine should be provided with PN at a dose of at least 1 μg/kg daily (Table 1). However, iodine balance studies in preterm infants on PN indicated that a mean daily intake of 3 μg/kg/d was associated with negative iodine balance [22] and administration of 1 μg/kg/day of iodine in older children resulted in very low urinary iodine excretion (<50–100 μg/day), indicating a risk for iodine deficiency [23]. Hence the above stated minimum dose will result in iodine deficiency in long-term PN, if other sources of iodine are not administered.

Because recommendations for daily enteral iodine intake in preterm infants range from 10 to 55 μg/kg/d [24] and enteral iodine absorption is generally high, there have been recommendations to administer iodine at doses of 10–30 μg/kg/day in preterm infants with PN [2,22]. The dose of 30 μg/kg/day of iodine with PN is currently evaluated in an ongoing randomized controlled trial [25].

Iodine status is ideally monitored by iodine excretion in 24 h urine samples, which may be difficult to obtain. Normal thyroid function tests may be considered as surrogate markers for adequate iodine status.

6. Selenium

R 7.14	**Se should be provided with PN at a dose of 7 μg/kg/day in preterms and 2–3 μg/kg/day in infants and children up to a maximum dose of 100 μg/day for routine supplementation. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 7.15	**Se status (plasma Se) should be monitored regularly in long term PN and in patients with renal failure. (LoE 4, RG 0, conditional recommendation, strong consensus)**

Selenium (Se) is an essential nutrient that acts mainly in antioxidant defense. Se is part of selenoenzymes and is an essential component of active glutathione peroxidase (GSHPx), an enzyme that may protect against oxidative tissue damage. Se deficiency, associated with low plasma Se, erythrocyte macrocytosis, depigmentation and muscle weakness, has been reported in children receiving long term PN without Se supplementation [2]. In adults, Se deficiency has been associated with hypertension, liver cirrhosis, osteopenia, immune disorders and carcinogenesis but causality has not been proven for any of these associations.

Se overload leads to selenosis in adults, characterized by headache, loss of hair and nails, skin rash, discoloration of teeth, paresthesia and paralysis. However there have been no reports of Se toxicity in children.

Dietary Se is highly bioavailable with an intestinal absorption of up to 80%. Se intake in breast-fed infants has been estimated to be 2.3 μg/kg per day [1,2].

Se status is usually monitored by measuring Se concentrations in serum or plasma and/or the activity of glutathione peroxidase (GSHPx) in plasma or red blood cells. Erythrocyte and platelet GSHPx activity are sensitive indices of Se status in PN patients [1], but in preterm infants, GSHPx activity is not a useful marker of Se status since it is affected also by immaturity and oxygen exposure.

Preterm babies are at high risk of oxidative injury (bronchopulmonary dysplasia [BPD], retinopathy of prematurity, white matter disease, particularly in the first days of life. In VLBW infants, plasma Se levels decrease during the first weeks of life [26]. Low Se status has been documented in pre-term infants and was associated with BPD [27].

Darlow et al. [28] performed a randomized, controlled, blinded trial of Se supplementation in 534 VLBW infants. Se dose was 5 μg/kg/day enterally or 7 μg/kg/day parenterally. A significant effect was observed on Se plasma concentrations, which reached similar levels as had been reported in healthy term infants.

We recommend a parenteral intake of 7 μg/kg/day in preterm infants, similar to the dose given in the Darlow study [28], allowing to reach Se status similar to that of term infants. In term infants and children, parenteral Se requirements are estimated to be 2–3 μg/kg/day, based on enteral requirements and high bioavailability [17,18] (Table 1).

7. Manganese

R 7.16	**Mn should be supplied in long term PN at a dose of no more than 1 μg/kg/day (maximum of 50 μg/d for routine supplementation) (LoE 4, RG 0, conditional recommendation, strong consensus)**
R 7.17	**Blood Mn concentrations should be monitored regularly in patients on long term PN (LoE 4, RG 0, conditional recommendation, strong consensus)**
R 7.18	**If the patient develops cholestasis, blood concentrations of Mn should be determined and parenteral Mn should discontinued (LoE 3, RG 0, strong recommendation, strong consensus)**

Manganese (Mn) is a cofactor for several enzymes including mitochondrial superoxide dismutase and pyruvate carboxylase and also activates other enzymes such as hydrolases, kinases and transferases. In animal models, Mn deficiency affects mucopolysaccharide and liposaccharide formation, and leads to impaired skeletal development and ataxia. High Mn intake during PN is probably one of several factors contributing to the pathogenesis of PN associated liver disease. It also causes a central catecholamine depletion state in the central nervous system, leading in adults to insomnia, headaches, anxiety, rapid eye movements, loss of coordination with a Parkinson-like disease [29]. Studies using magnetic resonance images (MRI) have reported high-intensity areas in basal ganglia, thalamus, brainstem and cerebellum due to Mn intoxication with disappearance of symptoms and MRI abnormalities after withdrawal of Mn administration [30]. Mn should, therefore, be carefully administered, particularly in patients receiving long-term PN. As central nervous system deposition of Mn can occur without symptoms, regular monitoring of Mn blood concentrations should be performed in children on long term PN. Taking into account the hazards of high Mn levels in children receiving long-term PN, a low dose regimen of no more than 1.0 μg (0.018 mmol)/kg per day (maximum of 50 μg/d for children) is recommended together with regular neurological examinations (Table 1).

8. Molybdenum

R 7.19	**Molybdenum should be provided in long term PN at a dose of 1 μg/kg per day in LBW infants and 0.25 μg/kg per day (up to a maximum of 5.0 μg/day) in infants and children. (LoE 4, RG 0, conditional recommendation, strong consensus)**

Molybdenum (Mo) is essential for several enzymes involved in the metabolism of DNA. It is required by 3 enzymatic systems: xanthine dehydrogenase/oxidase, aldehyde oxidase, and sulfite oxidase. Mo deficiency may lead to cardiac and neurologic symptoms, in particular tachycardia and coma, together with high blood concentrations of sulfite and urate. To our knowledge there are no reports of Mo deficiency in infants. However, low-birth-weight infants (LBW) might be at particular risk for Mo deficiency. There are no toxicity data available in humans. In animals, Mo intoxication may cause diarrhea, impaired growth, infertility, gout, and may affect lung, kidney and liver function. Excess of Mo may interfere with Cu metabolism. There is no need for Mo during short term PN. However, in long term PN (>4 weeks), an intravenous intake of 1 mcg/kg per day (0.01 mmol/kg per day) seems to be adequate and is recommended for the LBW infant [1]. A daily parenteral intake of 0.25 μg/kg per day is recommended for infants and children (to a maximum of 5.0 μg/day) [1] (Table 1).

9. Chromium

R 7.20	**Cr contaminates PN solutions to a degree that satisfies requirements; therefore, additional supplementation of Cr is considered unnecessary and Cr intake from PN should not exceed 5 μg/day. (GPP, conditional recommendation, strong consensus)**

Chromium (Cr) is believed to be an essential micronutrient required for carbohydrate metabolism. There are no reported cases of Cr deficiency in children. The main concern of Cr in PN is the risk of Cr contamination of PN components. Deficiencies as well as increased serum Cr level have been described in patients receiving long-term PN. High serum Cr competes with iron for binding to transferrin and, hence negatively interferes with iron metabolism and storage. A daily intake of 0.2 μg/kg per day has been recommended for infants and children (maximum of 5 μg/day) receiving PN, although there is some evidence that lower intakes would be adequate. Supplementation is unnecessary since Cr contaminates PN solutions to a degree that satisfies requirements [1] (See Table 1).

Table 1
Estimated parenteral requirements of iron and trace minerals (μg/kg/d).

Mineral	Preterm	0–3 mo	3–12 mo	1–18 y	Max dose
Iron	200–250	50–100	50–100	50–100	5 mg/d
Zinc	400–500	250	100	50	5 mg/d
Copper	40	20	20	20	0,5 mg/d
Iodine	1–10	1	1	1	
Selenium	7	2–3	2–3	2–3	100 μg/d
Manganese	≤1	≤1	≤1	≤1	50 μg/d
Molybdenum	1	0.25	0.25	0.25	5 μg/d
Chromium	–	–	–	–	5 μg/d

Conflict of interest

None declared.

Appendix

Table: List of recommendations for iron and trace minerals

R 7.1	In patients receiving PN, iron supplementation should preferentially be given enterally rather than parenterally, if tolerated. (LoE 4, RG 0, strong recommendation)
R 7.2	Routine provision of iron in parenteral nutrition should not be given for short term PN (<3 weeks) (LoE 4, RG 0, conditional recommendation)
R 7.3	Patients receiving long-term PN, who cannot maintain adequate iron status using enteral iron supplements, should receive parenteral iron supplementation. (LoE 4, RG 0, strong recommendation)
R 7.4	Parenteral iron can be given daily added to PN solution or as intermittent, separate infusions. (GPP, conditional recommendation)
R 7.5	If given daily, and assuming no enteral iron supplementation, routine parenteral iron supplements should be given at a dose of 200–250 μg/kg/day in preterm infants and 50–100 μg/kg per day up to a maximum dose of 5 mg/day in infants and children. (LoE 4, RG 0, conditional recommendation)
R 7.6	Even though currently no intravenous iron preparation is approved for pediatric use in Europe, iron sucrose is the most studied iron preparation in children, severe adverse events are rare and it is approved in the USA for use in children from 2 years of age. It is therefore recommended for intermittent infusions. (LoE 3, RG 0, strong recommendation)
R 7.7	Iron status (at least ferritin and hemoglobin) should be monitored regularly in patients on long-term PN in order to prevent iron deficiency and iron overload. (LoE 4, RG 0, strong recommendation)
R 7.8	Zn should be provided with PN at a dose of 400–500 μg/kg/d in preterm infants, 250 μg/kg/d in infants from term to 3 months, 100 μg/kg per day for infants from 3 to 12 months and 50 μg/kg/d in children >12 months of age, up to a maximum of 5 mg/d for routine supplementation. (LoE 4, RG 0, strong recommendation)
R 7.9	Zn status (serum Zn, alkaline phosphatase) should be periodically monitored in patients on long-term PN and more often in those with high gastrointestinal fluid output (usually ileostomy losses), who may have significantly higher Zn requirements. (LoE 3, RG 0, strong recommendation)
R 7.10	Cu should be provided with PN at a dose of 40 μg/kg/day in preterm infants and 20 μg/kg/day in term infants and children up to a maximum dose of 0.5 mg/d for routine supplementation.). (LoE 4, RG 0, strong recommendation)
R 7.11	Plasma Cu and ceruloplasmin should be monitored in patients on long term PN, especially if they develop PN associated liver disease or if they have high gastrointestinal fluid losses. (LoE 3, RG 0, conditional recommendation)
R 7.12	Iodine should be provided with PN at a daily dose of 1–10 μg/kg daily in preterms and at least 1 μg/kg/day in infants and children. (LoE 4, RG 0, strong recommendation)
R 7.13	Patients on long-term PN should be regularly monitored for iodine status by measuring at least thyroid hormone concentrations (LoE 4, RG 0, conditional recommendation)
R 7.14	Se should be provided with PN at a dose of 7 μg/kg/day in preterms and 2–3 μg/kg/day in infants and children up to a maximum dose of 100 μg/day for routine supplementation. (LoE 4, RG 0, strong recommendation)
R 7.15	Se status (plasma Se) should be monitored regularly in long term PN and in patients with renal failure. (LoE 4, RG 0, conditional recommendation)
R 7.16	Mn should be supplied in long term PN at a dose of no more than 1 μg/kg/day (maximum of 50 μg/d for routine supplementation) (LoE 4, RG 0, conditional recommendation)
R 7.17	Blood Mn concentrations should be monitored regularly in patients on long term PN (LoE 4, RG 0, conditional recommendation)
R 7.18	If the patient develops cholestasis, blood concentrations of Mn should be determined and parenteral Mn should discontinued (LoE 3, RG 0, strong recommendation)

(*continued*)

R 7.19	Molybdenum should be provided in long term PN at a dose of 1 μg/kg per day in LBW infants and 0.25 μg/kg per day (up to a maximum of 5.0 μg/day) in infants and children. (LoE 4, RG 0, conditional recommendation)
R 7.20	Cr contaminates PN solutions to a degree that satisfies requirements; therefore, additional supplementation of Cr is considered unnecessary and Cr intake from PN should not exceed 5 μg/day. (GPP, conditional recommendation)

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Clinical Nutrition 37 (2018) 2360–2365

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Calcium, phosphorus and magnesium

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

Literature search timeframe: Publications published after the previous guidelines [1] (i.e., from 2004–December 2014), were considered. Some studies published in 2015 or 2016 during the revision process have also been considered. References cited in the previous guidelines are not repeated here, except for some relevant publications; the previous guidelines are cited instead.

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https://doi.org/10.1016/j.clnu.2018.06.950
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Type of publications: Original papers, meta-analyses and overviews.

Key words: (Parenteral Nutrition or (Infusions, Parenteral)) or (parenteral and nutrition); (calcium or phosphorus or phosphate* or bone or mineralization or magnesium)

Age: Child, infant, preterm

Language: English.

Table: Recommendations for calcium, phosphorus and magnesium in PN

R 8.1	In infants, children and adolescents on PN appropriate amounts of Ca, P and Mg should be provided to ensure optimal growth and bone mineralization (GPP, strong recommendation)
R 8.2	The mineral accretion of the fetus, healthy infant, child, and adolescent may be used as a reference for Ca, P and Mg provision (GPP, conditional recommendation)
R 8.3	In the individual infant appropriate PN should provide a simultaneous slight surplus of Ca, P, and Mg to ensure optimal tissue and bone mineral accretion (GPP, conditional recommendation)
R 8.4	Ca infusion may be used for prevention and treatment of early neonatal hypocalcaemia that is common and generally not associated with obvious clinical problems such as tetany (GPP, conditional recommendation)
R 8.5	In preterm infants on PN who were exposed to maternal Mg therapy, Mg intakes need to be adapted to postnatal blood concentrations (LoE 2, RG B, conditional recommendation)
R 8.6	Acidic solutions packaged in glass vials, such as calcium gluconate, are contaminated with aluminum and should not be used in PN (LoE 3, RG 0, strong recommendation)
R 8.7	It is recommended to use organic Ca and P salts for compounding of PN solutions to prevent precipitation (GPP, strong recommendation)
R 8.8	The adequacy of Ca and P intakes in preterm infants can be adjusted until both start being excreted simultaneously with low urine concentrations (>1 mmol/L) indicative of a slight surplus (extrapolated evidence derived from enteral nutrition LoE 2+ studies, RG B, conditional recommendation)
R 8.9	The recommended parenteral intake for calcium, phosphorus, and magnesium intake in newborns and children on parenteral nutrition in mmol (mg)/kg/d is as follows (LoE 2, 3 and 4, RG 0, conditional recommendation)

Age	Ca mmol (mg)/kg/d	P mmol (mg)/kg/d	Mg mmol (mg)/kg/d
Preterm infants during the first days of life	0.8–2.0 (32–80)	1.0–2.0 (31–62)	0.1–0.2 (2.5–5.0)
Growing Premature	1.6–3.5 (64–140)	1.6–3.5 (50–108)	0.2–0.3 (5.0–7.5) infants
0–6 m*	0.8–1.5 (30–60)	0.7–1.3 (20–40)	0.1–0.2 (2.4–5)
7–12 m	0.5 (20)	0.5 (15)	0.15 (4)
1–18 y	0.25–0.4 (10–16)	0.2–0.7 (6–22)	0.1 (2.4)

*Includes term newborns.

R 8.10	In preterm infants with intrauterine growth restriction on PN careful monitoring of the plasma phosphate concentration within the first days of life is required to prevent severe hypophosphataemia that can result in muscle weakness, respiratory failure, cardiac dysfunction, and death (LoE 3, RG 0, strong recommendation)
R 8.11	In preterm infants on early PN during the first days of life lower Ca, P and Mg intakes are recommended than in growing stable preterm infants (Table 1) (LoE 2, RG B, conditional recommendation)
R 8.12	In early PN when calcium and phosphorus intakes are low (Table 1) and protein and energy are optimized it is recommended to use a molar Ca:P ratio below 1 (0.8–1.0) to reduce the incidence of early postnatal hypercalcaemia and hypophosphataemia (LoE 2, RG B, strong recommendation)
R 8.13	In infants and children on PN regular monitoring of the individual alkaline phosphatase, Ca, P and Mg serum concentrations and Ca and P urine concentrations is required (Extrapolated evidence from LoE 2 and 3 studies, RG 0, strong recommendation)
R 8.14	In infants and children on long term PN the risk of metabolic bone disease requires periodic monitoring of Ca, P, vitamin D and bone mineral status (LoE 2 + and 3, RG 0, strong recommendation)

2. Introduction

R 8.1	**In infants, children and adolescents on PN appropriate amounts of Ca, P and Mg should be provided to ensure optimal growth and bone mineralization (GPP, strong recommendation, strong consensus)**
R 8.2	**The mineral accretion of the fetus, healthy infant, child, and adolescent may be used as a reference for Ca, P and Mg provision (GPP, conditional recommendation, strong consensus)**
R 8.3	**In the individual infant appropriate PN should provide a simultaneous slight surplus of Ca, P, and Mg to ensure optimal tissue and bone mineral accretion, (GPP, conditional recommendation, strong consensus)**

Calcium (Ca), phosphorus (P) and magnesium (Mg) are considered together as 98%, 80% and 65% of their body content within the skeleton. The majority of Ca and P are found together as components of microcrystalline apatite [$Ca_5(PO_4)_3(OH)$], the bone mineral which is forming in bone only if Ca and P are simultaneously available in optimal proportions. Of the total body phosphorus 20% is found in tissue. The molar Ca:P ratio is 1.67 in apatite and 1.3 in the whole body. In addition to their function as skeleton component, Ca, P, and Mg also play major roles in many physiologic processes [1,2].

In infants and children growth is the major determinant of mineral requirements. This is best analyzed for fetal growth where there is a linear association between fetal weight and total body content of Ca and P (0.21 mmol (8.3 mg) Ca/g and 0.15 mmol (4.7 mg) P/g) [3–6]. Given an average fetal weight gain of 17 g/kg/d before 35 weeks of gestation [7] the average fetal accretion is 3.4 mmol Ca/kg/d and 2.6 mmol P/kg/d respectively. This has been proposed as a reference mark for growing preterm infants [8,9]. However, it is important to keep in mind that in infants, children, and adolescents the mineral intake should be adjusted to the individual weight gain/growth to avoid an intake that is either too low or too high.

The following model is based on the average fetal weight gain (17 g/kg/d) and mineral accretion. Approximately 98% of the fetal calcium accretion (3.4 mmol/kg/d) is used for bone mineralization (microcrystalline apatite formation). The corresponding phosphorus accretion in apatite is 2 mmol/kg/d (98 % × 3.4 mmol/kg/d/1.67). The remaining fetal phosphorus accretion of 0.6 mmol/kg/d is used for tissue accretion. Protein is the major determinant of tissue accretion. It has been estimated that 1 g of protein accretion needs 0.3 mmol (9.3 mg) of phosphorus [10–12]. Therefore, in the present calculation model the remaining 0.6 mmol of phosphorus corresponds to a protein accretion of 2 g/kg/d. This is a reasonable estimate of average fetal protein accretion [3–6].

Taking all these considerations into account, the following theoretical model for estimation of P requirements has been published: [10–12]

*P requirement (mmol) = [calcium deposition (mmol/kg)/ 1.67] + [protein accretion (g)*0.33]*

Ca, P and protein accretion are quantitatively not known in the individual infant. In any case, optimal PN should provide a simultaneous slight surplus of Ca and P to ensure optimal tissue and bone mineral accretion. Based on fetal total body analysis the theoretical optimal molar Ca:P ratio in PN for achievement of fetal body composition would be 1.3 in stable growing infants.

Physiologically the provision of P for tissue accretion in the growing body has priority. In cases of relative P deficiency, available P is primarily directed to the cellular metabolism, reducing bone mineralization or even inducing bone demineralization [13]. Therefore, the first priority in provision of early or incomplete PN is the provision of sufficient P in order to avoid severe hypophosphataemia, which may be life threatening. Consequently, especially in early or incomplete PN with high amino acid intake a molar Ca:P ratio in the PN solution less than 1.3 (i.e. 0.8–1.0) is required to prevent hypophosphataemia [11,13–16].

In PN minerals are directly available for tissue accretion and bone mineralization in contrast to enteral nutrition where the individual mineral absorption has to be considered (especially calcium absorption which varies considerably from 20% to 80% [17]). Losses via skin, feces and especially urine (e.g. transient phosphorus loosing tubulopathy [18]) have to be taken into account as well.

Owing to the lack of data, it is not possible to perform an equivalent calculation of the required mineral intake for infants and children.

3. Calcium

R 8.4	**Ca infusion may be used for prevention and treatment of early neonatal hypocalcaemia that is common and generally not associated with obvious clinical problems such as tetany (GPP, conditional recommendation, strong consensus).**

Ca is the most abundant mineral in the body. In blood, Ca exists in three fractions: ionized Ca (~50%), protein bound Ca (~40%), and a small amount of Ca that is complexed with other molecules such as citrate and phosphate. Blood Ca is tightly controlled by the actions of several hormones that maintain Ca homeostasis, especially parathyroid hormone (PTH), calcitonin and 1,25$(OH)_2$-vitamin D. The main homeostatic control of blood Ca is deposition in or release from bone. Renal reabsorption of filtered Ca depends on Ca plasma concentration, Ca requirements, renal tubular function, and last but not least the availability of P for microcrystalline apatite formation in growing infants (e.g. corresponding to hypophosphataemia there is paradoxical calciuria in preterm infants fed human milk in the absence of P fortification) [2,19–23].

Total body Ca content is around 28 g in term newborns. Approximately 1 kg of Ca is deposited between birth and adulthood. In children, daily Ca accretion rates average between 3.7 and 5.0 mmol/d (150 and 200 mg/d). However, since growth velocity is not uniform, accretion rates may be as high as 10 mmol/d (400 mg/d) during infancy and puberty. A study using dual energy x-ray absorptiometry found an average bone Ca accretion rate of 5.5 mmol/d (220 mg/d) and 7.9 mmol/d (317 mg/d) in girls and boys respectively during stage III puberty [24].

In newborns, owing to the interruption of placental transfer at birth, early hypocalcaemia rapidly occurs during the first 24–48 h of life owing to a relative immaturity of hormonal control (delayed PTH surge). This early neonatal hypocalcaemia is common and generally not associated with obvious clinical problems such as tetany. Ca infusion will usually prevent or treat early neonatal hypocalcaemia [25,26].

In children, recommendations for enteral intake assume an absorption rate of 50–60% [2]. In PN Ca supplies may be limited owing to the risk of precipitation of Ca-P-salts [12,19]. However, this can be prevented by using organic phosphorus compounds such as glycerophosphate [26–28].

4. Phosphorus

In addition to its presence in bone, P is also the principal intracellular anion, mainly in the form of phosphate. P plays a critical role in energy metabolism. In cells, most of the P is present in adenosine triphosphate, nucleic acids, and membranes. P deficiency results in inadequate supplies of energy-rich phosphates and, in particular, inhibition of glyceraldehyde-3-phosphate dehydrogenase, which plays a key position in glycolysis. Thereby P deficiency reduces adenosine triphosphate and 2,3-diphosphoglycerate levels and leads to left displacement of the oxygen-hemoglobin dissociation curve with decreased peripheral oxygen uptake and transport. Severe P deficiency may induce several clinical disorders including muscle weakness, delay in weaning from respiratory support, glucose intolerance, nosocomial infections and death [29–31].

Two thirds of blood P is organic and 1/3 is inorganic. Blood P concentration is usually measured as phosphate concentration that may vary according to growth, intake and renal excretion. Renal reabsorption threshold of phosphate is higher in infants than in adults [2,12,18,19]. Therefore, particular attention should be paid to phosphate laboratory reference values in newborns, especially in premature infants. Indeed, the lower limit of the reference value is higher in premature infants (1.6 mmol/l, 5 mg/dl) than in adults (1.0 mmol/l, 3 mg/dl). As laboratories frequently use adult references, this may result in underestimation of hypophosphataemia in these infants [12,19,31].

In newborn infants total body P is around 16 g rising to 600–900 g in an adult with 80% in bone and 9% in skeletal muscle [1]. P retention is related to bone mineralization, lean body mass accretion, and protein retention. Within physiological limits for compounding of PN the previously introduced equation may be used for estimation of the Ca:P ratio in PN.

*P intake (mmol) = [calcium intake (mmol/kg)/1.67] + [protein accretion (g)*0.3]*

In stable premature infants on parenteral nutrition considering an optimal protein accretion of 2–2.5 g/kg/d and a Ca intake of 2 mmol/kg/d (which is below the intrauterine Ca accretion), the ideal Ca:P ratio seems close to 1, between 0.8 and 1.2 [2,12,19]. Considering the identical protein accretion of 2–2.5 g/kg/d with a Ca intake of 3 mmol/kg Ca (which is closer to the intrauterine Ca accretion), a higher Ca:P ratio may be used. It is important to keep in mind that this is different in enteral nutrition.

5. Magnesium

R 8.5	**In preterm infants on PN who were exposed to maternal Mg therapy, Mg intakes need to be adapted to postnatal blood concentrations (LoE 2, RG B, conditional recommendation, strong consensus)**

Magnesium is the fourth most abundant mineral in the body and the second most abundant intracellular cation. In blood, about 1/3 of Mg is attached to plasma proteins and the

remaining 2/3 is filtrated by the kidney [2]. Particular attention should also be paid to Mg laboratory reference values in newborns, which are higher than in adults. Recently, a normal range of 0.7–1.5 mmol/L has been suggested for premature and term newborns during the first two weeks of life [32]. However, total blood Mg concentration is not the best estimate of the biologically active fraction (ionized Mg). The concentration in red blood cells (around 2.5 mmol/L) represents a better indicator of Mg content in tissues [2].

Fetal accretion is 0.12–0.20 mmol/kg/d (2.9–4.8 mg/kg/d) [8,33,34]. In the term newborn the total body Mg is around 0.8 g rising to 25 g in adulthood. Intakes and renal function play a critical role in Mg homeostasis. Around one third of Mg intake is usually excreted in the urine and 5–15% of filtrated Mg is reabsorbed. Mg is essential to the activity of the Mg-dependent adenyl-cyclase involved both in the PTH release and activity on bone. Thus, in Mg deficiency there is both deficient PTH release and peripheral resistance to PTH with subsequent hypocalcaemia [2].

Requirements are also frequently based on enteral nutrition data. Intestinal absorption rate is usually between 35 and 50%. Mg retention is usually around 0.08 mmol/kg/d in infants fed human milk and up to 0.15 mmol/kg/d in premature infants fed enriched preterm infant formulas [2].

Premature newborns exposed to maternal Mg sulfate therapy (preeclampsia, tocolysis) may have high levels of Mg in the first days of life. In addition, their low postnatal glomerular filtration rates during the first week of life limit their ability to excrete excessive Mg intakes. Thus, Mg intakes must be limited in newborns of mothers that received Mg sulfate before delivery and intakes need to be adapted to postnatal blood concentrations.

6. Parenteral mineral supply

R 8.6	**Acidic solutions packaged in glass vials, such as calcium gluconate, are contaminated with aluminum and should not be used in PN (LoE 3, RG 0, strong recommendation, strong consensus)**
R 8.7	**It is recommended to use organic Ca and P salts for compounding of PN solutions to prevent precipitation (GPP, strong recommendation, strong consensus)**
R 8.8	**The adequacy of Ca and P intakes in preterm infants can be adjusted until both start being excreted simultaneously with low urine concentrations (>1 mmol/L) indicative of a slight surplus (extrapolated evidence derived from enteral nutrition LoE 2+ studies, RG B, conditional recommendation, strong consensus)**

When selecting compounds suitable for PN, the potential for Ca cations to precipitate with inorganic phosphate anions must be considered. To some degree this can be avoided by initial mixing of the Ca salt with amino acids and glucose solution before diluting the solution and by adding phosphate salt at the end of the process. The use of organic phosphorus compounds circumvents this problem. Inorganic (Ca chloride) or organic (Ca gluconate, Ca glycerol-phosphate) Ca salts can be used in PN solutions. Chloride ions may increase the anion gap and lead to metabolic acidosis [12,35,36]. Ca gluconate stored in glass vials is contaminated with aluminum. Therefore, Ca gluconate packed in polyethylene is recommended to reduce aluminum contamination of parenteral nutrition (PN) [37]. Aluminum intake should not exceed 5 μg/kg/d. Ca glycerophosphate is an adequate source of Ca and P but it is not registered for parenteral use [12].

P can be provided as inorganic (sodium and potassium phosphate) or organic (fructose 1–6 diphosphate, sodium glycerophosphate, disodium glucose 1 phosphate) salts. Neutral potassium phosphate ([K_2HPO_4] in contrast to acid potassium phosphate [KH_2PO_4]) induces a risk of precipitation that limits its use in PN. Disodium glucose-1-phosphate is widely used but its sodium content may limit its early utilization in premature infants [12,28].

Mg may be provided using Mg sulfate or Mg chloride. However, Mg chloride usually increases the anion gap increasing the risk of metabolic acidosis. Thus, Mg is usually administered as Mg sulphate with few compatibility issues.

The adequacy of Ca and P intakes can be adjusted until both are excreted simultaneously with low urine concentrations (>1 mmol/L) indicative of a slight surplus [2,19–23].

6.1. Requirements for calcium, phosphate and magnesium in children

R 8.9	**The recommended parenteral intake for calcium, phosphorus, and magnesium in newborns and children on parenteral nutrition in mmol (mg)/kg/d is given in Table 1 (LoE 2, 3 and 4, RG 0, conditional recommendation, strong consensus)**
R 8.10	**In preterm infants with intrauterine growth restriction on PN careful monitoring of the plasma phosphate concentration within the first days of life is required to prevent severe hypophosphatemia that can result in muscle weakness, respiratory failure, cardiac dysfunction, and death (LoE 3, RG 0, conditional recommendation, strong consensus)**

Recommendations for parenteral intake of Ca, P and Mg are given in the Table 1. In individualized PN, especially if Ca and P intakes at the upper range are used, stability, compatibility and solubility of minerals need to be tested by the local pharmacy to avoid the risk of precipitation [27]. Blood concentrations and urine output require periodic monitoring during PN (see guideline on monitoring). In particular, monitoring of the plasma phosphate concentration is critical. In cases of relative P deficiency, available P is primarily directed to cellular metabolism, reducing bone mineralization or even inducing bone demineralization [13]. Hypophosphataemia was observed in preterm infants on PN with inappropriately low P intake [13] and high amino acid dosage [15,16] (refeeding-like syndrome) [11,12,14–16]. In significantly malnourished patients hypophosphataemia has also been observed during nutritional rehabilitation (refeeding syndrome). Extreme hypophosphataemia can result in muscle weakness, respiratory failure, cardiac dysfunction, and death [38].

6.2. Requirements in preterm infants and newborns

R 8.11	**In preterm infants on early PN during the first days of life lower Ca, P and Mg intakes are recommended than in growing stable preterm infants (Table 1) (LoE 2, RG B, conditional recommendation, strong consensus)**
R 8.12	**In early PN when calcium and phosphorus intakes are low (Table 1) and protein and energy are optimized it is recommended to use a molar Ca:P ratio below 1 (0.8–1.0) to reduce the incidence of early postnatal hypercalcaemia and hypophosphataemia (LoE 2, RG B, strong recommendation, strong consensus)**
R 8.13	**In infants and children on PN regular monitoring of the individual alkaline phosphatase, Ca, P and Mg plasma concentrations and Ca and P urine concentrations is required (Extrapolated evidence from LoE 2 and 3 studies, RG 0, strong recommendation, strong consensus)**

Owing to the wide range of individual growth velocities in preterm infants (5–20 g/kg/d), a wide range of requirements was proposed in previous recommendations: Ca 1.0–4.0 mmol/kg per day, P 0.75–3.0 mmol/kg per day, and a molar Ca:P ratio around 1.3 (mass ratio around 1.7) [1,39].

Table 1
Recommendations for calcium, phosphorus, and magnesium intake in newborns and children on parenteral nutrition.

Age	Suggested parenteral intake in mmol (mg)/kg/d		
	Ca	P	Mg
Preterm infants during the first days of life	0.8–2.0 (32–80)	1.0–2.0 (31–62)	0.1–0.2 (2.5–5.0)
Growing premature infants	1.6–3.5 (64–140)	1.6–3.5 (50–108)	0.2–0.3 (5.0–7.5)
0–6 m[a]	0.8–1.5 (30–60)	0.7–1.3 (20–40)	0.1–0.2 (2.4–5)
7–12 m	0.5 (20)	0.5 (15)	0.15 (4)
1–18 y	0.25–0.4 (10–16)	0.2–0.7 (6–22)	0.1 (2.4)

[a] Includes term newborns.

Very low birth weight and small for gestational age infants are at risk for early hypophosphataemia owing to their high P needs for growth [11,12,31]. In these infants, tubular phosphate reabsorption, which is usually 85–90%, increases to its maximum. In addition, Ca cannot be fixed in the bone inducing hypercalcaemia, hypercalciuria, and if prolonged bone demineralization, osteopenia, and nephrocalcinosis [11,19,31]. In early PN with low total Ca and P intake, molar Ca:P ratios below 1 (0.8–1.0) may reduce the incidence of early postnatal hypophosphataemia and consequent hypercalcaemia when protein and energy intakes are optimized from the first day of life [11,12,19].

Thereafter, the requirements of premature infants strongly depend on the individual growth velocity and are between 1 and 4 mmol/kg/d of Ca (40–160 mg/kg/d) and 0.75–3 mmol/kg/d of P (23–93 mg/kg/d) with a molar Ca:P ratio around 1.3 and between 0.2 and 0.3 mmol/kg/d for Mg [1,33]. It is important to consider that the individual Ca, P and Mg homeostasis needs to be monitored regularly.

For term infants, data obtained from breast fed infants can be applied to PN assuming an absorption rate of 50–60% for Ca, 85–95% for P, and 35–50% for Mg [1,2]. Therefore, taking into account a protein retention of 1–1.5 g/kg/d, term newborn requirements are estimated to be between 0.8 and 1.5 mmol/kg/d for Ca, between 0.7 and 1.3 mmol/kg/d for P, and between 0.1 and 0.2 mmol/kg/d for Mg.

6.3. Requirements in infants and children on long term PN

R 8.14	**In infants and children on long term PN the risk of metabolic bone disease requires periodic monitoring of Ca, P, vitamin D and bone mineral status (LoE 2 + and 3, RG 0, strong recommendation, strong consensus)**

Hypercalciuria and negative calcium balance are potential complications of PN and can be attenuated in the short-term by intravenous phosphate [41,42]. This effect is not caused by alterations in the PTH-1,25-dihydroxyvitamin D axis, but likely reflects P deficiency.

Infants and children on long term PN are at risk of developing “metabolic bone disease” (MBD) which is characterized by incomplete mineralization of osteoid with consequent disturbances ranging from osteopenia to severe bone disease with fractures [43–48]. The cause of MBD is multifactorial but mainly a calcium and/or phosphate deficiency. Other factors involved are negative calcium balance, hyperparathyroidism, and excessive vitamin D intake or vitamin D toxicity [49–53] and last but not least toxicity from aluminum in PN fluid. Although the latter has decreased with improvements in compounding [54,55], recent publications still suggest that it remains almost impossible to reduce the aluminum intake below 5 μg/kg/day in children <30 kg with currently available PN solutions [56,57]. Frequently hypercalciuria and MBD are associated.

Adequacy of phosphate intake has empirically been shown to be a key component in long term PN in infants and children not only for energy metabolism but also for optimal bone mineralization. In a cohort of children aged 4–13 years receiving home cyclic PN for 4 consecutive years hypercalciuria was reversed and painful bone disease did not occur at a Ca intake of 0.35 mmol/kg/d and a phosphorus intake of 0.7 mmol/kg/d in absence of vitamin D administration [58]. In these children Ca and P intake were significantly higher than previously recommended and an inverse Ca:P ratio of 0.5 in absence of vitamin D administration was used. These data suggest that the upper limit for recommended Ca and P intake should be increased (Table 1).

BMD scores assessed in the available pediatric studies [43–45] do not allow clear conclusions about optimum Ca and P intake for infants on long term PN. However, in contrast to the previous recommendation, these data suggest that increasing the Ca recommendation up to 0.35–0.4 mmol/kg/d and providing an excess of phosphorus (0.7 mmol/kg/d) using a Ca:P ratio less than 1 (close to 0.5) might be beneficial, even though this does not match the distribution of these elements in the human body [6,59].

The high prevalence of MBD [43–48] requires careful and periodic (see guideline on monitoring) monitoring of Ca, P, vitamin D and bone mineral status (e.g. by DEXA).

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Clinical Nutrition 37 (2018) 2366–2378

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPEN Guideline

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

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

Literature Search

A systematic literature search was conducted on 27/Dec/2014 including papers published between 2004 and 2014. In total, 150 abstracts were reviewed and an additional individual search was performed by the authors for each vitamin chapter, including searching the reference lists of selected papers. Some references from the previously published guidelines were preserved, where appropriate.

Key words: Parenteral Nutrition, Total, Infusions, Solutions, Home, Vitamin(s), Retinol, Cholecalciferol, Tocopherol(s), Ascorbic

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https://doi.org/10.1016/j.clnu.2018.06.951
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Table: Recommendations for vitamins in PN

R 9.1	Infants and children receiving PN should receive parenteral vitamins (LoE 4, RG 0, strong recommendation)
R 9.2	Whenever possible water and lipid soluble vitamins should be added to the lipid emulsion or a mixture containing lipids to increase vitamin stability. (LoE 4, RG 0, strong recommendation)
R 9.3	Vitamins should be administered daily, if possible. Lipid-soluble vitamins should be given simultaneously to lipid emulsions; an exception is vitamin K, which can be given weekly. Intermittent substitution twice or three times a week has a hypothetical risk of adverse effects from transient high levels. (LoE 4, RG 0, strong recommendation)
R 9.4	Optimal doses and infusion conditions for vitamins in infants and children have not been established. Vitamins should be given in doses mentioned in Table 1 of this chapter. However, these are based mainly on expert opinion. (GPP, conditional recommendation)
R 9.5	Routine monitoring of vitamin concentrations (except of vitamin D) is not recommended because of lack of evidence for adequate benefits. In patients on long-term PN (weeks) monitoring may be needed based on clinical indications. (LoE 4, RG 0, conditional recommendation)
R 9.6	Preterm infants on PN should receive 700–1500 IU/kg/day (or 227–455 ug/kg/day) of vitamin A, term infants 150–300 ug/kg/day (or 2300 IU (697 ug)/day), and older children 150 ug/day. (LoE 3, RG 0, strong recommendation)
R 9.7	There are substantial losses of vitamin A when given with a water-soluble solution; therefore, parenteral lipid soluble vitamins should be given with the lipid emulsion whenever possible. (LoE 3, RG 0, strong recommendation)
R 9.8	Preterm infants on PN should receive 200–1000 IU/day (or 80–400 IU/kg/day) of vitamin D, term infants up to 12 months of age 400 IU/day (or 40–150 IU/kg/day), and older children 400–600 IU/day. (LoE 3, RG 0, strong recommendation)
R 9.9	Paediatric patients receiving long-term PN should be monitored periodically for vitamin D deficiency. In patients with 25 (OH) vitamin D serum concentrations <50 nmol/L, additional supplementation with vitamin D should be provided. (LoE 3, RG 0, strong recommendation)
R 9.10	Oral supplementation of vitamin D should be considered in patients on partial PN as well as during weaning from parenteral nutrition. (LoE 3, RG 0, strong recommendation)
R 9.11	The total dose of vitamin E should be ≤11 mg/day for infants and children below 11 years, when new fat emulsions containing LC-PUFAs and vitamin E are given. (LoE 2+, RG B, strong recommendation)
R 9.12	For preterm infants, the total dose of vitamin E should be between 2.8 and 3.5 mg/kg/day, but should not exceed 11 mg/day. (LoE 2+, RG B, strong recommendation)
R 9.13	To properly assess vitamin E status, the ratio between serum vitamin E/total serum lipids should be used. (GPP, conditional recommendation)
R 9.14	Preterm and term infants up to 12 months of age on PN should receive 10 ug/kg/day, and older children 200 ug/day of vitamin K. (LoE 3, RG 0, strong recommendation)
R 9.15	Classical coagulation tests can be used in low-risk infants for indirect evaluation of vitamin K status, but are not specific to vitamin K deficiency. (LoE 3, RG 0, conditional recommendation)
R 9.16	Undercarboxylated Serum Vitamin K-Dependent Proteins (PIVKA-II) seem to be a useful biomarker of subclinical vitamin K deficiency for at-risk patient groups and should be used when locally available. (LoE 3, RG 0, conditional recommendation)
R 9.17	Newborns who are unable to take oral vitamin K or whose mothers have taken medications that interfere with vitamin K metabolism should follow a specific supplementation protocol, according to local policy. (LoE 4, RG 0, strong recommendation)
R 9.18	Preterm and term infants up to 12 months of age on PN should receive 15–25 mg/kg/day, and older children 80 mg/day of vitamin C. (LoE 3, RG 0, strong recommendation)
R 9.19	Preterm and term infants up to 12 months of age on PN should receive 0.35–0.50 mg/kg/day, and older children 1.2 mg/day of thiamine. (GPP, conditional recommendation)
R 9.20	Preterm and term infants up to 12 months of age on PN should receive 0.15–0.2 mg/kg/day, and older children 1.4 mg/day of riboflavin. (GPP, conditional recommendation)
R 9.21	Preterm and term infants up to 12 months of age on PN should receive 0.15–0.2 mg/kg/day, and older children 1.0 mg/day of pyridoxine. (GPP, conditional recommendation)
R 9.22	Preterm and term infants up to 12 months of age on PN should receive 0.3 ug/kg/day, and older children 1 ug/day of cobalamin. (GPP, conditional recommendation)
R 9.23	Preterm and term infants up to 12 months of age on PN should receive 4–6.8 mg/kg/day, and older children 17 mg/day of niacin. (GPP, conditional recommendation)
R 9.24	Preterm and term infants up to 12 months of age on PN should receive 2.5 mg/kg/day, and older children 5 mg/day of pantothenic acid. (GPP, conditional recommendation)
R 9.25	Preterm and term infants up to 12 months of age on PN should receive 5–8 ug/kg/day, and older children 20 ug/day of biotin. (GPP, conditional recommendation)
R 9.26	Preterm and term infants up to 12 months of age on PN should receive 56 μg/kg/day and older children 140 μg/day of folic acid. The adequacy of current recommendations needs to be confirmed. (LoE 3, RG 0, strong recommendation)

Acid, Thiamin(e), Riboflavin, Pyridoxin(e), Vitamin B 12, Cobalamin, Niacin, Pantothenic Acid, Biotin, Folic Acid, Folate

Age limit: 0–18 years (child* or boy* or girl* or adolescent* or pediatric* or paediatric* or infant* or newborn* or neonat* or toddle* or schoolchild*)

Language: English

2. Introduction

R 9.1	**Infants and children receiving PN should receive parenteral vitamins (LoE 4, RG 0, strong recommendation, strong consensus)**
R 9.2	**Whenever possible water and lipid soluble vitamins should be added to the lipid emulsion or a mixture containing lipids to increase vitamin stability. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 9.3	**Vitamins should be administered daily, if possible. Lipid-soluble vitamins should be given simultaneously to lipid emulsions; an exception is vitamin K, which can be given weekly. Intermittent substitution twice or three times a week has a hypothetical risk of adverse effects from transient high levels. (LoE 4, RG 0, strong recommendation, strong consensus)**
R 9.4	**Optimal doses and infusion conditions for vitamins in infants and children have not been established. Vitamins should be given in doses mentioned in Table 1 of this chapter. However, these are based mainly on expert opinion. (GPP, conditional recommendation, strong consensus)**
R 9.5	**Routine monitoring of vitamin concentrations (except of vitamin D) is not recommended because of lack of evidence for adequate benefits. In patients on long-term PN (weeks) monitoring may be needed based on clinical indications. (LoE 4, RG 0, conditional recommendation, strong consensus)**

A sufficient supply of vitamins is essential for growth and development. Little new data has been published in this area during the last 30 years. Parenteral vitamins are usually administered as a mixture of different vitamins. Some vitamins may adhere to the tubing and/or be degraded by light, whilst environmental humidity and temperature

also play a role. Therefore, the actual amount of vitamins delivered to the patient may be much lower than the intended dose, particularly in the case of retinol (vitamin A) and in premature infants who receive solutions with slow infusion rates. The optimal parenteral vitamin requirements for children and neonates have never been determined. Moreover, there are just a few multivitamin preparations available for preterm infants and neonates. The available products for infants contain the same relative amount of lipid soluble vitamins despite different pharmacological properties in different preparations (combined water and fat soluble vitamin solution versus only fat soluble vitamin preparation). Adult formulations containing propylene glycol and polysorbate additives are not recommended for use in infants because of concerns about potential toxicity. Furthermore, there is little data on vitamin needs of children with acute and chronic diseases whose requirements might differ.

All studies determining vitamin levels during intravenous supply have been undertaken with commercially available mixtures, either given in the glucose–amino acid solution or in the lipid emulsion. Therefore, current recommendations are based on the composition of specific products. Parenteral vitamin dosages that have been previously recommended [1–3] have been used without apparent harmful effects in clinical practice for a number of years.

3. Fat soluble vitamins (A, D, E and K)

Infants and particularly low birth weight infants have low body stores of vitamins at birth due to a limited transfer of lipid-soluble substrates across the maternal placenta. Preterm infants show higher risk of liposoluble vitamin deficiencies because they have: 1) low lipid stores, 2) low stores of fat-soluble vitamins, 3) low levels of protein and lipoprotein transport [4–7]. Therefore, a sufficient supply of fat-soluble vitamins to preterm infants from the first days of life is recommended.

Vitamin A is most vulnerable to degradation by light emitted near its absorption maximum at wavelengths of 330–350 nm, vitamin E at 285–305 nm. Red plastic bags offered for protecting the syringes are impervious for wavelengths from 190 to 590 nm and amber light-protecting tubing material absorbs wavelengths from 290 to 450 nm. The most detrimental factor for vitamins A and E is intense sunlight, consisting of the whole light spectrum including the ultraviolet range. In contrast, both neon light illuminating the intensive care unit at night and phototherapy lamps have little degrading effect on vitamin A. Exposure of PN solutions to light is also associated with increased production of peroxides and is not protectable by addition of multivitamins to the solution [8]. Losses to tubing and light degradation depend on whether vitamins are given with a lipid emulsion or in the glucose amino acid mixture and vary for different lipid soluble vitamins.

Generally, daily parenteral doses of the fat-soluble vitamins are similar to oral recommended daily allowances (higher bioavailability, but also higher requirements).

3.1. Vitamin A

R 9.6	**Preterm infants on PN should receive 700–1500 IU/kg/day (or 227–455 ug/kg/day) of vitamin A, term infants 150–300 ug/kg/day (or 2300 IU (697 ug)/day), and older children 150 ug/day. (LoE 3, RG 0, strong recommendation, strong consensus)**
R 9.7	**There are substantial losses of vitamin A when given with a water-soluble solution; therefore, parenteral lipid soluble vitamins should be given with the lipid emulsion whenever possible. (LoE 3, RG 0, strong recommendation, strong consensus)**

Vitamin A (group of retinoids = retinol + beta-carotene + carotenoids) plays an essential role in vision, normal differentiation and maintenance of epithelial cells, adequate immune function (T-cell function), reproduction, growth and development. There are provitamin A active compounds, beta-carotene, alpha-carotene and cryptoxanthin. Bioconversion efficiency from provitamin A ranges from 3.6:1 to 28:1. The dietary reference intakes mention retinol activity equivalents (RAEs).

1 RAE = 1ug retinol = 12 ug beta-carotene = 24 ug alpha-carotene = 24 ug beta-cryptoxanthin

1 RAE = 3.33 International Units (IU) of vitamin A

Vitamin A is stored in the liver and released bound to retinol-binding protein (RBP) and coupled to transthyreitin [9]. Prophylactic supplementation of vitamin A was reported to protect against bronchopulmonary dysplasia and to reduce the requirement for oxygen support [10,11]. There are clinical conditions that may be associated with vitamin A deficiency – such as infection (sepsis, HIV), burns, mechanical ventilation, steroid use, hepatobiliary dysfunction, renal failure, trauma, hematooncological, intestinal dysfunction (abetalipoproteinemia), protein-energy malnutrition, zinc deficiency or cystic fibrosis. What constitutes an 'adequate' supply of vitamin A for premature neonates remains controversial and the "adequate" concentration of plasma vitamin A in very low birth weight infants is not known. Serum concentrations below 200 μg/l (0.7 μmol/l) have been considered to indicate deficiency in premature infants and concentrations below 100 μg/l (0.35 μmol/l) indicate severe deficiency and depleted liver stores. The range of normal values for children older than 6 months of age (including adults) is 300–800 μg/l (1.05–2.8 μmol/l). Vitamin A status may be also assessed as serum retinol (normal range 1–3 μmol/l measured by HPLC) or the concentration of RBP (<0.48 mmol/L is associated with severe vitamin A deficiency). Both the plasma RBP response [12,13] and the relative rise in serum retinol concentration [14] following intramuscular (I.M.) vitamin A administration have been described as useful tests to assess functional vitamin A status. Under stress conditions, serum retinol is not reliable and it is recommended to use the RBP/transthyretin ratio instead [9].

Vitamin A undergoes substantial photo-degradation and adsorptive loss when given in combination with the water soluble vitamins as part of the glucose-amino acid infusion. In premature neonates, it has been proposed to use shorter I.V. tubing and a shorter infusion time or to supply the more stable vitamin A ester retinyl palmitate or to give the multivitamin solution with the lipid emulsion [15–17].

The total delivery of retinol from parenteral infusions has been consistently reported to be below 40% of the intended dose [15,18,19]. The major proportion of retinol losses is due to adsorption onto the tubing materials within the first hour of infusion, whereas retinyl palmitate tends to adsorb to tubing material to a lesser extent. The available "micro tubing" made of polyurethane is more prone to adsorb lipophilic substances than standard PE tubing [20]. PE and PVC tubing materials seem to have comparable adsorption behaviours. Supplying vitamin A in a lipid emulsion is the most feasible way to reduce losses.

Recommendations for intravenous vitamin A supply are given in Table 1. Supplementing vitamin A as retinyl palmitate (1000 IU/day vitamin A) in premature infants for 28 days in addition to parenteral nutrition (400 IU/day) and enteral supply (1500 IU/day) led to significantly higher serum levels than at birth but with a wide range of variation - 32% still had levels below 200 μg/l [21].

Table 1
Recommended doses for parenteral supply of fat soluble and water soluble vitamins for preterm infants, infants and children.

	Preterm infants	Infants – 12 months	Children and adolescents 1–18 years
Vitamin A[a]	700–1500 IU/kg/d (227–455 ug/kg/d)	150–300 ug/kg/d or 2300 IU/d (697 ug/d)	150 ug/d
Vitamin D[b]	200–1000 IU/d or 80–400 IU/kg/d	400 IU/d or 40–150 IU/kg/d	400–600 IU/d
Vitamin E[c]	2.8–3.5 mg/kg/d or 2.8–3.5 IU/kg/d	2.8–3.5 mg/kg/d or 2.8–3.5 IU/kg/d	11 mg/d or 11 IU/d
Vitamin K	10 ug/kg/d (recommended, but currently not possible)[d]	10 ug/kg/d (recommended, but currently not possible)[d]	200 ug/d
Vitamin C	15–25 mg/kg/d	15–25 mg/kg/d	80 mg/d
Thiamine	0.35–0.50 mg/kg/d	0.35–0.50 mg/kg/d	1.2 mg/d
Riboflavin	0.15–0.2 mg/kg/d	0.15–0.2 mg/kg/d	1.4 mg/d
Pyridoxine	0.15–0.2 mg/kg/d	0.15–0.2 mg/kg/d	1.0 mg/d
Niacin	4–6.8 mg/kg/d	4–6.8 mg/kg/d	17 mg/d
Vitamin B12	0.3 ug/kg/d	0.3 ug/kg/d	1 ug/d
Pantothenic acid	2.5 mg/kg/d	2.5 mg/kg/d	5 mg/d
Biotin	5-8 ug/kg/d	5-8 ug/kg/d	20 ug/d
Folic acid	56 μg/kg/d	56 μg/kg/d	140 μg/d

[a] 1 ug RAE (retinol activity equivalent) = 1 ug all-trans retinol = 3.33 IU vitamin A. In infants an intravenous vitamin A supply of about 920 IU/kg per day together with the water soluble mixture or 230–500 IU/kg per day with the lipid emulsion are often used. Since losses are quite variable and losses are higher in the water soluble mixture, the amount delivered to the patient may be estimated to be approx. 300–400 IU/kg per day for both options. Recommended daily parenteral dose for term neonates is 2300 IU and for preterm neonates approx. 700–1500 IU/kg [2,9,17,49,55,95].
[b] For practical reasons, recommended doses of vitamin D for preterm and term infants are given not only as absolute quantity but also as per kg body weight.
[c] Upper limit in preterm and term infants should not exceed 11 mg/d; however, higher doses of vitamin E/day after using the new lipid emulsions and multivitamins together have been shown with apparently no harmful effect. Upper limit for children and adolescents should be established in further well designed studies.
[d] Current multivitamin preparations supply higher vitamin K amounts without apparent adverse clinical effects. Dose is independent on local policy of VKDB prevention.

3.1.1. Vitamin A supplementation for preventing morbidity and mortality in very low birth weight infants

In premature infants, vitamin A deficiency probably plays a role in respiratory infections and development of bronchopulmonary dysplasia (BPD). A recent survey has shown that approximately 76% of VLBW neonates suffer from vitamin A deficiency (compared to 63% of term neonates). The rate of deficiency is higher in infants with lower gestational age and birth weight [4]. In another survey, more than 80% of neonatal departments introduced vitamins during the first three days of life [22]. In preterm infants with BPD, lower plasma beta-carotene and vitamin A concentrations were described [23]. Level 1 evidence exists only for VLBW infant with gestational age <32 weeks or birth weight <1500 g. A Cochrane review [24] found an association of vitamin A supply and a reduction in death or oxygen requirement at one month of age and of oxygen requirement of survivors at 36 weeks post-menstrual age, with this latter outcome being confined to infants with a birth weight <1000 g. This review was recently updated and previously reported outcomes were confirmed with data from nine RCTs that met the inclusion criteria [25]. Moreover, developmental assessment of 88% of surviving infants in the largest trial showed no differences between the groups at 18–22 months of age, corrected for prematurity. Similar results were reported in studies using different regimens of vitamin A dosage. Three trials with information on retinopathy of prematurity (ROP) suggested a trend towards reduced incidence in infants receiving vitamin A supplementation. There was no effect shown on spontaneous closure rate of patent ductus arteriosus, nosocomial sepsis or intraventricular haemorrhage. No adverse effects were reported. However, intramuscular injections of vitamin A were painful.

A recent double-blind RCT described the effect of omega-3 FA on the oxidative stress and vitamin A and E levels in preterm neonates. SMOF lipid emulsion led to a significant reduction of oxidative stress, however, vitamin A levels significantly increased during the intervention period of 14 days in both SMOF and control groups (Intralipid 20%). Both groups were supplemented with vitamins during the study [26].

Several eligible trials supplemented vitamin A intramuscularly starting soon after birth up to 28 days in various doses of 4000–5000 IU three times a week to 2000 IU every other day. One study supplemented vitamin A as retinyl palmitate in lipid emulsion at approx. 700 RE/kg per day for the first two weeks and 600–700 RE/kg per day for the next two weeks. Control and study infants also received "standard" vitamin A. The conclusion of the review was that whether clinicians decide to use repeat I.M. doses of vitamin A to prevent chronic lung disease may depend upon local incidence of this outcome and the value attached to achieving a modest reduction in this outcome balanced against the lack of other proven benefits and the acceptability of the treatment. The benefits, in terms of vitamin A status, safety and acceptability of delivering vitamin A in an intravenous emulsion compared with repeated intramuscular injection should be assessed in a further trial.

The NICHD trial necessitated 12 intramuscular injections with 5000 IU [27]. Compared with this regimen, once-per week (15,000 IU) worsened, and a higher dose (10,000 IU 3× per week) did not reduce vitamin A deficiency (serum retinol <200 μg/l, RBP <2.5 mg/dL, and/or RDR >10%) [28]. In the study by Porcelli et al., ELBW infants received triweekly I.M. vitamin A as chronic lung disease prophylaxis (5000 IU × 3 per week = 2143 IU/day), irrespective of patient weight. This regimen was necessary to achieve recommended daily vitamin A intake, but vitamin A was not a predictor of ROP surgery [29].

A modified parenteral vitamin regimen with the amount of vitamin A increased by 35% premixed with parenteral lipid emulsion led to higher plasma vitamin A concentrations in VLBW infants [30].

Vitamin A toxicity is rare, but may occur – e.g. in patients on intravenous supply with liver and renal disorders. There is a relatively narrow window between deficiency and toxicity. Acute toxicity (approx. > 150,000 ug) can present with increased intracranial pressure (headache, nausea/vomiting, vertigo, blurred vision, muscular incoordination). Chronic toxicity (approx. 30,000 ug/day) presents with bone abnormalities (malformations, fractures), dermatitis, alopecia, ataxia, muscle pain, cheilitis, skin and vision disorders, pseudotumor cerebri, hepatocellular necrosis, hyperlipidaemia and inhibition of vitamin K. Toxicity can be established by retinyl-ester levels [31].

In conclusion, vitamin A delivery is improved by the infusion of retinyl palmitate with lipids, but light protecting tubing provides only a marginal benefit. Dosage recommendations for parenteral vitamin supplementations for premature infants are based on clinical studies measuring vitamin levels during supplementation. Most of these studies were done with the water soluble solution

containing water and lipid soluble vitamins. The true needs of these infants are not known. From a clinical perspective, it seems that supplementing VLBW infants with vitamin A is associated with a trend toward a reduced number of deaths or oxygen requirement at one month of age, a trend towards reduced incidence of ROP and no benefit or harm to neurodevelopmental status at 18–22 months compared to controls [24].

3.2. Vitamin D

R 9.8	**Preterm infants on PN should receive 200–1000 IU/day (or 80–400 IU/kg/day) of vitamin D, term infants up to 12 months of age 400 IU/day (or 40–150 IU/kg/day), and older children 400–600 IU/day. (LoE 3, RG 0, strong recommendation, strong consensus)**
R 9.9	**Paediatric patients receiving long-term PN should be monitored periodically for vitamin D deficiency. In patients with 25(OH) vitamin D serum concentrations < 50 nmol/L, additional supplementation with vitamin D should be provided. (LoE 3, RG 0, strong recommendation, strong consensus)**
R 9.10	**Oral supplementation of vitamin D should be considered in patients on partial PN as well as during weaning from PN. (LoE 3, RG 0, strong recommendation, strong consensus)**

The main function of vitamin D is the regulation of calcium and phosphate. It is essential for bone health. Other health effects of vitamin D, such as prevention of immune-related and infectious diseases, cardiovascular disease, and cancer, have been discussed. However, high quality evidence is not sufficient to support vitamin D supplementation for theses outcomes [32]. Recently, there have been several reports on vitamin D deficiency and decreased bone mineral density among paediatric patients, both during and after weaning from PN [33–37].

The ESPGHAN Committee on Nutrition [32] as well as the American Academy of Pediatrics [38] and the Institute of Medicine [39] recommends a total daily vitamin D intake (from all sources) of 400 IU/day for infants and 600 IU/day for children and adolescents. Currently commercially available emulsions and multivitamin solutions often contain 400 IU as daily doses, and this i.v. dose does not seem to be associated with vitamin D deficiency. Therefore, a daily dose of 400–600 IU is recommended for children and adolescents. In infants and children, a serum 25(OH) vitamin D concentration > 50 nmol/L indicates sufficiency [32,38].

The optimum vitamin D requirements of preterm infants on PN are not known. Current recommendations vary to a great extent [40–43]. It has been suggested that as little as 30 IU/kg per day i.v. might be sufficient [40]. The AAP Committee on Nutrition, however, recommends providing vitamin D at 200–400 IU per day in order to reach normal 25(OH) vitamin D concentrations of 50 nmol/L [41].

According to the ESPGHAN Committee on Nutrition, a well-defined threshold for vitamin D acute toxicity has not been established. Prolonged daily intake up to 10,000 IU or up to serum concentrations of 25(OH)D of 240 nmol/L appears to be safe. Serum concentrations >375 nmol/L are associated with acute hypercalcaemia and hyperphosphataemia. Acute vitamin D intoxication is rare and usually results from vitamin D doses much higher than 10,000 IU/day [32]. Tolerable upper intake levels identified by the IOM are 1000 IU/day for infants ages 0–6 months, 1500 IU/day for infants ages 7–12 months, 2500 IU/day for children ages 1–3 years, 3000 IU/day for children ages 4–8 years, and 4000 IU/day for children and adolescents ages 9–18 years (and adults) [39].

3.3. Vitamin E

R 9.11	**The total dose of vitamin E should be ≤11 mg/day for infants and children below 11 years, when new fat emulsions containing LC-PUFAs and vitamin E are given. (LoE 2+, RG B, strong recommendation, strong consensus)**
R 9.12	**For preterm infants, total dose of vitamin E should be between 2.8 and 3.5 mg/kg/day, but should not exceed 11 mg/day. (LoE 2+, RG B, strong recommendation, strong consensus)**
R 9.13	**To properly assess vitamin E status, the ratio between serum vitamin E/total serum lipids should be used. (GPP, conditional recommendation, strong consensus)**

Vitamin E (tocopherol) is a lipid-soluble and powerful biological antioxidant which is present in most parenteral lipid emulsions; it is the major membrane bound antioxidant employed by the cell to protect the integrity of biologic membranes by inhibiting lipid peroxidation [44–49]. Tocopherol occurs in different isoforms, α, β, γ or δ, depending on the number and position of methyl groups attached to the chromanol ring. The different natural vitamin E isoforms vary in composition and biological activity. Natural α-tocopherol has the highest vitamin E activity given its 3 chiral centers in which methyl groups are in the R configuration and is referred to as RRR-α-tocopherol. The α-tocopherol isomer is the form with the highest concentration in human plasma and tissues [44,46]. Plant-derived oils contain the 4 isoforms, and are the most abundant dietary sources of vitamin E, but they are mostly enriched with γ-tocopherol [46]. Wheat germ, sunflower seeds, cotton seed and olive oil (plant germs and seed oils) are rich sources of RRR-α-tocopherol (50–100%), whereas γ-tocopherol dominates in soy and corn oil [50].

Conversion of IU α-tocopherol to mg:

- IU × 0.67 mg RRR-α-tocopherol, natural form (“d-α-tocopherol”) or
- IU × 0.45 mg all-rac-α-tocopherol, synthetic form (“dl-α-tocopherol”), or
- 1 IU = 1 mg = 1 USP unit dl-α-tocopheryl acetate which is used in IV multivitamin preparations

Appreciable prenatal vitamin E accretion occurs normally in the third trimester of pregnancy with increasing fetal lipid stores and maximum maternal–fetal vitamin exchange [4,27,49]. Pre-eclampsia and gestational diabetes increase the risk of hypovitaminosis in premature infants [4–7].

In general, no age differentiation is indicated in the literature regarding vitamin requirements due to the limited data available. The clinical assessment of vitamin E deficiency in preterm infants is difficult because plasma levels do not reflect tissue concentrations [46]; consequently, interpretation should be made with caution [30]. Abnormal lipid levels can affect vitamin E status, so a low ratio of serum α-tocopherol to lipids (deficiency: serum vitamin E/total lipid ratio <0.8 mg/g of total lipids) has been considered as the most accurate indicator of vitamin E status in children and adults with hyperlipidaemia [51]. The majority of the studies performed in preterm infants on parenteral PN have focused on analysing the effects of vitamin E supplementation on morbidity and mortality; it was reported that vitamin E effects depend on [6,52]: gestational age, vitamin E preparation and route of administration, total daily dose, time of initiation of the supplementation and intake of other nutritional components (iron, selenium, vitamin A, poly-unsaturated fatty acids (PUFAs)). Vitamin E is little affected by exposure to light, so specific protection of the infusion devices for

PN is not necessary. α-tocopherol tends to be absorbed to some extent onto tubing materials, which can be prevented by administering it simultaneously with fat emulsions or by using a vitamin E ester [49,53]. The risk of lipid peroxidation may be increased, which is of particular concern in premature infants who are often exposed to oxidative stress under intensive care conditions [30,54,55].

Early vitamin E administration to preterm infants leading to serum levels 1–3.5 mg/dL reduces the severity of retinopathy and blindness, the incidence and severity of intracranial haemorrhage and the development of bronchopulmonary dysplasia [7,56,57]; but levels >3.5 mg/dL increase the risk of sepsis and necrotizing enterocolitis [58,59], possibly due to a lower rate of bacterial destruction via oxidative pathways. The mechanism involved in the increased risk of infection and haemorrhage in relation to high serum tocopherol levels is unknown [6,51]. So, the current recommendation is to give a dose which will favour the maintenance of the normal range for serum tocopherol (1–2 mg/dL) and to start as soon as PN is commenced or as early as possible thereafter [6,51].

The amount and types of vitamin E homologues in various lipid emulsions can vary considerably, especially with respect to the α-isoform [5,50]. The first generation lipid emulsions contained 100% soybean oil sources [5,45]. Soybean oil is a good source of PUFAs being present in a high concentration (57.8%), but contains predominantly γ-tocopherol [46] so it may deplete antioxidant defences [45,46], and as a result may have negative effects on inflammatory response and on the immune system [5,45,60]. Vitamin E in emulsions based on soybean and MCT was shown to be more stable than in those based on soybean oil alone [44,46,61,62].

The new-generation lipid emulsions consist of a mixture of pure olive oil, pure fish oil, or various blends of soy, olive, medium-chain triglycerides, and fish oil [49,55,66–69]. The new mixture emulsions based on soybean oil, olive oil, MCT and fish oil (known as third generation lipid emulsions), provide a good source of PUFAs, energy, MUFAs and n-3 [30,44,63–65]. These emulsions also contain high levels of vitamin E which result in an increase in serum α-tocopherol concentrations and better liver protection [53,55,58]. The use of 20% LCT/MCT emulsion for PN in preterm infants provided important clinical benefits and equivalent vitamin E status compared to soybean oil emulsion with LCT [70]. α-tocopherol is abundant in pure fish oil and new-generation emulsion blends [50] and prevents lipid peroxidation attributable to the high content of long-chain polyunsaturated fatty acids (LC-PUFAs) [30,44]. In fact, the amount of tocopherol supplementation to be added into the new generation emulsions depends on the lipid source and the storage lifetime of the emulsion, and is calculated according to the number of double bonds in EPA and DHA [71,72]; the risk of lipoperoxidation is higher when PUFA-rich lipid emulsions are infused [44]. Lipid peroxides are unstable molecules which are converted to malondialdehydes and hydrocarbons; these new hydroperoxides are volatile molecules which can trigger oxidative stress and may oxidise proteins and DNA [73].

To maintain the normal range of serum vitamin E in premature infants receiving PN, the administration of a daily dose of 2.8 mg/kg/day* seems to be adequate; in general the recommendation for infants is between 2.8 and 3.5 mg/kg/day, and the maximal dose considered for paediatric patients is 7 mg/day [55]. Current lipid emulsions containing α-tocopherol provided to babies, in some cases, clearly exceed the current recommendations, especially if multivitamins containing vitamin E are supplied too. Porcelli et al. found that the regular recommended dose of vitamin E for PN was adequate in only 50–80% of the preterm infants studied [29].

Therefore, the content of α-tocopherol in some emulsions, where it has been added as a protective measure, is up to 4- to 5-fold higher than the γ-tocopherol content of soy-oil emulsions. In the last decade, several randomised clinical trials have been conducted to analyse the effects and tolerance of these new lipid emulsions in comparison with the older ones. Some of them seem to be safe and have good tolerance in premature infants and children aged 5 months to 11 years [54,63,74]. Mixture emulsions containing n-3-enriched fat improve serum levels of vitamin E compared to the 100% soybean oil emulsions; these new emulsions improve the total antioxidant capacity of the patients through the antioxidant function of α-tocopherol which has been associated with the preservation of liver function as well as beneficial effects on the immune system and clinical outcome [7,74–78]. After receiving PN based on olive oil emulsions, vitamin E status and fatty acid plasma composition of infants were better than in babies receiving soybean oil emulsions, and more similar to those found in breast-fed neonates; this effect is probably due to the lower PUFA content in the emulsions containing olive oil (20%); consequently, olive oil emulsions improve the ratio of vitamin E/PUFAs [46,62,79,80]. These emulsions were reported to be associated with a lower peroxidation index and anti-inflammatory effect in malnourished children [62,79].

Clinical studies have tested the therapeutic effect of dietary vitamin E to prevent non-alcoholic fatty liver disease with mixed success [81,82]. A very recent study performed in preterm piglets has shown that α-tocopherol in a pure fish oil lipid emulsion and added to soybean oil one prevented serum and liver increases in biliary and lipid markers of PN –associated liver disease (PNALD); these authors concluded that vitamin E plays an important hepatoprotective role in preventing PNALD [83]. In a recent study Shouroliakou et al. [27] demonstrated that after receiving a new fish oil based lipid emulsion for fourteen days, preterm infants had a higher total antioxidant potential compared with those which received a standard lipid emulsion, confirming the reduction of oxidative stress by n-3 fatty acids; in addition, significantly lower levels of bilirubin where observed in these preterm babies at discharge. However, the evidence and mechanisms that explain any possible benefits of the vitamin E or n-3 PUFA are not yet completely understood in humans [78].

In Europe, combined vitamin supplements are available and used very often in PN by dissolving the vitamins in the lipid emulsion; their use reduces peroxide formation in the lipid emulsions [84,85]. A new sterile ready to administer emulsion in parenteral nutrition for infants and composed of a mixture of soybean oil, glycerol and egg lecithin, also contains soluble vitamins; each dose of this emulsion supplies 0.64 mL dl-α-tocopherol; the dose to be administered is 1 ml per kg, with a maximum daily dose of 10 mL. Considering the components of the emulsion and the contribution of lipids, the amount to be supplied should be taken into account in the daily amount of total lipids administered [64]. There is also a lyophilized preparation for infants and children up to 11 years, which must be reconstituted for intravenous administration; a reconstituted 5 ml single dose provides 7 mg of dl-α-tocopherol acetate. The single daily dose to be administered should be adjusted according to para-clinical reports for evidence of deficit or excess vitamin E [30]. For children over 11 years the indicated doses are the same as for adults, 10 mL/day [65].

The last available Cochrane review concluded that a fixed daily intravenous dose of vitamin E is not advisable because there is an inverse relationship between serum tocopherol levels and body weight; consequently, using a fixed dose places the smallest infants at risk of excessive intake and the largest infants at risk of deficiency [46,52]. Children with short bowel syndrome (SBS) are at special risk for malabsorption of different nutrients for a long time after weaning off PN. Therefore, they need long-term, regular monitoring and intensive nutritional care to prevent various nutrient deficiencies, such vitamin E [86]. However, more trials are

necessary to determine safe parenteral doses for paediatrics patients at different ages [6,29,55].

In conclusion, the combination of vitamin E supplementation (as part of the multivitamins) and using some of the new mixed emulsions could result in administration of amounts which are twice those recommended. The current data suggests that a higher amount of α-tocopherol through PN than previously recommended (7 mg/day) could be given in infants and children below 11 years; these amounts have shown no harmful effects, but a preservation of liver function and better vitamin E status. Consequently, we recommend an increase of the vitamin E dose/day for infants and children receiving PN up to 11 mg/day or 11 IU; this amount seems to be safe and beneficial when given together with the amounts of EPA and DHA provided by the lipid emulsions or multivitamin supplements. We strongly recommend research to develop individualized PN therapy depending on the infant's status, clinical situation and the type of fat emulsion which is being used.

3.4. Vitamin K

R 9.14	**Preterm and term infants up to 12 months of age on PN should receive 10 ug/kg/day, and older children 200 ug/day of vitamin K. (LoE 3, RG 0, strong recommendation, strong consensus)**
R 9.15	**Classical coagulation tests can be used in low-risk infants for indirect evaluation of vitamin K status, but are not specific to vitamin K deficiency. (LoE 3, RG 0, conditional recommendation, strong consensus)**
R 9.16	**Undercarboxylated Serum Vitamin K-Dependent Proteins (PIVKA-II) seem to be a useful biomarker of subclinical vitamin K deficiency for at-risk patient groups and should be used when locally available. (LoE 3, RG 0, conditional recommendation, strong consensus)**
R 9.17	**Newborns who are unable to take oral vitamin K or whose mothers have taken medications that interfere with vitamin K metabolism should follow a specific supplementation protocol, according to local policy. (LoE 4, RG 0, strong recommendation, strong consensus)**

Vitamin K (phylloquinone) regulates carboxylation of the coagulation factors II, VII, IX, X. Protein C and protein S are also vitamin K dependent. Vitamin K plays a role in the synthesis of osteocalcin, a marker of bone formation. Coagulation factors do not cross the placenta. Recommended doses of vitamin K are given in Table 1. Premature infants supplemented with vitamin K (1 mg) intramuscularly, followed by PN with 60 ug/d (<1000 g) and 130 ug/d (>1000 g) had high plasma vitamin K levels compared with those at 40 weeks postconceptual age [87]. A parenteral vitamin K supply of 80 ug/kg per day [88] in premature infants might be excessive if combined with an i.m. dosage of 1 mg on day 1, and lower supplies may suffice during the first weeks of life. Many current multivitamin preparations contain high amounts of vitamin K which tend to supply 100 ug/kg (10 times higher than recommended enteral intakes), but adverse clinical effects have not been reported. On the other hand, there are other multivitamin preparations (like Cernevit™) that do not contain any vitamin K. This should be taken into account especially when treating premature infants and newborns. FAO/WHO recommends a vitamin K intake of at least 1 ug/kg/d [89], which is suggested to be a conservative estimate of the dose of phylloquinone required to maintain coagulation factor synthesis in depleted individuals [90]. In the absence of vitamin K, bleeding (gastrointestinal, skin, intracranial etc.) in newborns and infants may occur. Risk factors for such an event are: underlying disease (such as cystic fibrosis, alpha-1-antitrypsin deficiency, cholestasis (e.g. biliary atresia)), maternal drugs (warfarin, anticonvulsants, tuberculostatic drugs) and exclusive breastfeeding [91].

Newborns who are unable to take oral vitamin K or whose mothers have taken medications that interfere with vitamin K metabolism should be given 0.1–0.2 mg/kg vit. K by intravenous or intramuscular injection at birth (may vary according to local policy) and a sufficient daily intake should be ensured (recommended oral or parenteral intake: 10–20 ug/kg/d) [92,93].

Measurement of vitamin K status: Classical coagulation tests are not specific to vitamin K deficiency. Measurement of triglyceride-rich lipoprotein–borne phylloquinone reflects recent dietary intake and should be determined in fasting individuals. Undercarboxylated Serum Vitamin K-Dependent Proteins (PIVKA-II) seem to be a useful biomarker of subclinical vitamin K deficiency for at-risk patient groups [90].

4. Water soluble vitamins (B, C, Niacin, Pantothenic acid, Biotin, Folic acid)

4.1. Introduction

Current recommendations are expert opinions based on observed biochemical responses to variations in parenteral intake and on comparison with enteral recommendations. Generally, daily parenteral doses of the water-soluble vitamins are several times higher than the oral recommended daily allowances (due to higher requirements and increased urinary excretion). Controlled randomized trials in this field are lacking, thus it is recommended to maintain dosages that have been recommended previously [1–3] and which have been used without apparent harmful effects in clinical practice. However, in the case of thiamine (vitamin B1), the needs of preterm infants might be higher than previously recommended [94].

Water-soluble vitamins must be administered on a regular basis as they are not stored in significant amounts, except for B12. Excess is excreted by the kidneys and there is little toxicity. Term infants and children appear to adapt to large variations in vitamin intakes. By contrast, the finding of marked elevation of some vitamins and low levels of others seen in infants less than 1500 g suggests that this group has less adaptive capacity to high- or low dose intakes [95,96]. Therefore, there may be a need to develop specific vitamin preparations for low birth weight infants [1,2,97]. Some of available paediatric multivitamin formulations can be used according to the recommendation of the producer in reduced doses also for infants below 3 kg or 1 kg, respectively. Some water-soluble vitamins (like B1, B6, B12 and C) are also available as parenteral single-vitamin products.

The administration of multivitamins with intravenous lipid emulsions provides a practical way to reduce peroxidation of the lipid while limiting vitamin loss [98,99]. Vitamins B1, B2, B6 and C in pediatric parenteral formulation for neonatal use are stable for 72 h when stored between 2 and 8 °C. When stored at 25 °C, vitamin C presented instability after 48 h [100].

4.2. Vitamin C

R 9.18	**Preterm and term infants up to 12 months of age on PN should receive 15–25 mg/kg/day, and older children 80 mg/day of vitamin C. (LoE 3, RG 0, strong recommendation, strong consensus)**

Vitamin C (ascorbic acid) is a cofactor for many enzymes and a strong antioxidant. The average body pool in adults is 1500 mg;

40–60 mg is used daily. In adults, requirements for vitamin C are usually defined on serum concentrations and pharmacokinetic data [101]. Requirements for vitamin C for preterm infants, term infants and older children are not known. Inflammatory diseases induce higher needs for vitamin C in order to maintain normal serum concentrations [101]. There is no clear clinical indicator for vitamin C deficiency. The risk of scurvy is usually a consequence of complete or nearly complete vitamin C depletion associated with severe malnutrition and has become a very rare condition in Western societies.

In premature infants, the infusion of vitamin C at a dose of 48 mg/kg per day over 4 weeks resulted in serum concentrations that were substantially higher than in term infants or older children [102]. Parenteral administration of 100 mg/kg per day of vitamin C for 7 days led to serum concentrations twice as high as the level of the umbilical artery [103]. One study demonstrated that the recommended daily dosage of 25 mg/kg per day would be adequate for most premature infants [94]. One RCT in very preterm infants demonstrated no significant benefits or harmful effects associated with treatment allocation to higher or lower vitamin C supplementation throughout the first 28 days of life [104]. Therefore, doses of 15–25 mg/kg per day have been recommended for parenteral nutrition in preterm infants [97].

4.3. Thiamine (Vitamin B1)

R 9.19	**Preterm and term infants up to 12 months of age on PN should receive 0.35–0.50 mg/kg/day, and older children 1.2 mg/day of thiamine. (GPP, conditional recommendation, strong consensus)**

Thiamine pyrophosphate is involved in carbohydrate and lipid metabolism. Its requirements depend on carbohydrate intake. Deficiency of thiamine may lead to beriberi with neurologic and cardiovascular symptoms. In parenterally fed infants and children a deficient thiamine supply may lead to severe lactic acidosis, Wernicke's encephalopathy and even death within a period of days to weeks [105–109]. In children after abdominal surgery, thiamine concentration was below the normal range on postoperative day 3 in the group receiving peripheral parenteral nutrition without thiamine [110]. In preterm infants a parenteral thiamine intake of 780 ug/kg per day led to 10-fold higher serum levels than in cord blood [102]. Consequently, a considerably lower parenteral intake (200–350 ug/kg per day) has been recommended. Friel et al. challenged this recommendation [94]. In their study a mean parenteral and enteral intake of thiamine of 510 ug/kg per day maintained a normal functional thiamine status and levels slightly below cord blood concentrations [94]. Therefore, the current parenteral recommendation for preterm infants (200–350 ug/kg per day) might be too low and dosages up to 500 ug/kg per day seem more appropriate, but further information is required.

4.4. Riboflavin (Vitamin B2)

R 9.20	**Preterm and term infants up to 12 months of age on PN should receive 0.15–0.2 mg/kg/day, and older children 1.4 mg/day of riboflavin. (GPP, conditional recommendation, strong consensus)**

Riboflavin participates in energy metabolism. The requirement for riboflavin is associated with protein intake. The adequacy of riboflavin status can be assessed by measuring plasma concentrations and by the erythrocyte glutathione reductase test (EGRAC). Clinical manifestations of deficiency include hyperaemia of mucous membranes, stomatitis, dermatitis, ocular disturbances and anaemia. Riboflavin is also essential for proper functioning of vitamin B6 and niacin. Riboflavin is rapidly photodegraded in PN solutions. A trial showed tolerance of a combined enteral and parenteral riboflavin intake up to 624 ug/kg per day in preterm infants [94], however, parenteral riboflavin dosages above 281–500 ug/kg per day were repeatedly shown to exceed requirements [17,111–113]. Therefore, the recommended dosage of 0.15–0.2 mg/kg per day to preterm infants remains unchanged. As suggested by Greene et al. [2], the recommended dosage of 1.4 mg riboflavin per day for term infants and children is more than necessary, but due to the lack of toxicity and studies of actual requirements, this suggested dosage remains unchanged. However, some VLBW infants receiving parenteral vitamin supplementation reach up to 50-times higher plasma riboflavin when compared to cord blood. Such levels may be undesirable, because photodegradation products of riboflavin may be a source of oxidant cell injury [30]. Loss of riboflavin through photo-degradation can be very high (65%) and can be halved by adding the water soluble vitamin solution to the lipid solution, and further reduced by using dark tubing [98]. Data on the signs and symptoms of riboflavin toxicity in infants and children is insufficient. The precise requirement of riboflavin in parenterally fed infants and children has not yet been defined. In very low birth weight infants, the current practice of riboflavin supply leads to elevated plasma levels after birth. Porcelli et al. described a modified vitamin regimen in VLBW infants providing 0.19–0.35 mg/kg/d of riboflavin in parenteral vitamin infusion premixed in lipid emulsion. This modified regimen led to 37% lower plasma riboflavin during the first postnatal month (133.3 ± 9.9 ng/mL) when compared to standard group receiving 0.42–0.75 mg/kg/d. Riboflavin intake and plasma riboflavin concentrations were directly correlated, thus plasma concentrations are partially dose-dependent at least during the first postnatal month in VLBW infants [30].

4.5. Pyridoxine (Vitamin B6)

R 9.21	**Preterm and term infants up to 12 months of age on PN should receive 0.15–0.2 mg/kg/day, and older children 1.0 mg/day of pyridoxine. (GPP, conditional recommendation, strong consensus)**

Vitamin B6 (B6) is found in different forms, such as pyridoxine, pyridoxal, pyridoxamine and pyridoxal phosphate (active form) [94]. Pyridoxine is necessary cofactor for over 100 enzymes that are mostly involved in glycolysis, gluconeogenesis and amino acid (AA) metabolism, including transamination, deamination, decarboxylation of AA in neurotransmitters (dopamine, serotonin, glutamate, etc.) [94,114,115], and the development of the immune system [114]. It is also needed for the synthesis of sphingolipids, haemoglobin and gene expression [114,115].

Infant and children B6 deficiency is associated with dermatitis, anaemia, seizures, depression, encephalopathy, immune function decline and hyperhomocystinemia, owing to accumulation of S-adenosylhomocysteine [94,114]. Excessive supplementation of B6 can produce painful neuropathy and skin lesions owing to axonal degeneration of sensory nerve fibres [114,116]. Preterm neonates have a high immaturity of the enzymatic system involved in B6 levels. Differences in B6 homoeostasis between preterm and term infants have been reported. These differences should be taken into

account for diagnosis and treatment of epilepsy and B6 deficiency in neonates [115]. Pyridoxine has an established role in the treatment of certain neonatal seizures and homocystinuria. However, there is no systematic review to guide the maximum safe dose and clinical utility of this vitamin in the treatment of peripheral neuropathy [116,117].

The optimal parenteral B6 dose for infants and children is not clear. The ESPGHAN 2005 guidelines proposed doses of 0.15–0.2 mg/kg/d for infants and of 1.0 mg/kg/d for children. In infants intakes of more than 1.0 mg/kg/d should be avoided owing to possible toxicity [49]. In preterm infants considerably higher intakes were tolerated [49,94]. However, these data are not sufficient for altering current recommendations.

4.6. Cobalamin (Vitamin B12)

R 9.22	**Preterm and term infants up to 12 months of age on PN should receive 0.3 ug/kg/day, and older children 1 ug/day of cobalamin. (GPP, conditional recommendation, strong consensus)**

Vitamin B12 is an organometallic complex. It participates in metabolic reactions involving the synthesis of DNA nucleotides. A supply of 0.6 ug/kg per day has led to elevated serum levels [102]. The adequacy of current recommendations remains to be confirmed. Infants and children after aboral small-bowel (distal ileum) resection are at the risk of vitamin B12 deficiency typically presenting with haematologic or neurologic disorders. Also patients after gastrectomy or bariatric surgery are at risk. A RCT has shown that adding vitamin B12 to erythropoietin, iron and folate seemed to increase in the effectiveness of treatment of anaemia in premature infants [118].

4.7. Niacin

R 9.23	**Preterm and term infants up to 12 months of age on PN should receive 4–6.8 mg/kg/day, and older children 17 mg/day of niacin. (GPP, conditional recommendation, strong consensus)**

Niacin is essential for the synthesis of nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate which serve as cofactors for electron transport and energy metabolism. Niacin deficiency results in pellagra characterized as cutaneous, gastrointestinal and neurologic symptoms. Deficiency can be seen also in carcinoid syndrome. Nicotinamide has no reported toxicity. Nicotinic acid in high doses (3–9 g/d) can cause flushing, nausea, vomiting, liver toxicity, blurred vision and impaired glucose tolerance [9]. No new studies are available. The adequacy of current recommendations needs to be confirmed in ELBW infants.

4.8. Pantothenic acid

R 9.24	**Preterm and term infants up to 12 months of age on PN should receive 2.5 mg/kg/day, and older children 5 mg/day of pantothenic acid. (GPP, conditional recommendation, strong consensus)**

Pantothenic acid (vitamin B5) is required for the synthesis of coenzyme A and therefore essential for fatty acid metabolism. Deficiency of pantothenic acid has rarely been reported in humans. Due to the lack of scientific evidence, requirements for pantothenic acid in infants and children are not known. Therefore, recommendations for administration of pantothenic acid in parenteral nutrition are usually based on expert opinion [9,119].

4.9. Biotin

R 9.25	**Preterm and term infants up to 12 months of age on PN should receive 5–8 ug/kg/day, and older children 20 ug/day of biotin. (GPP, conditional recommendation, strong consensus)**

Long term PN free of biotin together with long-term use of broad spectrum antibiotics leads to lethargy, hypotonia, irritability, alopecia, dermatitis, anorexia, pallor, glossitis, nausea, hyperaesthesia, muscle pain and elevated serum cholesterol and bile pigments. Recurrent lactic acidosis due to secondary biotin deficiency has been described in children with short bowel syndrome [120]. No toxicity associated with biotin has been reported. The adequacy of current recommendations needs to be confirmed.

4.10. Folic acid

R 9.26	**Preterm and term infants up to 12 months of age on PN should receive 56 μg/kg/day and older children 140 μg/day of folic acid. The adequacy of current recommendations needs to be confirmed. (LoE 3, RG 0, strong recommendation, strong consensus)**

Folic acid (FA) (also known as folate, vitamin M, vitamin B9, vitamin Bc (or folacin), pteroyl-L-glutamic acid, pteroyl-L-glutamate and pteroylmonoglutamic acid) are forms of the water-soluble vitamin B9. FA is formed by an aromatic ring of pteridine linked to the para-aminobenzoic acid and one or more glutamate residues. Dietary folate polyglutamates are hydrolized into monoglutamate forms. The biological importance of FA is due to tetrahydrofolate and other derivatives after its conversion to di-hydrofolic acid in the liver [117,121].

FA is essential for humans and acts as a cofactor in certain biological reactions [122]; it is needed in the biosynthesis of purines and pyrimidines, for mitotic cell division, in the metabolism of some amino acids and for hystidine catabolism [49,123]. FA is involved in the modulation of one-carbon metabolism; it provides methyl donors for biosynthetic methylation of DNA and histones, influencing gene expression, neurotransmitter synthesis and restoration of DNA; it is especially important in aiding rapid cell division and growth, becoming essential for foetal development and growth [118,124]. However, the role of FA in the establishment of an individual's DNA methylation profile during development is not yet known, nor its involvement in methylation profiles during the life course and, ultimately, the consequences of these profiles for long term health and wellbeing.

Preterm infants show low serum FA in the first 2–3 months of life; the demand for FA is high particularly during the period of rapid growth. Several factors (rapid growth, increase of erythropoyesis, use of antibiotics, use of anticonvulsants, intestinal malabsorption) can have an influence in diminishing hepatic stores of FA? potentially leading to deficiency. The most important factors influencing serum FA levels during the first month of life are maternal supplementation during gestation [125] and mother smoking [123].

FA stimulates the haematopoietic system and is used in the treatment and prevention of folate deficiencies and megaloblastic

Table 2a
List of parenteral multivitamin products available on the European and American market (in alphabetical order).

Product (Distributor)	Vial volume	Content per vial												
		A (IU)	D (IU)	E (IU)	K (ug)	B1 (mg)	B2 (mg)	B3 (mg)	B5 (mg)	B6 (mg)	B12 (ug)	C (mg)	Biotin (ug)	FA (ug)
Adult														
Cernevit (Baxter)	5 mL	3500	220	11.2	0	3.5	4.1	46	17.3	4.5	6	125	69	414
Infuvite Adult (Baxter)	10 mL	3300	200	10	150	6	3.6	40	15	6	5	200	60	600
M.V.I.-12 (Hospira)	10 mL	3300	200	10	0	6	3.6	40	15	6	5	200	60	600
M.V.I. Adult (Hospira)	10 mL	3300	200	10	150	6	3.6	40	15	6	5	200	60	600
Pabrinex: ampule no.1	5 mL	0	0	0	0	250	4	0	0	50	0	0	0	0
(Archimedes Pharma)	10 mL	0	0	0	0	500	8	0	0	100	0	0	0	0
Pabrinex: ampule no.2	5 mL	0	0	0	0	0	0	160	0	0	0	500	0	0
(Archimedes Pharma)	10 mL	0	0	0	0	0	0	320	0	0	0	1000	0	0
Solivito N (Fresenius Kabi)	10 mL	0	0	0	0	2.5	3.6	40	15	4	5	100	60	400
Soluvit N (Fresenius Kabi)	10 mL	0	0	0	0	3.2	3.6	40	15	4	5	100	60	400
Vitamin B-Complex 100 (Bioniche Pharma)	1 mL	0	0	0	0	100	2	100	2	2	0	0	0	0
Vitalipid N Adult (Fresenius Kabi)	10 mL	3300	200	10	150	0	0	0	0	0	0	0	0	0
Paediatric														
Infuvite PEDiatric (Baxter)	5 mL	2300	400	7	200	1.2	1.4	17	5	1	1	80	20	140
M.V.I. Pediatric (Hospira)	5 mL	2300	400	7	200	1.2	1.4	17	5	1	1	80	20	140
Vitalipid N Infant (Fresenius Kabi)	10 mL	2300	400	7	200	0	0	0	0	0	0	0	0	0

anaemia in infants, children and adults [118,126]. The haematological diagnosis of FA deficiency is generally accompanied by low serum and erythrocyte levels. FA deficiency is associated with hyperhomocysteinemia owing to reduced enzyme activities [117]. Among pregnant women, high homocysteine (Htcy) levels are associated with subfertility, congenital developmental effects, pre-eclampsia, IUGR, risk of miscarriage, gestational diabetes, premature rupture of membranes, placental abruption and risk for Down Syndrome. There is an inverse relationship between maternal intake of folic acid and high levels of Htcy in the offspring; high Htcy levels are associated with type of feeding, especially PN in preterm infants [127]. In paediatric patients, high Htcy is associated with ischaemic stroke, intraventricular haemorrhage, periventricular leukomalacia, retinopathy of prematurity and necrotizing enterocolitis [127].

FA is described as not toxic for humans; preterm infants receiving PN with high FA content have no risk of folate deficiency during 2 months of age. However, the higher, so-called pharmacological doses can mask neurological manifestations of pernicious anaemia and may reduce the efficacy of anticonvulsant medications [123].

Table 2b
List of parenteral single vitamin products available on the European and American market.

Vitamin A	*Aquasol A*
Vitamin D	*Calcitriol*
	Paracalcitol
	Doxercalciferol
Vitamin K	*Phytonadione*
	Kanavit
Vitamin B1	*Thiamine*
Vitamin B6	*Pyridoxine*
	Pyridoxin Leciva
Vitamin B12	*Cyanocobalamin*
	Vitamin B12
Vitamin C	*Ascorbic acid*
	Acidum ascorbicum Biotika
	Vitamin C-Injektopas
Folic acid	*Folic acid*

Routine FA supplementation is recommended to prevent the development of FA deficiency in preterm infants; due to the availability of new PN products and preterm infant formulas containing FA, additional supplementation has become a source of controversy [123]. Erythropoietin therapy which is an effective way to prevent and to treat anaemia of prematurity, could increase FA deficiency. Therefore, ESPGHAN has recommended specific doses of a combined therapy of B12 and FA to enhance erythropoiesis. According to the ESPGHAN 2005 Guidelines, the current recommended dose of FA in PN is 56 μg/kg/day for infants and 140 μg/day for children [49]; when needed, as a treatment to improve erythropoiesis, the PN dose considered is 35–100 μg/kg/day [118,123]. Additional research is need because the number and types of studies in the literature are limited [49,124]. Without such studies the current recommendations should be maintained.

Commercially available multivitamin and single-vitamin products for intravenous use in the European and American market are listed in Table 2 (partly based on reference no. [9]).

Conflict of interest

None declared.

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Clinical Nutrition 37 (2018) 2379–2391

Contents lists available at ScienceDirect

Clinical Nutrition

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ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Venous access

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

Literature search

Timeframe: publications from 2004 until December 2016 were considered

Type of publications: randomized trials, observational studies (case-controls, prospective cohort studies, time series, retrospective data), meta-analyses, and systematic reviews

Key words: catheterization, central venous catheters, central line, central catheter, central venous access, parenteral nutrition, intravenous nutrition, Broviac, Hickman, ultrasound, placement, catheter related thrombus, catheter blockage, catheter related infection, skin hygiene, skin site, topical treatment, dressing type & change, catheter submersion, swimming, bathing, care standardization, multimodal preventive strategies, bundles

Language: English

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https://doi.org/10.1016/j.clnu.2018.06.952
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Search: Searches were performed in three stages. First, all the titles on the relevant key words were retrieved by the Cochrane Collaboration Department from Budapest/Hungary, who also performed the first reduction. 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.

Table: List of recommendations on venous access

R 10.1	In newborns and children, PICC and tunneled CVC should be used for administration of prolonged PN during hospitalization (GPP, strong recommendation for)
R 10.2	In children requiring long-term PN and home PN a tunneled CVC is recommended (GPP, strong recommendation for)
R 10.3	Where possible a CVC should be used only for giving PN (LOE 2−, RG B, strong recommendation for)
R 10.4	A catheter with the minimal number of ports or lumens may be used (LOE 2−, RG 0, strong recommendation for)
R 10.5	If a multi-lumen CVC is in place, dedicate one lumen to PN; blood sampling, transfusion and central venous pressure monitoring from the CVC should be avoided (Extrapolated evidence from adult studies rated as LOE 1−, RG B, strong recommendation for)
R 10.6	To improve quality of life for patients on long term PN, blood sampling via CVC for routine monitoring is recommended providing full aseptic protocol is followed (GPP, strong recommendation)
R 10.7	Catheters used for long-term PN made of silicone or polyurethane may be preferred (LOE 2−, RG 0, strong recommendation for)
R 10.8	Antimicrobial coated CVC should not be used for children on long-term PN (Extrapolated evidence from adult studies rated as LOE 1+, RG B, conditional recommendation against)
R 10.9	In infants and children in whom CVC cannot be placed in superior vena cava, an option of femoral vein catheter insertion can be recommended as a higher incidence of mechanical and infectious complications has not been shown in comparison with jugular and subclavian sites (LOE 2−, RG 0, conditional recommendation for)
R 10.10	In children, an option of subclavian venous access can be recommended as the risk of mechanical complications does not exceed the rate of complications with other insertion sites under appropriate conditions of insertion (LOE 2−, RG 0, conditional recommendation for)
R 10.11	Subclavian insertion can be recommended for long-term use (GPP, conditional recommendation for)
R 10.12	In newborns, umbilical vessels can be used for short term PN (GPP, conditional recommendation for)
R 10.13	The CVC tip should lie outside the pericardial sac to avoid the risk of pericardial effusion/tamponade (GPP, strong recommendation for)
R 10.14	In small infants (body length 47–57 cm) the catheter tip of a jugular or subclavian CVC should lie at least 0.5 cm above the carina on a chest x-ray, while in older/larger infants (body length 58–108 cm) that distance should be at least 1.0 cm (GPP, strong recommendation for)
R 10.15	In children, as in adults, we recommend that positioning the CVC tip above the carina means it is likely to be in the superior vena cava and therefore outside the pericardial sac (LOE 3, RG 0, strong recommendation for)
R 10.16	The catheter tip of a femoral catheter should lie above the renal veins (first lumbar vertebra) (GPP, strong recommendation for)
R 10.17	A percutaneous, radiologically or ultrasound guided insertion method may be used since this is equally effective as a surgical cut-down, and carries less risk of complications (LOE 2−, RG 0, strong recommendation for)
R 10.18	Ultrasound guidance may be used in order to reduce complications during venous catheterization (LOE 2−, RG 0, strong recommendation for)
R 10.19	CVC shall not be changed routinely in order to reduce the risk of sepsis (Extrapolated evidence from adult studies rated as LoE 1+, RG A, strong recommendation against)
R 10.20	If a CVC requires removal, replacement rather than exchange over a guidewire decreases the risk of infection. CVC exchange may be reserved for those patients with difficult venous access (Extrapolated evidence from adult studies rated as LoE 3, RG 0, conditional recommendation for)
R 10.21	Prophylactic antibiotics do not reduce the risk of CRBSI, therefore they should not be administered (LoE 2+, RG B, conditional recommendation against)
R 10.22	Antibiotic line locks should not be used alone for treating catheter related blood stream infection (CRBSI) as these have not been shown to be effective (LoE 1−, RG B, conditional recommendation against)
R 10.23	Antibiotic line locks can be used in conjunction with systemic antibiotics to assist in the eradication of CRBSI in some patients (LoE 3, RG 0, conditional recommendation for)
R 10.24	Ethanol line locks may be considered for preventing CRBSI (LoE 3, RG 0, conditional recommendation for)
R 10.25	Taurolidine is effective in preventing CRBSI and should be used during long term catheter use (Extrapolated evidence from adult studies rated as LoE 1+, RG B, strong recommendation for)
R 10.26	Routine use of heparin flush for the prevention of thrombotic occlusion in CVC being used on a daily basis cannot be recommended over use of saline flush due to lack of proven benefit in children (LoE 2−, RG 0, conditional recommendation against)
R 10.27	For CVC that are being accessed intermittently, flushing with 5–10 U/mL heparinized saline 1–2 × weekly helped maintain patency and therefore can be recommended (Extrapolated evidence from adult studies rated as LoE 2−, RG 0, conditional recommendation for)
R 10.28	Routine use of heparin has been shown to be effective in prevention of PICC occlusion in newborns, but since the potential risks have not been defined, its routine use cannot be recommended (LoE 3, RG 0, recommendation for research)
R 10.29	In infants and children recombinant tissue plasminogen activator or urokinase shall be used to unblock a catheter (LoE 1+, RG A, strong recommendation for)
R 10.30	There is insufficient evidence to advocate the prophylactic use of anticoagulants in children receiving home parenteral nutrition to reduce catheter related thrombosis, occlusion and infection (LoE 3, RG 0, strong recommendation against)
R 10.31	Appropriate hand hygiene procedures should be followed before accessing the intravascular device or the insertion site (Extrapolated evidence from adult studies rated as LoE 1+, RG B, strong recommendation for)
R 10.32	Before insertion of an intravascular device and for post-insertion site care, clean skin should be disinfected with 2% chlorhexidine solution in 70% isopropyl alcohol (Extrapolated evidence from adult studies rated as LoE 1, RG B, strong recommendation for)
R 10.33	Antiseptic solution should remain on the insertion site and be allowed to air dry before catheter insertion or dressing application (GPP, strong recommendation for)
R 10.34	Due to potential side effects, skin antisepsis with chlorhexidine in infants younger than two months cannot be recommended (LOE 2−, RG 0, conditional recommendation against)
R 10.35	Catheter connectors, ports and hubs should be disinfected before accessing, preferably with 2% chlorhexidine solution in 70% isopropyl alcohol (LoE 2+, RG B, strong recommendation for)
R 10.36	Both sterile gauze with tape and transparent semi-permeable polyurethane dressing can be used to cover the catheter insertion site (LoE 3, RG 0, conditional recommendation for)
R 10.37	Sterile gauze dressing is preferable if the catheter site is bleeding or oozing (GPP, conditional recommendation for)
R 10.38	For short term CVC, site dressings may be replaced every 2 days for gauze dressing, and every seven days for transparent dressing. (LoE 2−, RG 0, conditional recommendation for)
R 10.39	A dressing should be changed sooner if it becomes damp, loosened or soiled (GPP, strong recommendation for)
R 10.40	A tunneled CVC with a well-healed exit site does not require dressing to prevent dislodgement, however, in children it is useful to have them looped and covered (GPP, conditional recommendation for)
R 10.41	Chlorhexidine-impregnated sponge dressing should be considered in patients older than two months with short-term catheters who are at high risk for infection (LoE 2+, RG B, strong recommendation for)
R 10.42	

(*continued*)

	Topical antimicrobial treatment at the insertion site cannot be routinely used as it may promote fungal infection, antimicrobial resistance and damage the surface of the catheter (LoE 3, RG 0, strong recommendation against)
R 10.43	Children with well-healed tunneled catheters may be allowed to swim, provided that a water resistant dressing is used to cover the whole catheter. Immediately after swimming the catheter exit site should be cleaned and disinfected, and the dressing changed (GPP, conditional recommendation for)
R 10.44	Regular training and education of healthcare staff with respect to catheter insertion and maintenance should be recommended (LoE 2+, RG B, strong recommendation for)
R 10.45	Multimodal protocols for health care providers, aiming to standardize clinical practice on insertion and maintenance of the intravascular devices, should be developed and regularly audited (LoE 2+, RG B, strong recommendation for)

2. Introduction

Securing reliable venous access is of paramount importance when considering parenteral nutrition (PN). However, the presence of a central venous catheter (CVC) is the principal risk factor for major, potentially lethal complications, such as nosocomial bloodstream infection [1] and venous thrombosis [2]. Moreover, the most important risks associated with complications arising from the use of CVC are administration of PN, young age and extended use (long indwelling time) [3–5]. CVC related complications in children on long-term PN contribute significantly to patient morbidity, mortality, and health care costs [6]. Notably, a large proportion of complications are preventable by means of appropriate catheter choice, selection of site and method of insertion, nursing care, handling and hygiene of venous access, all of which are addressed in this chapter.

In the following discussion it is necessary to differentiate between peripheral and central venous access, and between non-tunneled CVC (i.e. inserted via a peripheral vein - PICC) and tunneled CVC inserted subcutaneously.

3. Intravascular catheters: choice and insertion

3.1. Types of catheter

R 10.1	**In newborns and children, PICC and tunneled CVC should be used for administration of prolonged PN during hospitalization (GPP, strong recommendation for, strong consensus)**
R 10.2	**In children requiring long-term PN and home PN a tunneled CVC is recommended (GPP, strong recommendation for, strong consensus)**

High osmolality solutions are more likely to induce phlebitis and a CVC is generally required to maintain long term venous access (i.e. more than a few weeks). Although peripheral venous access can be used in preterm infants, extravasation injuries may be severe and frequent loss of venous access can compromise effective nutritional support. Central venous access is obtained by advancing a catheter into one of the central veins, either directly via a deep vein (subclavian, internal jugular or femoral), peripherally through a subcutaneous vein, or through the umbilical vein. CVC are usually selected according to the anticipated duration of use: short and medium term non-tunneled PICC and long-term use cuffed, tunneled CVC or implantable ports [7]. Any type of CVC can be used for providing short term PN in hospitalized patients, however, the advantages of a PICC are that it can often be inserted without general anesthesia, does not require manipulation of the vein, and has proven to be safe and effective for PN in newborns and children [3,8–11] (LoE 2−), although complications were more frequent in younger patients [12]. There is, however, limited and weak evidence showing that prolonged use (>14–21 days) of a PICC increases the risk for catheter-related bloodstream infection (CRBSI) [3,8,13] (LoE 2−).

For long term PN and home PN, cuffed tunneled CVC (e.g. Broviac, Hickman catheter) are recommended [7,14]. These devices have several advantages: the subcutaneous cuff attached to the catheter provides better fixation, and the longer distance between the insertion site and the entry into the vein decreases migration of microorganisms from skin to bloodstream [15,16] (LoE 1−). Implantable ports are useful for long-term intermittent use, but because port access requires insertion of a specially designed transdermal needle, their value for long-term PN in children is limited [7,14].

3.2. Catheter dedicated only to PN

R 10.3	**Where possible a CVC should be used only for giving PN (LOE 2−, RG B, strong recommendation for, strong consensus).**
R 10.4	**A catheter with the minimal number of ports or lumens may be used (LOE 2−, RG 0, strong recommendation for, strong consensus).**
R 10.5	**If a multi-lumen CVC is in place, dedicate one lumen to PN; blood sampling, transfusion and central venous pressure monitoring from the CVC should be avoided (Extrapolated evidence from adult studies rated as LOE 1−, RG B, strong recommendation for, strong consensus).**
R 10.6	**To improve quality of life for patients on long term PN, blood sampling via CVC for routine monitoring is recommended providing full aseptic protocol is followed (GPP, strong recommendation, strong consensus).**

To reduce the risk of infection it is recommended that the CVC should be used exclusively for administration of PN and not for blood sampling or giving other fluids and drugs [17] (LoE 2−). However, in critically ill children with poor venous access multi-lumen catheters may be used, with one lumen dedicated to PN. Double and triple lumen catheters appear to be associated with an increased risk of bacteremia compared to single lumen ones [18–21] (LoE 2−). They may be more at risk of becoming infected, possibly because of more frequent catheter manipulations [17,22,23] (LoE 2−) with rates of sepsis as high as 10–20% compared to 0–5% with single lumen catheters [17,23,24] (LoE 1−). In some adult studies, catheter sepsis does not appear to have been increased with multi-lumen devices [25–30] (LoE 1−). The authors of these studies suggested that PN can be given safely through multi-lumen catheters only when the following conditions are implemented:

- one lumen reserved exclusively for PN;
- only compatible medications and solutions to be given;
- not to be used for blood sampling, blood transfusion or central venous pressure measurement.

3.3. Catheter material

R 10.7	**Catheters used for long-term PN made of silicone or polyurethane may be preferred (LOE 2−, RG 0, strong recommendation for, strong consensus)**
R 10.8	**Antimicrobial coated CVC should not be used for children on long-term PN (Extrapolated evidence from adult studies rated as LOE 1+, RG B, conditional recommendation against, strong consensus)**

More flexible catheters made of silicone or polyurethane are less thrombogenic and less traumatic than CVC made of stiffer material [14] (LoE 2−). Because of this, in clinical practice, more flexible materials such as silicone or polyurethane have gradually replaced stiffer ones.

For short-term use, non-tunneled CVC impregnated with mini cycline/rifampicine or chlorhexidine/silver sulfadiazine in adults reduce infection rates more effectively than conventional catheters [31]. Similarly, RCT in critically ill children show that antibiotic-impregnated CVC significantly reduced the risk of bloodstream infection compared with standard catheters [32]. However, meta-analysis for adult patients showed that impregnated (coated) CVC do not prevent infection during prolonged PN [33] (LoE 1+; adult studies). There are no studies in children receiving long term PN.

3.4. Insertion sites

R 10.9	**In infants and children in whom CVC cannot be placed in superior vena cava, an option of femoral vein catheter insertion can be recommended as a higher incidence of mechanical and infectious complications has not been shown in comparison with jugular and subclavian sites (LOE 2−, RG 0, conditional recommendation for, consensus)**
R 10.10	**In children, an option of subclavian venous access can be recommended as the risk of mechanical complications does not exceed the rate of complications with other insertion sites under appropriate conditions of insertion (LOE 2−, RG 0, conditional recommendation for, strong consensus)**
R 10.11	**Subclavian insertion can be recommended for long-term use (GPP, conditional recommendation for, strong consensus)**
R 10.12	**In newborns, umbilical vessels can be used for short term PN (GPP, conditional recommendation for, strong consensus)**

CVC are commonly inserted via the internal jugular, subclavian, or femoral veins. The choice of vein is affected by several factors including venipuncture technique, the risk of related mechanical complications, the feasibility of appropriate nursing of the catheter site, the risk of thrombotic and infective complications, duration of anticipated central venous access, and operator experience [7,34]. Overall, there are no randomized controlled trials (RCT) comparing all three sites for CVC placement. Meta-analysis performed in adult studies [35] found that subclavian and internal jugular routes had similar risks for catheter-related complications in long-term catheterization in cancer patients (LoE 1+; adult studies). Subclavian was preferable to femoral insertion for short-term catheterization because femoral insertion was associated with higher risks of catheter colonization and thrombotic complications [35] (LoE 1+; adult studies). No significant differences were found between femoral and internal jugular CVC in catheter colonization, CRBSI and thrombotic complications, but fewer mechanical complications occurred in femoral CVC [35] (LoE 1+; adult studies). According to a recent meta-analysis which included RCT and cohort studies in adults, there were no differences in the incidence of CRBSI between those three sites of vascular access [36] (LOE 1+; adult studies). In children data are more scarce; there is a suggestion that the cannulation of the subclavian vein is more often associated with haemothorax, and that cannulation of the internal jugular vein is associated with a lower risk of pneumothorax, and is more easily compressible if bleeding occurs [37] (LoE 2−). A prospective, multicenter cohort study in children showed an increased incidence of venous thromboembolism with femoral and subclavian compared to jugular CVC [38] (LoE 2−). With regard to infection, a large case−control study of critically ill children found no association between femoral insertion and sepsis [39]. Similarly, in a cohort study of 4512 children, no association was found between femoral CVC placement and greater occurrence of infection, regardless of whether the catheter was placed in the emergency department, PICU or operating room [40] (LoE 2−). Moreover, a retrospective analysis of all the tunneled CVC placed in newborns found that total complication and catheter infection rates were significantly higher in neck lines [41] (LoE 3). For PICC in newborns no significant difference in complications was found between upper versus lower extremity [42] (LoE 2−). However, femoral access is uncomfortable for the child and the consequences of inferior vena cava thrombosis may be severe [14]. Moreover, subclavian insertion means there is a tunneled section of the CVC, and the site can be easily maintained so that it is preferred when longer use is anticipated [43,44].

In neonates umbilical vessel catheterization is often used for short term vascular access [45]. The incidences of catheter colonization and infections are similar for umbilical vein catheters and umbilical artery catheters [45]. Umbilical artery catheters placed above the diaphragm are associated with a lower incidence of vascular complications (LoE 2−) [14]. A recent randomized trial found that long-term umbilical venous catheterization (up to 28 days) resulted in a higher incidence of CRBSI compared with short term catheterization (7−10 days), but the result was not significant and the study was underpowered [46] (LoE 1−). However, there are studies indicating a similar infection rate at day 14 for umbilical venous catheter and PICC lines [47] (LoE 2−). Because there is a lack of quality data (and head to head comparisons) it was decided not to change the previous recommendation on the duration of umbilical catheter use [14].

3.5. Positioning of the catheter tip

R 10.13	**The CVC tip should lie outside the pericardial sac to avoid the risk of pericardial effusion/tamponade (GPP, strong recommendation for, strong consensus)**
R 10.14	**In small infants (body length 47−57 cm) the catheter tip of a jugular or subclavian CVC should lie at least 0.5 cm above the carina on a chest x-ray, while in older/larger infants (body length 58−108 cm) that distance should be at least 1.0 cm (GPP, strong recommendation for, strong consensus)**
R 10.15	**In children, as in adults, we recommend that positioning the CVC tip above the carina means it is likely to be in the superior vena cava and therefore outside the pericardial sac (LOE 3, RG 0, strong recommendation for, strong consensus)**
R 10.16	**The catheter tip of a femoral catheter should lie above the renal veins (first lumbar vertebra) (GPP, strong recommendation for, strong consensus)**

There is continuing debate regarding the optimal position of the catheter tip: the lower third of the superior vena cava, atrio-caval junction or the upper portion of the right atrium [7,48]. Case reports of cardiac tamponade associated with a catheter tip within the right atrium led to the recommendation that the CVC tip should lie outside the pericardial sac [14]. However, in adults erosive perforation has almost exclusively been described for CVC made of more rigid materials and these materials have gradually been replaced by more flexible ones [48]. There are unequivocal data in adults indicating that tip positioning peripherally to the right atrium increases the risk for symptomatic venous thrombosis [49−51]. Taking this into account, adult guidelines recommend that high osmolarity PN should be delivered through a catheter with the tip sited in the lower third of the superior vena cava, at the atrio-caval junction, or in the upper portion of the right atrium [7].

In children, there are reports of cardiac tamponade caused by the CVC eroding into the pericardial sac [52]. The risk is especially increased in preterm neonates where a tamponade incidence of 1.8% was reported even with CVC made of new polyurethane

material [53,54] (LoE 3). Weil et al. reported a pericardial effusion causing pericardial tamponade due to CVC in 1.3% of all children who experienced tamponade and all of these children were newborns [55] (LoE 3). Although rare, cardiac tamponade associated with a CVC is a life threatening complication, and it is therefore advisable that the CVC tip lies outside the pericardial sac and is repositioned whenever necessary.

In adults, the level of the carina can be used as a landmark for CVC tip positioning because the pericardial boundaries are below the tracheal bifurcation [56]. Radiological confirmation that the CVC tip is above the level of the carina reduces the risk of pericardial perforation in adults and older children [14]. In newborns it has been found that the pericardial reflection is located at a distance of 4 mm above to 5 mm below the carina [57] (LoE 3). Therefore, the carina is not a good landmark for newborns and infants; it has been shown that the catheter tip should be localized at least 0.5 cm for smaller infants (body length: 47–57 cm) and 1 cm for older infants (body length: 58–108 cm) above the carina to ensure that it is outside the pericardial sac [58] (LoE 3). Similarly, it has been shown that the mean distance from the carina to the atriocaval junction was 22.0 ± 9.98 mm [59]. In children beyond infancy the carina can be used as a landmark. Optimal catheter tip positioning following femoral vein insertion has not been elucidated, but for long-term use, the catheter tip should be positioned above the entry points of the renal veins (mainly above 1st lumbar vertebra) [14,60] (LoE 3).

3.6. Methods of insertion

R 10.17	**A percutaneous, radiologically or ultrasound guided insertion method may be used since this is equally effective as a surgical cut-down, and carries less risk of complications (LOE 2–, RG 0, strong recommendation for, strong consensus)**
R 10.18	**Ultrasound guidance may be used in order to reduce complications during venous catheterization (LOE 2–, RG 0, strong recommendation for, strong consensus)**

Meta-analyses and randomized controlled trials in adults [61–65] indicate that real-time ultrasound guided venipuncture compared with the anatomic landmark approach has a higher first insertion attempt success rate, reduced access time and higher overall successful cannulation rate. Based on this finding, guidelines for adults recommend real time ultrasound support for all CVC insertions [7]. A meta-analysis of five pediatric randomized trials found that ultrasound guidance decreased the number of punctures required and tended to decrease the time spent accessing the internal jugular vein, however, there was no significant difference in the rate of access failure, arterial puncture or other complications [66] (LoE 1+). Retrospective studies have indicated that ultrasound guided placement and tip position confirmation of lower-extremity CVC at the bedside in critically ill newborns and infants has similar complications and catheter outcomes when compared with fluoroscopic guidance [67] (LoE 2–). Similarly, results of RCTs for PICC placement also show shorter insertion time and fewer manipulations and radiographs when compared with conventional placement [68,69] (LoE 1–).

Methods of CVC insertion (including tunneled catheters) are by percutaneous placement and by surgical cut-down technique. The percutaneous insertion method under radiological surveillance is as effective as the surgical cut-down [70] (LoE 2–). While evidence suggests that tunneled CVC can be successfully placed percutaneously using ultrasound guidance [71–73], in order to minimize complications an experienced team is required [74] (LoE 2–).

3.7. Alternative sites

CVC complications following multiple catheterizations can cause depletion of commonly used venous access sites especially in children requiring long-term PN. Alternative sites for CVC placement include azygous, transhepatic, translumbar, intercostal veins, together with direct right atrial insertion and arteriovenous fistula [75–78] (LoE 3).

4. Interventions to reduce CVC infection

4.1. Antibiotics prior to CVC insertion, and routine catheter exchange

R 10.19	**CVC shall not be changed routinely in order to reduce the risk of sepsis (Extrapolated evidence from adult studies rated as LoE 1+, RG A, strong recommendation against)**
R 10.20	**If a CVC requires removal, replacement rather than exchange over a guidewire decreases the risk of infection. CVC exchange may be reserved for those patients with difficult venous access (Extrapolated evidence from adult studies rated as LoE 3, RG 0, conditional recommendation for, strong consensus)**
R 10.21	**Prophylactic antibiotics do not reduce the risk of CRBSI, therefore they should not be administered (LoE 2+, RG B, conditional recommendation against, strong consensus)**

A systematic review by Lee and Johnston [79] concluded that there was no evidence on which to base recommendations for the degree of barrier precautions or the type of aseptic technique used at the time of catheter insertion. Moreover, there is insufficient evidence to support the use of antibiotic flushes, and a lack of evidence with regard to use of in line filters and frequency of administration set changes with regard to prevention of CRBSI [79]. In line filtration is used to trap particulate contaminants of PN fluids, as well as to retain bacteria in the unlikely event the feed product is contaminated. There is no data relating to an effect of filters on CRBSI or blockage. Some centres have advocated routine changes of CVC after a specified period of time. A meta-analysis of 12 trials failed to demonstrate any reduction in risk of infection [80] (LoE 1+; adult studies); there is no evidence to support this practice in children.

It is possible for a malfunctioning CVC to be taken out and a new catheter inserted via a different site, or removed over a guidewire and replaced by a new device (catheter exchange). In a retrospective review of adult patients, those in the catheter exchange group had 3.2 greater odds of infection compared with the catheter replacement group [81] (LoE 3). The authors suggested reserving catheter exchange for those patients with very limited venous access.

Use of antibiotic prophylaxis prior to CVC insertion is controversial. In adult cancer patients, a systematic review or prophylactic antibiotics for preventing early Gram-positive infection indicated no benefit from vancomycin/teicoplanin prior to catheter insertion, but a possible role for flushing with heparin and vancomycin [82] (LoE 2++). One case control study in children suggested that peri-operative administration of antibiotics reduced the risk of early CVC infection [83] (LoE 2–). A systematic review by Huang et al. concluded however that there is no benefit from systemic prophylactic antibiotics at the time of catheter insertion [84] (LoE 2++).

4.2. CVC locks and flushes

R 10.22	**Antibiotic line locks should not be used for treating catheter related blood stream infection (CRBSI) as these have not been shown to be effective (LoE 1−, RG B, conditional recommendation against, strong consensus)**
R 10.23	**Antibiotic line locks can be used in conjunction with systemic antibiotics to assist in the eradication of CRBSI in some patients (LoE 3, RG 0, conditional recommendation for, strong consensus)**
R 10.24	**Ethanol line locks may be considered for preventing CRBSI (LoE 3, RG 0, conditional recommendation for, strong consensus)**
R 10.25	**Taurolidine is effective in preventing CRBSI and should be used during long term catheter use (Extrapolated evidence from adult studies rated as LoE 1+, RG B, strong recommendation for, strong consensus)**

Rather than removing an infected CVC, attempts have been made to fill the catheter with a high concentration of antibiotic and leave for a specified period of time with the intention of sterilizing the internal lumen. In a systematic review (largely of adult patients) the authors concluded that antibiotic locks could not be endorsed because the antibiotics tested were heterogeneous, outcome measures were non-specific, and the estimated effect of marginal significance [85] (LoE 1−).

In a randomized double blind study in very low birth weight critically ill infants, PICC were locked 2−3 times daily for 20 or 60 min with either heparinized normal saline or heparinized saline containing vancomycin [86]. There was a significant reduction in CRBSI in the vancomycin lock group (2.3 v 17.8/1000 catheter days) but asymptomatic hypoglycemia was noted in 26/85 patients at the end of the lock period (LoE 1+). A Cochrane review found only 3 studies in neonates (including ref 86) and suggested antibiotic lock might decrease infection risk by 18.5% without increasing risk of hypoglycemia (LoE 1−) [87].

A recent meta-analysis of anti-microbial line lock solutions mostly in adult patients suggested a potential 67% reduction in CRBSI [88]; line locks under investigation included a variety of different antibiotics, taurolidine and ethanol (LoE 1−).

Ethanol is an antiseptic and commonly used to sterilize catheter hubs. Studies of ethanol line locks to prevent CRBSI are mostly small and retrospective, but do suggest a positive effect [89,90] (LoE 3). A meta-analysis of studies comparing heparin and ethanol locks suggested that use of ethanol reduced CRBSI by 81% and need for CVC replacement by 72% [91]. Ethanol and heparin together may cause a precipitate, and ethanol can be damaging to catheters. In a group of seven children with intestinal failure, a retrospective study suggested that 70% ethanol used as a line lock on a daily basis compared with heparin saline decreased CRBSI rates from 10.3 to 1.4/1000 catheter days [92] (LoE 3); there was, however, an increasing trend in CVC thrombosis and need for catheter repair (LoE 3). In a randomized trial involving 307 paediatric oncology patients with CVC, 2 h ethanol lock was compared with heparin at a maximum frequency of once a week; infection rate was 10% in the ethanol and 19% in the heparin groups (LoE 1+) [93].

Taurolidine is a potent anti-septic agent derived from the amino acid taurine, and is active against a wide range of micro-organisms, both Gram negative and positive bacteria, and fungi. It is used as a line lock to prevent CVC sepsis, together with citrate to prevent catheter blockage. A systematic review of the literature (largely observational studies) concluded that it deserved further investigation before use could be recommended [94]. In a retrospective review of children on home PN, CRBSI rate was examined before and after the introduction of taurolidine; catheter sepsis rate fell from 8.6/1000 catheter days with heparin as line lock to 1.1/1000 with taurolidine [95] (LoE 3). Similarly, in high risk adult home PN patients, a retrospective study of taurolidine suggested a reduction from 5.71 to 0.99 episodes of CRBSI per 1000 patient PN days [96] (LoE 3). Bisseling et al. conducted a prospective randomized trial of adult home PN patients who had previously suffered an episode of CRBSI; patients were given either taurolidine or heparin (controls) [97]. Re-infections occurred in 10/14 heparin controls, while there was only one episode of sepsis in a patient randomized to taurolidine during a total of 5370 days of home PN (LoE 1+). In a trial of taurolidine versus heparin in children with cancer, 129 tunneled CVC were randomized [98]. The rate of CRBSI was 0.4/1000 catheter days in the taurolidine group and 1.4/1000 in the controls (LoE 1+). The authors concluded that taurolidine significantly reduced the risk of CRBSI. In a retrospective study of adult home PN patients over an 11 year period during which use of taurolidine became standard, CRBSI occurred 1.1 times/1 year of PN with heparin line lock and 0.2 times with taurolidine [99]; CVC occlusion was halved with taurolidine. In patients using taurolidine who still get recurrent infections, no evidence of adaptation of organisms (i.e. resistance to taurolidine) has been found [100]. A number of different taurolidine products are available including 2% solution, 1.34% with citrate, and 1.34% with citrate and heparin. An investigation into their relative efficacy [101] showed equal effectiveness in killing *Escherichia coli, Staphylococcus aureus* and *Candida glabrata*, with no difference in their effects on the catheter biofilm [101]. In a study of pediatric patients with cancer, Handrup et al. found use of taurolidine was associated with reduced risk of CRBSI compared with heparin, but electron microscopy of removed CVC found no difference in intraluminal biofilm formation or catheter colonization [102]. Some free fatty acids have antithrombotic and antimicrobial properties. Luther et al. [103] conducted an in vitro investigation of different line locks including a novel free fatty acid emulsion ML8-X10. This demonstrated activity against biofilm-forming *Staphylococci* similar to or greater than that of vancomycin. Taurolidine was the most active lock solution at 8 and 24 h, but all three demonstrated high activity at 72 h.

5. Interventions to decrease thrombotic complications and CVC occlusion

R 10.26	**Routine use of heparin for the prevention of thrombotic occlusion in CVC being used regularly in children cannot be recommended over use of saline flush due to lack of proven benefit (LoE 2−, RG 0, conditional recommendation against)**
R 10.27	**For CVC that are being accessed intermittently, flushing with 5−10 U/mL heparinized saline 1−2 × weekly helped maintain patency and therefore can be recommended (Extrapolated evidence from adult studies rated as LoE 2−, RG 0, conditional recommendation for, strong consensus)**
R 10.28	**Routine use of heparin has been shown to be effective in prevention of PICC occlusion in newborns, but since the potential risks have not been defined, its routine use cannot be recommended (LoE 3, RG 0, recommendation for research, strong consensus)**
R 10.29	**Recombinant tissue plasminogen activator or urokinase shall be used to unblock a catheter (LoE 1+, RG A, strong recommendation for, consensus)**
R 10.30	**There is insufficient evidence to advocate the prophylactic use of anticoagulants in children receiving home parenteral nutrition to reduce catheter related thrombosis, occlusion and infection (LoE 3, RG 0, strong recommendation against, strong consensus)**

Catheter-related thrombus occurs at the CVC tip and where the CVC enters the vein wall. Thrombus can lead to catheter blockage or

thromboembolism. The pediatric and adult literature reports a wide range of catheter-related thrombus formation (often subclinical), from 0.4% to 61% [104] (LoE 2−). Risk factors include length of catheter, low ratio of catheter and vessel diameter, and long indwelling time. Valved and tunneled catheters (i.e. Groshong) were expected to prevent thrombus formation at the tip by preventing backflow of blood into the lumen; this was not confirmed in clinical practice [105,106] (LoE 1−). CVC are the most frequent cause of venous thromboembolism and are responsible for over 80% of thromboembolism in newborns and 40% in other children [107]. CVC thrombosis is one of the most clinically significant complications of PN [107,108] (LoE 2+). Risk factors for thrombosis include endothelial damage during catheter placement, blood vessel occlusion, low flow states, blood stasis, turbulent flow, hyperviscosity or hypercoagulability, catheter composition, and characteristics of patients and infusates [109,110] (LoE 3). Adult oncology patients are known to be at high risk of CVC related thrombosis. In a large trial involving 1590 such patients, randomization was to no warfarin, warfarin at fixed dose, or warfarin to maintain an international normalized ratio between 1.5 and 2.0 [111]. There was no demonstrable reduction in symptomatic catheter related or other thromboses in patients given warfarin (LoE 1+). Schoot et al. [112] reviewed three randomized controlled trials and three controlled clinical trials of systemic treatment (low molecular weight heparin, antithrombin supplementation or low dose warfarin) and found no significant effects compared with no intervention in preventing venous thromboembolic events in pediatric cancer patients with tunneled CVC, and no differences in adverse events. In an investigation of the role of prophylactic anticoagulation in children receiving home PN, Vegting et al. [113] compared outcomes with retrospective data from a time when their patients did not receive this treatment. Sixteen children received low molecular weight heparin (nadoparin) and two vitamin K antagonists. CVC related thrombosis developed in 9 (33%) of patients with no prophylaxis, and 1 (6%) of patient with prophylaxis. Cumulative five-year thrombosis free survival was 48% and 93% respectively. Per 1000 PN days, CVC occlusion for non-prophylaxis and prophylaxis patients were 2.6 and 0.1, and for CRBSI 4.6 and 2.1. No complications (including bleeding) were observed with anticoagulation.

Heparinisation has been suggested as a way of prolonging CVC patency as well as reducing the risk of thrombosis and embolism [114,115] (LoE 2+); there is little new evidence since the first edition of these PN guidelines. Heparin is a glycosaminoglycan with anticoagulant effects mediated through its interaction with antithrombin III, accelerating its ability to inactivate coagulation enzymes (thrombin, factor Xa and factor IXa) [116]. Giving heparin during PN has the following theoretical advantages:

1. Anticoagulant action − besides reducing CVC fibronectin deposition, heparin makes the catheter hydrophobic, giving it a negative charge, both effects potentially influencing catheter thrombogenicity [109,117,118].
2. Prevention of infection − a thrombus or the biofilm in the internal lumen of the catheter may serve as a nidus for microbial colonization [119,120]. Heparin bonded catheters are reported to decrease bacterial adherence [121] as well as lowering the incidence of positive blood cultures, possibly by lowering the incidence of thrombus [109], or reducing the number of organisms attached to the surface of the catheter [117].
3. Activation of lipoprotein lipase − given in infusion, heparin also activates lipoprotein lipase and increases lipolysis and re-esterification of infused triglycerides, but has no effect on lipid oxidation and net energy gain [122–125].

There are, however, potential disadvantages:

1. Bleeding, thrombocytopenia, allergic reactions, osteoporosis, all of which may result in harm [116,126–128] (LoE 2+); in premature newborns who are unique in their resistance and sensitivity to heparin [129], there may be an increased risk of intraventricular hemorrhage [130] (LoE 2+). Both low molecular weight heparin and heparin when used as a catheter coating are associated with these complications, and the risk is even higher if unfractionated heparin is given [127,131,132] (LoE 1−).
2. Destabilization of lipid emulsions − calcium and heparin can destabilize lipid emulsions so that coalescence of fat droplet occurs with lipid emboli [133]. This is unlikely to be a problem if low heparin concentrations are used (0.5–1.0 U/mL) (LoE 2−) and is reduced if mixing of lipid emulsion and PN solution occur as close to the CVC as possible, and by co-administration of vitamin preparations [134] (LoE 2−).

Unresolved questions in relation to heparin include whether to use or not; if yes − how much, and whether to give as a flush or infusion? In practice there is considerable variation [135–141] with, for example, flushes given from twice a day to once every three weeks. Boluses in children often contain 200–300 U of heparin, and for infants weighing <10 kg, a dose of 10 U/kg is frequently used [131]. In a meta-analysis evaluating the benefits of heparin prophylaxis (3 U/mL in PN solution; 5000 U every 6–12 h flush or 2500 U of low molecular weight heparin subcutaneously) the risk of CVC thrombosis was significantly reduced. Although bacterial colonization was also reduced, no reduction in the rate of catheter related infection was seen [142] (LoE 1−; adult studies). Only one of these 11 studies involved children; in this randomized cross-over study, there were no difference in the incidence of blocked catheters or other complications comparing twice daily flushes with heparin with once weekly saline [136] (LoE 2−). Another randomized double-blind study in children compared saline infusion with or without 1 U/mL heparin and found no significant effect on catheter patency [143] (LOE 2−), although there was a trend to fewer blockages in the heparin group. Neither study was sufficiently powered to draw firm conclusions. In a study of implantable venous access devices in adult cancer patients, randomization was to saline flush or heparin saline (100 U/mL) [144]. The device was flushed before and after blood sampling, at the end of IV therapy, after blood transfusion or PN, or every eight weeks if not in use. No differences were found in frequency of port malfunction or sepsis (LoE 1−). Conway et al. performed a systematic review of CVC flushing in pediatric oncology patients [145]. Once daily flushing of Broviac/Hickman catheters (when not in use for infusing fluids) with 10 U/mL heparin was widely used but with little evidence to support. A Cochrane review in adult patients comparing heparin with normal saline flushes found no convincing difference in maintaining CVC patency [146]. After a change in practice, Rosenbluth et al. [147] explored the effect of using 100 U/mL v 10 U/mL heparin solution for flushing implantable vascular ports in pediatric oncology patients, and found no difference in complication rates.

A systematic review on the prophylactic use of heparin for prevention of complications in PICC for newborns by Shah et al. [148] indicated that use of heparin decreased the frequency of CVC occlusion but studies were not adequately powered to assess the potential risks (LoE 1−). Subsequently a trial was performed showing that use of 1 U/mL heparin was not associated with any differences with respect to blocked or infected catheters, hypertriglyceridaemia, hyperbilirubinaemia, coagulopathy or intraventricular hemorrhage [149] (LoE 2+). It seems unlikely that use of heparin (with the aim of maintaining catheter patency in newborns

and infants) has any impact on risk of thrombosis [150,151] (LoE 4). In a recent Cochrane review comparing heparin-bonded and non-heparin bonded CVC [152], two eligible studies were included. The mean duration of CVC use was only one week, and there was no difference in catheter related thrombosis. One study showed a significant reduction in CVC occlusion, CRBSI and CVC colonization.

Baskin et al. reviewed the management of catheter occlusion or thrombosis [153]. For blocked central venous infusion devices, a double blind randomized trial demonstrated the superiority of urokinase (5000 U/mL) via the catheter lumen over placebo with patency restored in 54% and 30% of catheters [154] (LoE 1+). Other than this study there is little data to support evidence−based recommendations for unblocking CVC. Van Miert and colleagues found seven studies that investigated different strengths of thrombolytic and anticoagulant drug interventions for treating catheter occlusion thought to be caused by thrombus [155]. The quality of evidence was low but urokinase appears to be more effective than placebo in restoring patency. Following a review of the adult and paediatric literature on management of CVC occlusion and CVC related thrombosis, Giordano et al. recommended that either tissue plasminogen activator or urokinase be used for unblocking thrombosed CVC. (LoE 2++) [156].

6. Hygiene and antisepsis on CVC insertion and during subsequent care

R 10.31	**Appropriate hand hygiene procedures should be followed before accessing the intravascular device or the insertion site (Extrapolated evidence from adult studies rated as LoE 1+, RG B, strong recommendation for, strong consensus)**
R 10.32	**Before insertion of an intravascular device and for post-insertion site care, clean skin should be disinfected with 2% chlorhexidine solution in 70% isopropyl alcohol (Extrapolated evidence from adult studies rated as LoE 1, RG B, strong recommendation for, strong consensus)**
R 10.33	**Antiseptic solution should remain on the insertion site and be allowed to air dry before catheter insertion or dressing application (GPP, strong recommendation for, strong consensus)**
R 10.34	**Due to potential side effects, skin antisepsis with chlorhexidine in infants younger than two months cannot be recommended (LOE 2−, RG 0, conditional recommendation against)**
R 10.35	**Catheter connectors, ports and hubs should be disinfected before accessing, preferably with 2% chlorhexidine solution in 70% isopropyl alcohol (LoE 2+, RG B, strong recommendation for, strong consensus)**

Migration of microbes from the skin surrounding the insertion site is the commonest route for catheter colonization and subsequent infection in short-term CVC [157]. In tunneled CVC the most important source are direct contacts with contaminated hands of health care providers, contaminated devices and fluids [158]. Therefore, appropriate hand, skin and catheter hygiene on insertion and on all subsequent contacts before, during and after CVC manipulations, cleansing, setting up the PN infusion and dressing exchange are crucial for prevention of infectious complications. How to perform hand hygiene, regarded as the most scientifically sound and cost-effective method for infection prevention, is described elsewhere [7,45,159] (LoE 1+).

Chlorhexidine-based antiseptic solutions, particularly as 2% chlorhexidine gluconate in 70% isopropyl alcohol, have been confirmed in adult patients as the most effective way of removing micro-organisms from the skin surface before catheter insertion and during subsequent catheter care [84,160,161] (LoE 1+). Pediatric studies have considered the possible side effects of systemic chlorhexidine absorption and skin irritation in preterm babies and critically ill newborns. In their pilot trial, Garland et al. did not identify contact dermatitis as an important problem. However, chlorhexidine was present in the blood of five out of ten treated infants after the first application and in seven of ten patients at some time during the study [162]. Visscher et al. reported that skin erythema and dryness occurred in their NICU patients most frequently when chlorhexidine was used in conjunction with an adhesive dressing [163], and Andersen et al. found erythema present only in preterm infants with BW less than 1000 g (4/36 study neonates − 11%) [164]. Therefore, the use of chlorhexidine in infants younger than two months of age is not recommended on the basis of the present evidence, and awaits further studies (LoE 2−). With the aim to prevent the skin damage, aqueous solution of octenidin has been used and recommended in some European countries for children younger than 2 months [165]. However, it is well documented that water based solutions are less efficacious than alcohol-based products [166], and the evidence to support the aqueous solution of octenidin in preterm neonates for successful skin antisepsis is almost non-existent [167]. Moreover, a recent survey on the use of octenidin in German NICU has documented that skin complications were also frequent (reported in 27% of patients), and that their prevalence did not differ with respect to the type of octenidin solution used (aqueous *vs.* octenidin + phenoxyethanol *vs.* alcohol-based octenidin product) [168].

Catheter connectors, ports and hubs are important entry sites for intraluminal contamination, and should therefore be accessed in a sterile way and disinfected prior to access. Besides studies in adult patients, two recent pediatric trials showed that addition of 2% chlorhexidine to 70% isopropanol resulted in significantly decreased number of positive blood cultures compared to disinfection with 70% alcohol only [169,170] (LoE 2+).

7. Dressing methods

R 10.36	**Both sterile gauze with tape and transparent semi-permeable polyurethane dressing can be used to cover the catheter insertion site (LoE 3, RG 0, conditional recommendation for, strong consensus)**
R 10.37	**Sterile gauze dressing is preferable if the catheter site is bleeding or oozing (GPP, conditional recommendation for, strong consensus).**
R 10.38	**For short term CVC, site dressings should be replaced every 2 days for gauze dressing, and every seven days for transparent dressing (LoE 2−, RG 0, conditional recommendation for, strong consensus)**
R 10.39	**A dressing should be changed sooner if it becomes damp, loosened or soiled (GPP, strong recommendation for, strong consensus)**
R 10.40	**A tunneled CVC with a well-healed exit site does not require dressing to prevent dislodgement, however, in children it is useful to have them looped and covered (GPP, conditional recommendation for, strong consensus)**
R 10.41	**Chlorhexidine-impregnated dressing should be considered in patients older than two months with short-term catheters who are at high risk for infection (LoE 2+, RG B, strong recommendation for, strong consensus)**
R 10.42	**Topical antimicrobial treatment at the insertion site cannot be routinely used as it may promote fungal infection, antimicrobial resistance and damage the surface of the catheter (LoE 3, RG 0, strong recommendation against, strong consensus)**
R 10.43	**Children with well-healed tunneled catheters may be allowed to swim, provided that a water resistant dressing is used to cover the whole catheter. Immediately after swimming the catheter exit site should be cleaned and disinfected, and the dressing changed (GPP, conditional recommendation for, strong consensus)**

The purposes of a dressing are to secure the CVC, protect it from external contamination, and prevent trauma and dislodgement. Traditionally, the CVC insertion site was dressed with dry sterile gauze and tape. This method gave way to a transparent dressing

composed of a thin polyurethane membrane coated with a layer of acrylic adhesive. Potential advantages include improved security, visibility of the insertion site, provision of a barrier to colonization, and therefore, less frequent need for dressing changing. However, studies have indicated that transparent polyurethane dressing may increase skin surface humidity resulting in increased colonization of the insertion site and of the catheter. To enable better evaporation, highly permeable polyurethane dressings have been developed. Numerous studies have examined the differences between dressing regimens. A recently updated Cochrane Systematic Review by Webster J et al. [161], summarized the results of RCT in hospitalized children and adults that evaluated the effect of the dressing type on CVC-related infection, catheter security, tolerance and dressing condition. Six studies were included, four of which compared gauze and tape to transparent polyurethane dressings, while two compared different types of polyurethane dressings. With respect to CRBSI and other outcomes there were no differences between the highly and less permeable transparent polyurethane dressings. However, when compared with sterile gauze and tape, a four-fold increase in CRBSI was found with use of polyurethane dressing (OR 4.19). Despite this apparently large difference in favor of gauze and tape, the authors commented that the trials were small and of poor quality, with a high risk of bias and wide confidence intervals (95% CI 1.02–17.23) such that better quality research would be required to confirm this finding [171] (LoE 1−).

Optimum frequency of dressing changes for short-term CVC is another unresolved issue. Based on the evidence summarized elsewhere, it has been suggested that gauze dressings are exchanged every 2 days and transparent dressings at least every 7 days [45] (LoE 2−). However, a recent Cochrane review suggested that evidence on the frequency of dressing changes is inconclusive with respect to the frequency of catheter-related infection, mortality or pain [172].

Recently published evidence-based recommendations, reviews and meta-analyses summarized the evidence for the use of chlorhexidine-impregnated dressings both in adult [7,45] and pediatric patients [45,84,173], concluding that they are effective in reducing contamination of the catheter insertion site and the tip (LoE 1+). Moreover, subsequent randomized trials in adult patients have shown that chlorhexidine impregnated sponge dressings also decrease the incidence of CRBSI [174,175]. With respect to pediatric patients, a substantial risk of contact dermatitis at the dressing site limits their use in very low birth weight infants, as has already been addressed in the previous edition of this guideline [176] (LoE 1+). Since the chlorhexidine impregnated sponge is designed to release the antiseptic material onto the skin maximally in the first three days, followed by a slower release within the next week, this dressing type is recommended for use with short term CVC [7,45].

Children on long-term home PN and their families are restricted in many ways. They should be encouraged to undertake normal daily activities whenever possible as long as this does not pose an increased risk. Recreational swimming including submerging the well healed tunneled CVC in water would be a welcome activity, however, according to a recent review which aimed to evaluate the risk of catheter-related infections after swimming, the existing evidence is of low quality and cannot support a recommendation that swimming with tunneled CVC is safe [177] (LoE 3). In the same article, the authors investigated the current practice of home PN programs in the United States. Only 3/16 home PN programs that responded to the survey did not allow swimming of any sort. The others differed with respect to allowing swimming in the ocean and private pools only, or including hot tubs, etc. Instructions on the procedures to be followed before and after swimming were also inconsistent; most recommended the use of a transparent dressing to cover the whole catheter during swimming, and immediately after swimming to clean the site and to change the dressing [177] (LoE 3).

8. Multimodal strategies for prevention of CVC-related complications

R 10.44	**Regular training and education of healthcare staff with respect to catheter insertion and maintenance should be recommended (LoE 2+, RG B, strong recommendation for, strong consensus)**
R 10.45	**Multimodal protocols for health care providers, aiming to standardize clinical practice on insertion and maintenance of the intravascular devices, should be developed and regularly audited (LoE 2+, RG B, strong recommendation for, strong consensus)**

Most of the guidelines identify and address scientific evidence on single topics. Recently, multimodal protocols (“bundles”) have been developed within hospitals in which different strategies are applied together to improve clinical performance and compliance with the guidelines. Such “bundles” provide instructions on who should have access to intravascular devices, methods of staff education and training, procedures on insertion and catheter maintenance, etc. There is good evidence in adults [178–180] and in children [181,182] although coming mostly from “before and after” studies, that standardization of catheter related care results in clinically relevant and persistent reduction in the incidence of complications (LoE 2+).

Conflict of interest

None declared.

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Clinical Nutrition 37 (2018) 2392–2400

Contents lists available at ScienceDirect

Clinical Nutrition

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ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Organisational aspects

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

Literature search

Timeframe: publications from 2004 until December 2017 were considered

Type of publications: randomized trials, observational studies (case-controls, prospective cohort studies, case series, retrospective data), meta-analyses, systematic reviews

Key words: nutrition support; nutrition assessment; nutrition team; nutrition and monitoring; nutritional rehabilitation; parenteral nutrition and filter; infusion pumps; anthropometry and parenteral nutrition; nutrition and ordering

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https://doi.org/10.1016/j.clnu.2018.06.953
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Table: Recommendations on organizational aspects of parenteral nutrition

R 11.1	Supervision of nutritional support in intestinal failure may be provided by a multidisciplinary nutritional support team (LoE 2−, RG 0, strong recommendation for)
R 11.2	Accurate anthropometrics and thorough clinical evaluation of patients receiving PN may be undertaken by a skilled practitioner (GPP, strong recommendation for)
R 11.3	The frequency of laboratory assessment may be based on patient's clinical condition (from once daily to 2−3 times per week) (LoE 4, RG 0, strong recommendation for)
R 11.4	All PN solutions may be administered with accurate flow control; the infusion system should be under regular visual inspection; peripheral infusions should be checked frequently for signs of extravasation or sepsis; the pump should have free flow prevention if opened during use, and have lockable settings (GPP, strong recommendation for)
R 11.5	PN solutions may be administered through a terminal filter: lipid emulsions (or all-in-one mixes) can be passed through a membrane pore size of 1.2 −1.5 μm; aqueous solutions can be passed through a 0.22 μm filter (GPP, strong recommendation for)
R 11.6	PN solutions for the premature newborns should be protected against light in order to prevent generation of oxidants (LoE 1−, RG B, strong recommendation for)
R 11.7	Cyclical PN may start once patients are in a stable clinical condition and can maintain normoglycaemia during a period without PN infusion (GPP, strong recommendation for)
R 11.8	In order to prevent hypo/hyperglycaemia infusion rate may be tapered up gradually during the first 1−2 h and tapered down during the last 1−2 h of infusion when cyclic PN is administered (GPP, strong recommendation for)
R 11.9	Complete enteral starvation (i.e. 'TPN') may be avoided by giving some enteral feed whenever possible, even if only a minimal amount is tolerated (GPP, strong recommendation for)
R 11.10	When increasing enteral feed, only one change at a time may be made, to assess tolerance (GPP, strong recommendation for)
R 11.11	In severe intestinal failure, feed volumes may be increased slowly, according to digestive tolerance (GPP, strong recommendation for)
R 11.12	Enteral feeding may be introduced as a liquid feed infused continuously by tube over 4−24 h periods, using a volumetric pump (GPP, conditional recommendation for)
R 11.13	Bolus liquid feed may be given via feeding tube, or by mouth as sip feed if tolerated (GPP, conditional recommendation for)
R 11.14	Children who rapidly recover intestinal function may be weaned straight onto normal food (GPP, conditional recommendation for)
R 11.15	In newborns and infants with intestinal failure breast milk may be the enteral feed of first choice (GPP, strong recommendation for)
R 11.16	If breast milk is not available, the choice of substitute can be based on clinical condition; in early infancy and severe illness it is reasonable to start with elemental formula, switching to extensively hydrolysed and then to polymeric feeds (GPP, strong recommendation for)
R 11.17	Enteral feed may be given at normal concentrations (i.e. not diluted) (GPP, conditional recommendation for)
R 11.18	PN should be reduced in proportion to, or slightly more than the increase in EN (GPP, conditional recommendation for)
R 11.19	If a chosen weaning strategy fails, try again more slowly (GPP; conditional recommendation for)

Language: English

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. 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.

2. Ordering and monitoring parenteral nutrition in hospital

2.1. Introduction

The purpose of parenteral nutrition (PN) is to correct or prevent nutritional deficiencies when adequate enteral nutrition is precluded by impairment or immaturity of gastrointestinal function. Having identified a patient in need of PN, the process of ordering and monitoring is aimed at ensuring safe and effective nutritional support. Provision of PN should be part of an overall nutritional care plan that includes detailed nutritional assessment. Nutritional goals should be set, and an estimate made of the probable duration of PN. The whole process is dynamic: ongoing nutritional support should reflect changes in nutritional and clinical status and be overseen by a multidisciplinary nutrition team.

2.2. Nutrition support teams

R 11.1	**Supervision of nutritional support in intestinal failure may be provided by a multidisciplinary nutritional support team (LoE 2−, RG 0, strong recommendation for, strong consensus)**

A multidisciplinary nutrition support team (NST; e.g. doctor, nurse, dietitian/nutritionist, pharmacist, etc.) has an important role in promoting and coordinating optimum nutritional care, educating staff, developing guidelines, promoting research [1] (LoE 2−) and reducing inappropriate use of PN [2] (LoE 2−). A team approach to nutritional support was associated with a reduction in catheter related blood stream infection rates in a number of different studies involving adult patients [3−8] (LoE 2−). Staff training by a nutrition nurse reduces the prevalence of catheter sepsis in infants [9] (LoE 2−). Other aspects of quality of care such as monitoring of nutritional status and assessment of requirements [8] are improved by a multidisciplinary approach [8,10] (LoE 2−). Savings made can more than justify the appointment of specialised staff such as nutrition nurse and dietitian [11] (LoE 2−). Experience in paediatric intensive care suggests introduction of a NST both decreases inappropriate use of PN in favour of enteral feeding and reduces mortality [12] (LoE 2−). In other settings it may be difficult to clearly document improvements in nutritional management, sometimes because of clinical factors that cannot be easily overcome [13]. Implementation of a NST has been recommended by the ESPGHAN Committee on Nutrition [14], and teams can play an important role in raising awareness of the importance of nutritional management throughout the paediatric department [15]. Outcome for patients with PN dependent intestinal failure (IF) appears to be improved by management under a multidisciplinary team [16] (LoE 2−) and such an approach is to be encouraged [17−21]. A NST is also essential for facilitating and supporting home parenteral nutrition [22,23].

2.3. Nutritional assessment

R 11.2	**Accurate anthropometrics and thorough clinical evaluation of patients receiving PN may be undertaken by a skilled practitioner (GPP, strong recommendation for, strong consensus)**
R 11.3	**The frequency of laboratory assessment may be based on patient's clinical condition (from once daily to 2−3 times per week) (LoE 4, RG 0, strong recommendation for, strong consensus)**

A multidisciplinary NST should oversee the process of PN [24] and patients be regularly nutritionally assessed. This provides a baseline of nutrition parameters, determines nutrition risk factors, identifies specific nutrition deficits, establishes nutrition needs for individual patients, and identifies factors that may influence the prescribing and administering of nutrition support therapy [25]. Nutritional assessment is divided into clinical examination, anthropometry, laboratory indices, and assessment of dietary intake [24].

2.3.1. Clinical examination

Clinical examination gives an important overall impression of health and includes the general appearance and activity level of the patient [24]. Monitoring parameters include vital signs and thorough physical assessment, together with clinical indicators of fluid and nutrient excess or deficiency [25].

2.3.2. Anthropometry

There should be accurate measurement of anthropometric variables such as weight, length/height and head circumference [24,26]. Anthropometric measures are reported with reference to population data, and plotted on appropriate growth charts. These charts include, in children <36 months of age: length-for-age, weight-for-age, head circumference-for-age, and weight-for-length, and in children ages 2–18 years: standing height-for-age, weight-for-age, and body mass index (BMI)-for-age and BMI centile (LoE 2+) [27]. Measures are usually expressed as percentiles or standard deviation scores (SDS). SDS allow changes over time to be detected more easily than with percentiles, which do not so readily reveal the precise degree of deviation from population norms [24].

Anthropometric measures have some limitations, for example, severe illness is often associated with fluid retention and oedema making weight measurements unreliable. Therefore, an assessment of fluid intake and output should accompany an evaluation of weight gain to determine whether the source of the weight is an increase in fluid or lean body mass [25]. Alternative anthropometric tools have been proposed for assessing malnutrition in patients affected by lower extremity oedema, ascites, steroid treatment or large solid tumour mass. Mid upper arm circumference (MUAC) may be a better indicator than weight for classification of acute malnutrition (LoE 2+) [26–29]. MUAC together with triceps skin fold thickness allows calculation of mid arm fat and muscle area, giving an insight into body composition [24]. Measurements should be undertaken by a trained and experienced individual such as dietician or nutrition support nurse, using standardized techniques. Serial measurements show changes over time and therefore provide a dynamic picture. The frequency of monitoring will depend on gestational age, postnatal age, underlying disease, severity of illness, degree of malnutrition, and level of metabolic stress [25].

2.3.3. Laboratory assessment

Besides laboratory investigation of baseline metabolic status before ordering PN, some laboratory data can be used as a marker of nutritional assessment. Routine electrolyte, mineral (calcium, phosphorus and magnesium), triglyceride and serum urea determination help to determine nutritional deficiencies (LoE 2+) [30]. Some laboratory tests which relate to visceral protein concentrations (e.g. haemoglobin, total lymphocyte count) help in the identification of malnutrition (LoE 2+) [31]. Proteins with the shorter half-life (i.e. pre-albumin or retinol-binding protein) when sequentially assessed reflect improving nutritional status better than albumin (LoE 2+) [32]. In hospitalised patients, albumin is most commonly low as part of an acute phase response to inflammation and redistribution of protein so that hypoalbuminaemia should not be attributed to malnutrition. No single protein is ideal as an indicator of nutritional status since they are all affected by other non-nutritional physiological and pathologic states [24]. Other laboratory tests, such as the nitrogen excretion, nitrogen balance and plasma amino acid profile can help characterize protein deficit [33] but are not commonly used in clinical practice. Serum vitamin and trace element concentrations should be evaluated in long-term PN dependent patients (LoE 4) [25]. Daily monitoring may be required for newborns, infants, critically ill patients, those at risk of refeeding syndrome, patients transitioning between PN and enteral feeding, or those that have experienced complications associated with nutritional therapy (LoE 4) [25]. In clinically stable children, measurements may be repeated 2–3 times per week (LoE 4) [24].

2.3.4. Dietary intake

Nutritional assessment must include estimates of dietary and fluid intake (oral, enteral, and parenteral), output (urine, gastrointestinal losses), and a record of gastrointestinal symptoms. Information should be sought with respect to religious restrictions and food preferences or aversions [24,25].

2.4. PN ordering

Accepted goals for PN include prevention or correction of weight loss, and maintenance of normal growth. Any professionals ordering PN should be trained in its indications, complications and administration [34] and the whole process of PN (prescribing, compounding, delivering and monitoring) standardized as far as possible in order to decrease risk and promote effectiveness [35–37]. Protocol driven implementation of nutrition therapy may lead to better outcomes and has, for example, been shown to help preserve lean body mass in intensive care patients [38,39] (LoE 3). Electronic ordering systems can reduce the risk of prescription errors [40] and use of a standardised electronic PN ordering system or an order template as an editable electronic document is recommended [41]. The process of ordering requires very close collaboration between physician, clinical pharmacist and dietitian. In some centres, prescribing of PN has been passed from doctors to an experienced and trained pharmacist working with the NST [42]. Reference to established guidelines for ordering and managing PN encourages appropriate selection of patients and tailoring prescriptions to the particular needs of individuals [24]. Clinical practice guidance as an aide memoire can be included on PN ordering forms [43]. The whole process of PN requires audit and critical scrutiny since life threatening errors may occur during prescribing, transcription (conversion of prescription to volumes of additives in pharmacy), dispensing, delivery to wards, and during the administration process (incorrect infusion rates) [44].

2.5. Infusion equipment and in line filters

R 11.4	**All PN solutions may be administered with accurate flow control; the infusion system should be under regular visual inspection; peripheral infusions should be checked frequently for signs of extravasation or sepsis; the pump should have free flow prevention if opened during use, and have lockable settings (GPP, strong recommendation for, strong consensus)**
R 11.5	**PN solutions may be administered through a terminal filter: lipid emulsions (or all-in-one mixes) can be passed through a membrane pore size of 1.2–1.5 μm; aqueous solutions can be passed through a 0.22 μm filter (GPP, strong recommendation for, strong consensus)**
R 11.6	**PN solutions for the premature newborn should be protected against light in order to prevent generation of oxidants (LoE 1−, RGB, strong recommendation for, strong consensus)**

One of the greatest hazards to patients during administration of intravenous nutrition arises from the risk of free flow or poor rate control of the infusion. To the potential risks of fluid overload and heart failure are added complications such as hyperglycaemia, hyperkalaemia and hyper-triglyceridaemia. A modern infusion pump with the capability to accurately deliver at low flow rates should be used whenever possible [45,46] (LoE 4). Alarm functions are essential, but sensitivity is often limited at low rates of flow. The ability of children to learn to manipulate devices and interfere with settings should not be underestimated. If pumps are not available, the use of portable, battery powered drop counting devices can provide effective warning of free flow conditions. New 'smart pumps' can be programmed so that starting and finishing infusion rates increase and decrease respectively when delivering cyclical PN in order to prevent hyper- and hypoglycaemia.

PN solutions contain particulate matter [47] (LoE 2−) and biochemical interactions can lead to chemical precipitates and emulsion instability; they also act as a media for microbiologic growth should contamination occur. Particulates in infusion fluid play a role in causing phlebitis with peripheral venous infusion [48] (LoE 2+). Particles can also harm the pulmonary endothelium and provoke a granulomatous pulmonary arteritis [47] (LoE 3). The routine use of in-line filtration has been advocated in children receiving large volume parenterals, and a randomised trial in a paediatric intensive care unit showed that filters were associated with a significant reduction in overall complication rate, a reduction in systemic inflammatory response syndrome, and a reduction in length of stay [48] (LoE 1++). In critically ill children therefore, it appears that infused particles may impair the microcirculation, induce systemic hypercoagulability and inflammation [49] (LoE 1++). A Cochrane review of inline filtration in the newborn found four studies (low quality evidence) that showed no benefits from use of filters [50] (LoE 2−). Some endotoxin retaining 0.22 μm filters allow cost saving, through extended use of the administration set. With the appropriate filters, giving sets can be used for 72–96 h. Many solutions are stable for extended hang-times but explicit stability advice should be sought from the manufacturer or a competent independent laboratory. Filter blockage is more likely to indicate a problem with the solution than the filter, and must be thoroughly investigated.

Intravenous PN solutions that are not photoprotected generate oxidants, which are harmful to cells. Premature infants in particular face an imbalance between high oxidant loads and immature antioxidant defences. A meta-analysis found that mortality in patients with light protected PN was half that in the light exposed group [51] (LoE 1+).

2.6. Cyclical PN

R 11.7	**Cyclical PN may start once patients are in a stable clinical condition and can maintain normoglycaemia during a period without PN infusion (GPP, strong recommendation for, strong consensus)**
R 11.8	**In order to prevent hypo/hyperglycaemia infusion rate may be tapered up gradually during the first 1–2 h and tapered down during the last 1–2 h of infusion when cyclic PN is administered (GPP, strong recommendation for, strong consensus)**

PN is always introduced as a continuous infusion over 24 h. Once patients are tolerating a full amount of PN and are stable both clinically and biochemically, the infusion time can be gradually reduced by hourly decrements over a period of days/weeks with frequent assessment of volume/rate tolerance and blood glucose [52,53]. This 'cycling' of PN (discontinuing nutrient infusion for a period time each day) should be established while in hospital so that tolerance/safety can be confirmed prior to discharge home [53]. Cyclical PN has a protective effect against intestinal failure associated liver disease (IFALD) [54], and is generally a prerequisite for home PN since daytime freedom from infusion pumps improves quality of life. Several studies have shown metabolic differences between cyclical and continuous PN [24,55] while nitrogen balance is similar. In young children (<2 yr) abrupt discontinuation of PN infusion may causes hypoglycemia; in older children the risk is much lower [55] (LoE 2++). Calcium loss increases during infusion of cyclical PN but not total daily loss of calcium, phosphorus, magnesium, or vitamin D compared with continuous infusion [55] (LoE 2++).

There is some evidence that cycling PN can prevent cholestasis [56–58] (LoE 2−), although the risk was not decreased in VLBW neonates when only the amino acid component of PN was cycled [59] (LoE 1−). Children almost always tolerate night time infusion over 10–14 h [24]. The optimal time to initiate cyclical PN is unknown, and cycling may not be tolerated in young infants due to immature gluconeogenesis, limited glycogen stores, and large glucose demands [56]. However, there is evidence that cycling of PN is safe even in clinically stable newborns [56,57] (LoE 2−).

Cycle time may be shortened by 1–2 h each or every other day until the desired/tolerated goal for duration of infusion is achieved (LoE 4) [53]. In infants with poor enteral tolerance, infusion time should be decreased in 1 h steps. The most common adverse events associated with cyclical PN are hyperglycemia, and respiratory distress due to the increase in the rate of dextrose and fluid infusion [53,55]; abrupt discontinuation of infusion may also precipitate hypoglycaemia [55]. In order to prevent these adverse events, use of an infusion pump that allows a gradual increase in infusion rate during the first 1–2 h, and a tapering down during the last 1–2 h, is recommended (LoE 2−). Infusion rate of glucose, lipids and potassium should also be taken into account when final infusion rate is calculated (see Guideline section on 'Carbohydrates and Lipids').

2.7. PN monitoring

PN monitoring involves frequent clinical assessment including nutritional status and laboratory results. Biochemical monitoring needs to be tailored to the underlying clinical condition and also the duration of PN [60]; a suggested protocol is given in the Table 1. Good catheter care and aseptic delivery of nutrients are mandatory for prevention of catheter related infection. Assessment of fluid and electrolyte balance, particularly when there are abnormal losses from the gastrointestinal tract should result in early intervention when necessary. In stable patients, sudden changes in biochemical status are uncommon [61] (LoE 3); patients with organ failure or unusual fluid losses clearly require closer monitoring. For patients who are PN dependent long term, body composition is often abnormal with significant deficit in limb lean mass [62]. Metabolic bone disease is related to aluminium contaminating fluids, low serum vitamin D and insulin-like growth factor, and inflammation [63]. Bone mineral density is reduced particularly in children with congenital enterocyte disorders or severe dysmotility [64]. Annual bone mineral density assessment should be considered in children who remain PN dependent and are old enough (usually >5 y) to cooperate with a DEXA scan procedure. Once weaned from PN to full enteral feeding, periodic monitoring is still required to identify complications [65]. Children with short bowel continue to have bile salt malabsorption [66] and may develop fat soluble vitamin and trace element deficiencies [67], gallstones and renal stones [68], and anaemia from peri-anastomotic ulceration [69]. Despite resolution of cholestasis and portal inflammation, significant liver fibrosis and steatosis persist [70].

Table 1
Laboratory monitoring of parenteral nutrition. (X – when to perform the test. S – serum, plasma, WB – whole blood, CB – capillary blood, US – urine sample).

Investigation	Sample	Before starting parenteral nutrition	During parenteral nutrition, before clinical and metabolic stabilisation			During parenteral nutrition, during clinical and metabolic stabilisation		
			Once/1–2 days	At least once a week	As required	Once/1–2 weeks	Once a month	As required
Sodium	S	X	X			X		
Potassium	S	X	X			X		
Chloride	S	X	X					X
Calcium	S	X	X			X		
Phosphorus	S	X		X		X		
Magnesium	S	X			X	X		
Zinc	S				X			X
Blood gasses	CB	X		X		X		
Glucose	WB, CB	X	X			X		
Total protein	S	X		X		X		
Albumins	S	X		X			X	
BUN	S	X		X			X	
Creatinine	S	X		X			X	
Triglycerides	S	X			X			X
Cholesterol	S	X			X			X
Bilirubin	S	X			X		X	
AST	S	X			X		X	
ALT	S	X			X		X	
GGTP	S	X			X			X
AP	S	X			X			X
CBC	WB	X		X		X		
INR	S	X			X		X	
CRP	S	X			X			X
Vit. B12	S				X			X
Fe	S				X			X
Ferritin	S				X			X
PTH	S							X
25OHD3	S				X			X
Trace elements: Se, Zn, Cu				X				X
Urine	US	X		X			X	
Electrolytes in urine	US				X			X

3. Weaning and establishment of enteral feeding

R 11.9	**Complete enteral starvation (i.e. 'TPN') may be avoided by giving some enteral feed whenever possible, even if only a minimal amount is tolerated (GPP, strong recommendation for, strong consensus)**
R 11.10	**When increasing enteral feed, only one change at a time may be made, to assess tolerance (GPP, strong recommendation for, strong consensus)**
R 11.11	**In severe intestinal failure, feed volumes may be increased slowly, according to digestive tolerance (GPP, strong recommendation for, strong consensus)**
R 11.12	**Enteral feeding may be introduced as a liquid feed infused continuously by tube over 4–24 h periods, using a volumetric pump (GPP, conditional recommendation for, strong consensus)**
R 11.13	**Bolus liquid feed may be given via feeding tube, or by mouth as sip feed if tolerated (GPP, conditional recommendation for, strong consensus)**
R 11.14	**Children who rapidly recover intestinal function may be weaned straight onto normal food (GPP, conditional recommendation for, strong consensus)**

As with many aspects of the management of IF, there is little evidence base for specific nutritional practices [71]. Children with an acute episode of severe IF (e.g. following surgery or chemotherapy) may tolerate rapid reintroduction of normal diet. Those with primary gut disease need reintroduction of enteral feed tailored according to the underlying disorder. Appropriate minimal enteral feed should be given whenever possible to maintain gut mucosal structure [72] (LoE 3), encourage adaptation [73–76] (LoE 4) and reduce the risk of PN-associated liver disease [54,77] (LoE 3). In the newborn infant with short bowel, expressed breast milk is thought to optimise adaptation [78,79]. Maternal expressed breast milk (MEBM) can be given either fresh (in case of small bolus feeds) or pasteurised (in case of continuous feeding); donor milk may be available if there is no MEBM [80]. In order to assess tolerance, no more than one management change should be made at a time, for example, when enteral volume is increased, the osmolality of the feed should remain the same. With limited gastrointestinal function, feed volumes must be increased cautiously and according to tolerance (usually assessed by diarrhoeal stools/stoma output) [81].

Potential life threatening risks from PN mean that the overriding clinical priority is to try and establish enteral autonomy. Risk of cholestasis is directly related to duration of PN [82] (LoE 1–) [83] (LoE 3). Enteral nutrition can be introduced as liquid feed infused continuously over 4–24 h periods via a feeding tube, using a volumetric pump [84]. The advantage of continuous feed is that full use is made of the functional capacity of the intestinal tract, particularly if given over 24 h [85]. Liquid enteral nutrition can be given by bolus via a feeding tube, or orally as sip feeds once gastrointestinal function has sufficiently improved. Oral feeding provokes release of epidermal growth factor from salivary glands and increases gastrointestinal secretion of trophic factors [65]. If vomiting or poor gastric emptying is a limiting factor in advancing feed volumes, jejunal tube feeding can be considered; in short bowel this has the potential to worsen diarrhoea.

Children who rapidly recover intestinal function can be weaned straight onto normal food. However, if there is any possibility of persisting intestinal inflammation, diet may need to be adjusted. There may be an increased incidence of cow milk or soya protein intolerance in newborns with short gut and prognosis is improved with breast milk [77] (LoE 3) or amino acid based formula feed [86] (LoE 3).

Every possible attempt must be made to encourage children to eat normally. Even small bolus feeds by mouth can help to avoid the development of oral hypersensitivity and feed aversion. Spoon

feeding should be introduced at the normal time of 4–6 months of age, even if only small amounts of feed can be offered. Sometimes solids appear better tolerated than an increase in liquid feed. Occasionally, oral aversion is associated with underlying gastro-oesophageal reflux [87] that worsens with an increase in feed.

3.1. Type of feed

R 11.15	**In newborns and infants with intestinal failure breast milk may be the enteral feed of first choice (GPP, strong recommendation for, consensus)**
R 11.16	**If breast milk is not available, the choice of substitute can be based on clinical condition; in early infancy and severe illness it is reasonable to start with elemental formula, switching to extensively hydrolyzed and then to polymeric feeds (GPP, strong recommendation for, strong consensus)**

Enteral feeding may be limited in IF because of dilated small bowel, dysmotility, bacterial overgrowth and increased permeability [88]. In infancy, feeding options include breast milk, polymeric, extensively hydrolyzed or amino-acid based elemental formula [54]. There is evidence that breast milk is associated with shorter duration of PN (LoE 3) [77,89,90]. In some patients the use of polymeric feeds may be associated with the development of cow milk protein allergy [91,92]. Case reports and small case series have shown that amino-acid based formulae were more efficient in decreasing the requirements for PN then extensively hydrolyzed feeds (LoE 3) [77,86,93–95]. However, the only small randomized study (involving ten infants with SBS) compared hydrolyzed with non-hydrolyzed enteral formula, found no difference in terms of weight gain, tolerance and energy expenditure (LoE 1–) [96].

In children with SBS, continuous enteral nutrition is often recommended [79,97–101]. It has been found that in children both with protracted diarrhoea and SBS continuous feeding improved enteral tolerance and weight gain (LoE 3) [102]. However, bolus feeding is more physiological, helps in development of oral motor skills, provides a cyclical hormonal surge and stimulates gallbladder emptying [103]. Therefore, small oral bolus feeds during the day should be initiated as soon as possible (usually as an adjunct to continuous enteral feeding during the night) in order to avoid tube-feeding associated complications. In preterm infants guidelines for enteral nutrition should be followed [104].

3.2. Weaning from parenteral nutrition

R 11.17	**Enteral feed may be given at normal concentrations (i.e. not diluted) (GPP, conditional recommendation for, strong consensus)**
R 11.18	**PN should be reduced in proportion to, or slightly more than the increase in EN (GPP, conditional recommendation for, consensus)**
R 11.19	**If a chosen weaning strategy fails, try again more slowly (GPP, conditional recommendation for, strong consensus)**

A reduction in the amount of PN may be attempted as soon as the child is stabilised i.e. intestinal losses from vomiting and diarrhoea have been minimised and an optimal nutrition state reached. All children on PN should continue to have a minimum amount of enteral feed to maintain pancreatico-biliary secretion and promote gut mucosal integrity [105] (LE 3) whenever possible. As soon as a small amount of feed is tolerated, the volume should be increased [81,106–108] (LoE 4). Feed should be given at normal concentrations and not diluted, otherwise the child will achieve normal fluid volume intake without adequate nutrition. The aim should be to maintain a good nutritional intake by decreasing parenteral and increasing enteral feed by similar amounts. Enteral tolerance is more likely to be achieved by avoiding excessive fluid intake. In children with more severe IF, enteral feeds may need to be increased as slowly as 1 mL/kg/24 h. If a chosen weaning strategy fails it is worth trying again, but at a slower pace (smaller increments). Overfeeding may promote bacterial overgrowth causing inflammation, increased permeability, sensitisation and allergy, translocation, sepsis and cholestasis [109].

In children who are stable and thriving at home, PN can be reduced by dropping one night/week of PN providing there is no risk of dehydration. If tolerated, further reductions are made by reducing one night at a time over several months. Alternatively, weaning can be facilitated by reducing/halving the PN given one night a week and seeing how well the child tolerates this approach. If fluid and electrolyte loss is the main issue, administration of glucose and electrolyte solution by enteral feeding tube may maintain hydration. In infants a night off PN would usually only be tried when at least 50% of nutrients are being tolerated enterally. Tolerance of a night without PN varies according to the underlying disease, the size of the child and their ability to maintain hydration. A night off is usually well tolerated by children with SBS who are stable and have improving intestinal function, but may be delayed in the presence of bacterial overgrowth and associated enteritis [110]. In children with chronic intestinal pseudo-obstruction, especially with ileostomy and major gastrointestinal fluid losses, increased enteral fluid intake during a night off PN may provoke diarrhoea. The child's ability to tolerate a reduction in PN is assessed by monitoring weight gain, growth and blood indices. Unabsorbed enteral feed in the colon may lead to D-lactic acidosis due to fermentation by the colonic bacterial flora. Although some studies have indicated that bacterial fermentation is more of a problem in the absence of ileocaecal valve [111] (LoE 3), this does not always seem to be the case [110] (LoE 3). This complication may be prevented/treated by a low fibre diet, bicarbonate, and sometimes antibiotics such as metronidazole or the non-absorbable rifaxamin; probiotics may also be helpful [110] (LoE 3). Sometimes it is necessary to reduce intestinal nutrient load and increase PN whilst waiting for intestinal adaptation to progress allowing for recommencement or continuation of the weaning process.

3.3. Psycho-social and developmental aspects of feeding

Maintaining small volumes of feeds by mouth is important to prevent oral hypersensitivity and promote the development of oromotor feeding skills. If continuous feeds are being given, an hours worth of feed can be taken by mouth every 4 h. Solids should be started at the usual recommended age for healthy infants where possible. It is best to limit these initially to a few foods that are least likely to have an allergenic effect (e.g. rice, chicken, carrot) especially if there is intestinal inflammation. Foods should also be suitable for the underlying intestinal disease e.g. low lactose, low in LCT fat or low fibre in short bowel and/or extensive colonic resection. When solids are introduced the aim is to encourage normal textures for age [87] (LoE 4). Maternal bonding can be supported by encouraging involvement with feeding and close contact between mother and child. In younger infants when bolus feeds are required, active involvement of parents may have beneficial psychological and social effects. Feeding by mouth should be a pleasurable experience for both infant and parent. Even if the amount and range of foods are limited, normal feeding behaviour will be promoted and the risk of longer term feeding problems reduced [112]. A proportion of children will remain feeding tube dependent [113,114] but are amenable to specific treatment programmes aimed at establishing full oral feeding [115].

Conflict of interest

None declared.

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Clinical Nutrition 37 (2018) 2401–2408

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

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

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

Literature search timeframe: Publications published after the previous guidelines (i.e., from 2004–December 2014), were considered. Some studies published in 2015 or 2016 during the revision process have also been considered. The references cited in the previous guidelines are not repeated here, except for some relevant publications; the previous guidelines are cited instead.

Type of publications: Systematic reviews, randomised controlled trials, case–control or cohort studies

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https://doi.org/10.1016/j.clnu.2018.06.954
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Table: Recommendations for home parenteral nutrition (PN)

R 12.1	A child who is expected to need PN for more than 3 months can be discharged home as soon as clinically stable for improved quality of life with less complications, e.g. reduced CRBSI and less IFALD, improved psychosocial circumstances, and reduced costs; as long as: • There is a safe environment (e.g. running water, reliable electricity) • At least one parent/caregiver has been trained by a specialised nutrition nurse/team, and • appropriate social support is available (LoE 2− and 4, RG 0, strong recommendation for)
R 12.2	Management of home PN by centralised units with expertise in the investigation of intestinal failure rehabilitation and with a multidisciplinary nutrition team to support care at home may minimise complications, improve outcome and allow weaning from PN as soon as possible (LoE 2−, RG 0, strong recommendation for)
R 12.3	Complications can be reduced and quality of life may be improved by: • Using existing evidence-based guidelines • Limiting the number of infusions/week if possible • Limiting the hours of PN to the minimum possible aiming for 10–12 h • Incorporating replacement of excessive fluid losses in PN if at all possible • Use of portable pumps • Care as close to home as possible (LOE 3 and 4; RG 0, strong recommendation for)
R 12.4	Paediatric HPN patients must be followed-up by an experienced team on a regular basis with a minimum of about 4 visits per year in older children (LOE 4; RG 0, strong recommendation for)
R 12.5	Monitoring should be considered on an annual/alternate year basis for complications including: • Liver disease by US • Bone density, vitamin D and body composition if available • Radionuclear lung perfusion scan for pulmonary emboli if indicated • Chest X-ray to assess appropriate position of central line (LOE 4; RG O, conditional recommendation for)
R 12.6	PN mixtures that are stable for >7–14 days may be used to minimise the frequency of deliveries required (LoE 4; RG 0, conditional recommendation for)
R 12.7	The use of a single bag may be recommended (LOE 4; RG 0, conditional recommendation for)
R 12.8	The patient should be on a stable regimen before starting home PN (LOE 2− and 4, RG 0, strong recommendation for)
R 12.9	PN solutions should be compounded according to the individual patient's macro- and micronutrients needs (LOE 2−, 4; RG 0, strong recommendation for)
R 12.10	The aim of home PN should be survival into adult life with the best possible growth and psychosocial development, school attendance and participation in other activities, e.g. sport, swimming, family holidays (LOE 4; RG 0, strong recommendation for)
R 12.11	Early referral of long-term PN patients to an expert centre may reduce PN-associated complications (LOE 2−, RG 0, strong recommendation for)
R 12.12	Early referral to a centre for intestinal transplantation can minimise mortality from Home PN related complications whilst on the waiting list (LOE 2−, RG 0, conditional recommendation for)
R 12.13	Home PN expert centres should provide 24-h phone support and support weaning off PN at the earliest opportunity (LOE 4; RG 0, strong recommendation for)

Language: English, Dutch and German

Key words: Infants, children, home parenteral nutrition, quality of life, complications, liver disease, catheter-related sepsis, thrombosis, metabolic bone disease, electrolyte disturbances, hypoglycemia, hyperglycemia, prevention, long-term outcome, costs.

Abbreviations: CRBSI – catheter-related blood stream infections; CVC – central venous catheter; IF – intestinal failure; IFALD –intestinal failure associated liver disease; PN – parenteral nutrition; US – ultrasound examination

2. Introduction

Home parenteral nutrition (Home PN) is the best alternative to prolonged hospitalisation and the best option for improving the quality of life of children dependent on long-term PN [1]. Furthermore, Home PN is associated with lower risks of complications such as catheter related blood stream infections (CRBSI) and overall cost [1,2]. Therefore, Home PN should be considered for any child who is clinically stable and expected to remain dependent on PN for at least three more months [3]. Over the last decade, Home PN has increased rapidly due to improvement in survival with better quality of care of surgical treatment, of neonatal care, of daily catheter care and also of the composition of PN [3]. Reported prevalence varies across studies ranging from 9.6 children per million in the Netherlands to 13.7 children per million in the U.K [3,4]. In this chapter, we will discuss indications, organisational aspects, requirements, follow-up, complications, quality of life and long-term outcome of Home PN.

3. Indications

3.1. Why start a home PN program?

Long-term total or complementary PN is required to preserve nutritional status when oral or enteral nutrition cannot meet protein-energy needs, especially in diseases that impair digestive function. When a child does not need hospitalisation but depends on long-term PN, home parenteral nutrition (Home PN) is the best alternative to prolonged hospitalisation and is recognized as the best option for improving the quality of life of these children and their families [1]. In addition, compared to PN in the hospital setting, Home PN is associated with lower risks of catheter related blood stream infections (CRBSI) and a decreased risk of intestinal failure associated liver disease (IFALD) [2]. Therefore, Home PN should be considered for any child who is clinically stable and expected to remain dependent on PN for at least three more months [3].

National prevalences are difficult to compare because of the use of different definitions and inclusion criteria. Therefore, it would be helpful to have national or even a European register for Home PN in children using the same definitions and inclusion criteria to improve the quality of data on prevalence, outcome and complications. A Dutch study estimated a point prevalence of 9.6 children per million for instance, but a study from the UK published a higher point prevalence of 13.7 children per million [3,4]. However, in recent years, the incidence of children on Home PN has increased rapidly due to improvement in quality of care, of surgical treatment, of neonatal care, of daily catheter care and also of the composition of PN [3]. Children on treatment with Home PN should be managed by a multidisciplinary team. A European study showed that in both adults and children, the risk of death is increased by the absence of such a specialist team [5].

3.2. Underlying indications

The most common indications for prolonged PN and thus Home PN in children are primary digestive diseases causing intestinal failure (IF). Short bowel syndrome (SBS), mainly acquired during the neonatal period, is the largest group of patients, which

has increased rapidly in frequency, accounting for at least 40% of all cases [1,3–7]. The main other digestive indications are intractable diarrhoea of infancy, such as tufting enteropathy/epithelial cell dysplasia or microvillous inclusion disease and motility disorders, such as chronic intestinal pseudo-obstruction. Other less frequent indications are inflammatory bowel diseases, especially Crohn's disease, and primary nondigestive indications such as immune deficiency, tumours, metabolic diseases and neurological impairment with intestinal hyperaesthesia. The need for Home PN in these diseases is usually shorter than for primary digestive diseases [1].

3.3. Age

There is no minimum age criterion at which Home PN can be safely started, but it will depend on each individual case [1,3–5,7]. Most infants are not sufficiently stable to be discharged home until about 4 months of age (corrected for prematurity), although some have been discharged by 2 months. Data from a cohort of 139 children showed that almost 15% of the children on Home PN were younger than 1 year [3]. It should be considered that starting Home PN prior to 4 months of age may carry a greater risk of mortality [5].

3.4. Condition

Children can be discharged from the hospital to continue PN at home if they are expected to need PN for at least 3 further months, and have a well-inserted central venous catheter. In addition, they have to be in a stable condition regarding their underlying disease and their fluid and electrolyte requirements. Ideally they should be able to tolerate PN infused over just 10–14 h overnight, but in certain cases it may be necessary to send children home on PN for up to 18 h and in extremely unusual circumstances, 24 h.

3.5. Social and family requirements for home PN

Before starting Home PN, the team should decide if the indication is appropriate and ethical. Furthermore, parents/caregivers but also the (older) child have to be able to cope with all the medical, emotional and technical issues related to PN. Practical issues should be discussed such as space for a refrigerator, pumps and the need for home nursing assistance [1]. Preferably, both parents/care givers should be trained simultaneously. A single-parent family is not always a contraindication for Home PN, but social help and home nursing assistance may become more necessary [1]. The professional status of both parents needs also to be discussed, since one parent may have to stop working for a certain time, although parents should be supported to continue working if at all possible.

3.6. Cost savings

An economic evaluation study of pediatric small bowel transplantation in the United Kingdom showed mean costs up to 30 months of £207,000 for those transplanted or on the waiting list, and £159,000 for those stable on home PN [8]. A recent adult study showed that Home PN costs were €13,276 for treatment introduction, followed by €77,652 annually [9]. Home PN is thus very expensive. However, cost-benefit studies have demonstrated that it is about 65% more cost-effective than hospital treatment for children as for adults [10–12]. The longer a patient survives at home on PN, they will have fewer complications with time and the more cost-effective home-treatment becomes.

4. Preparation for PN care at home

R 12.1	**A child who is expected to need PN for more than 3 months can be discharged home as soon as clinically stable for improved quality of life with less complications, e.g. reduced CRBSI and less IFALD, improved psychosocial circumstances, and reduced costs; as long as:** • **There is a safe environment (e.g. running water, reliable electricity),** • **At least one parent/caregiver has been trained by a specialised nutrition nurse/team, and** • **Appropriate social support is available (LOE 2− and 4, RG O, strong recommendation for, strong consensus)**

Once it is established that the child will be discharged home on PN treatment, the medical team needs to discuss the management of PN at home and what is involved with the family. It is best practice for both parents to meet with a consultant specialising in PN and nutrition nurse specialist. If possible a social worker should also discuss any social concerns that the professionals and/or family have. The home needs to be inspected to ensure that it is adequate for caring for a child on PN. There needs to be a reliable electricity supply for the pump and accessible running water to wash hands, preferably without a step between the bedroom and washing area. Accessible toilet facilities are also essential for the older child. If the child is young/shares a room with a young sibling the PN equipment needs to be situated so that the toddler cannot tamper with it.

If at all possible both parents should be trained to administer PN. In a single parent family setting, that parent alone can be trained along with another family member/close friend as well, if available. In practice it is unusual for a non–parent to be willing to be trained when made aware of the responsibility involved, and ascertaining the capability of the caregiver to take care of the child receiving Home PN is part of the evaluation and approval of the home environment as discussed below. If parents live separately and the child spends time in both homes then both parents will need to be trained. They should be trained at the same time in order to ensure that each is aware of the training the other has had, that they cooperate over the care of their child's PN and to use health resources as efficiently as possible. In certain circumstances when no healthy parent is available a trained nurse will need to come into the home to connect and disconnect the PN, but this should be avoided if at all possible since it reduces family flexibility. Furthermore, if several different nurses take turns to do it, it may increase risk of CRBSI.

Funding for the home PN needs to be secured. In many countries this will be obtained from the National Health Care System. A reliable supply of PN and ancillary equipment must be procured. There are three possible methods:

1. Dedicated homecare companies with compounding facilities to manufacture the PN that will also supply the ancillary equipment.
2. Supply of the PN by the hospital pharmacy and ancillary equipment from the hospital or community services.
3. In exceptional circumstances parents have been trained to compound the PN at home with supplies obtained from a hospital [13].

The parents need to be available for a 1–2-week period to undergo a structured training programme to manage PN at home. Flexibility during the 1–2-week period may be needed by the nurse undertaking the training to enable parents to fulfil other commitments (including work/other childcare) during the training period. Training should include learning techniques for connecting and

disconnecting the PN bags from the CVC, understanding how to recognise complications and what to do when they arise. Once training commences all medical investigations, other than the most routine should have been completed. It is difficult for parents to concentrate effectively on learning PN if their child is still undergoing tests/surgical procedures.

In some countries/circumstances PN training can be undertaken by specialist nurses working in the community. These nurses would usually work with a home care company that supplies PN to the home. Parents will be trained to manage the PN after discharge home. On completion of training parents should be assessed and re-trained on any area in which they fail to demonstrate appropriate standard of care.

A planning meeting should be held around the time of discharge to ensure that professionals and family members are all aware of the child's treatment plan and where to manage different complications that may arise. A community nurse/health worker, the specialist hospital consultant and nutrition nurse, the consultant at the hospital closest to the patient's home and the parents should all be present with other available professionals involved in the child's care. A shared care plan should be made between the local hospital, specialist team and community professionals. A system for direct access to the local hospital in an emergency should be set up. Minutes of the meeting should be circulated for future reference.

5. Organisation, monitoring and follow-up

R 12.2	**Management of home PN by centralised units with expertise in the investigation of intestinal failure rehabilitation and with a multidisciplinary nutrition team to support care at home may minimise complications, improve outcome and allow weaning from PN as soon as possible (LOE 2−; RG 0, strong recommendation for, strong consensus)**
R 12.3	**Complications can be reduced and quality of life can be improved by:** • **Using existing evidence-based guidelines,** • **Limiting number of infusions/week if possible,** • **Limiting hours of PN to minimum possible aiming for 10–12 h,** • **Incorporate replacement of excessive fluid losses in PN if at all possible,** • **Use of portable pumps, and** • **Care as close to home as possible (LOE 3 and 4; RG 0, strong recommendation for, strong consensus).**
R 12.4	**Paediatric HPN patients must be followed-up by an experienced team on a regular basis with a minimum of about 4 visits per year in older children (LOE 4; RG 0, strong recommendation for, strong consensus)**
R 12.5	**Monitoring can be considered on an annual/alternate year basis for complications including:** • **Liver disease by US** • **Bone density, vitamin D and body composition if available** • **Radionuclear lung perfusion scan for pulmonary emboli if indicated** • **Chest X-ray to assess appropriate position of central line (LOE 4; RG O, conditional recommendation, strong consensus)**

As mentioned previously, management of children on Home PN should be performed in specialist centres with a multidisciplinary IF rehabilitation hospital PN team in order to reduce the risk of complications and even mortality [5]. Home PN centres should have adequate expertise and resources to ensure a good standard of care by using existing evidence-based guidelines and aiming to wean the child from PN as soon as clinically appropriate [1]. The aim is to try to limit the number of infusions per week and also hours of PN to the minimum, possible aiming for 10–12 h. A portable pump should be used (see chapter “Techniques”). Physicians should be trained and qualified to be responsible for the appropriate use, prescription and follow-up of patients on Home PN programmes. Nurses responsible for parents' teaching and training should work with the specialist IF team and evaluate their capacity to deal with all medical and technical issues related to the child's treatment. Pharmacists or pharmaceutical companies specialising in PN at home should ensure safety of compounding and storage of the PN mixtures. Replacement of excessive fluid losses should be incorporated in PN if at all possible. Once discharged from hospital, regular out-patient follow-up should be planned to check clinical and biologic parameters (Table 1) with a minimum of 4 visits/year to the specialist centre [14,15]. Investigations should be tailored for each child and will depend on the underlying disease. Visits should be tailored according to each individual situation, initially 1–3 months after discharge, but more frequently if necessary, especially in infants. During visits, oral and/or enteral feeding opportunities should always be reconsidered and discussed with parents or caregivers. A 24 h phone contact with the on-call team at the specialist centre should be provided [1]. A close connection with general practitioners and local non specialised hospital units is warranted. Whilst the specialist team should lead care they should support the child's local medical services in delivering as much care as possible as near to the home as possible. Some children live long distances from the specialist centre and it is not practical or necessary for them to travel all the way to the centre for every problem that arises.

6. Techniques

6.1. Vascular access

A centrally placed cuffed catheter is the most secure venous access for PN at home. A peripherally inserted centrally placed catheter (PICC) can be safely used for many months [16]. A PORT should only be used in exceptional circumstances since it can be difficult to eradicate infection. In exceptional circumstances a-v fistulae have been used successfully [17].

6.2. The infusion cycle

R 12.6	**PN mixtures that are stable for >7–14 days may be used to minimise the frequency of deliveries required (LOE 4, RG 0, conditional recommendation for, strong consensus)**
R 12.7	**The use of a single bag may be recommended. (LOE 4, RG 0, conditional recommendation for, strong consensus)**

PN at home is normally infused over 10–12 h overnight (up to 16–18 h in some infants) leaving the child free to participate in activities, including school, during the day [18]. The number of nights/week that PN is infused should be minimised at the earliest opportunity. An oral/enteral sodium supplement should be given the day before and after a night off PN in children with high sodium requirements/excessive loss. Some children with excessive stoma/stool fluid losses and those with difficulty maintaining a normal blood glucose level may need a prolonged infusion cycle. In exceptional circumstances children can be sent home on PN over 24 h e.g. a toddler or older child who is unlikely to significantly improve and will benefit from the opportunity to return to the family home and participate in usual activities such as school. The PN infusion rate should be gradually reduced over the final hour prior to disconnection, particularly in the younger child to avoid the risk of hypoglycaemia on stopping [19].

PN for home use may be compounded by a hospital pharmacy, a specialist homecare company pharmacy or even by parents at home [13]. Stability can be obtained for 14–21 days for most

Table 1
Clinical and biologic monitoring in children on PN at home.

Intervals	Clinical assessment	Other investigations
1–3 months	• Weight, height • Clinical examination • Dietetic assessment	• Blood count, coagulation • ALT, AST, bilirubin, GGT, alkaline phosphatase, Na, K, Ca, PO_4, Mg, glucose, urea, creatinine • Urinary electrolytes (Na, K, osmol)
6–12 months		• Plasma vitamins A, D, E, B12 • Ferritin, iron, zinc, copper, selenium, manganese • When indicated: - anti X-a level (in case of low-molecular-weight heparin use), - blood gas analysis, albumin, PTH, thyroid function - duplex ultrasonography (if using an arteriovenous fistula) • Bone densitometry • Body composition (if available) • Liver and biliary tract ultrasonography • Renal ultrasound • Radionuclear lung perfusion scan (when indicated)
12 months		• Chest X-ray to assess appropriate position of central line

formulations when made by a homecare company enabling delivery to the home on a 2-weekly basis. In smaller children or those with variable stool/stoma losses weekly deliveries may be appropriate when first discharged home. If changes to the PN are needed it is best if these can be made by increasing or decreasing the volume infused in the first instance before changing the formulation. Any excess stoma losses should be replaced by incorporating appropriate fluid and sodium in the PN (see chapter "Fluid and nutrients"). In all cases there should be extra fluid, 'overage', in the PN bag in addition to the amount prescribed in case needed.

PN for home use should ideally be provided in a single bag system. Every effort should be made by the pharmacy to obtain stability as a single bag and the clinical team should adjust the prescription if possible to enable an all-in-one bag to be used. In certain circumstances a two-bag system may be needed, but some units are able to avoid two bags – even when achieving 14–21 days stability.

6.3. Pumps, equipment and ancillaries

The PN should be infused via a filter (if available) with a portable pump when at home [20]. The pump should be as quiet and light as possible. It needs to be reliable in order to avoid unnecessary alarming and waking the family at night. A good battery life and rucksack are particularly important when the child is active whilst connected to PN. Ideally, there should be a contract for the pump to be rapidly replaced as if it breaks (a 4-h replacement service may be possible) and serviced on an annual basis. The family should have a second pump at home – essential for children who need a 24-h infusion in order to avoid hypoglycaemia.

Ideally all ancillary equipment should be delivered to the home. Families should not have to collect it from different sources.

7. Fluids and nutrients

PN requirements depend on age, weight, underlying disease, nutritional and current hydration status, and environmental conditions. When PN is not the sole source of protein-calorie intake, intestinal absorptive function should be estimated.

7.1. Fluid and electrolytes

R 12.8	**The patient should be on a stable regimen before starting home PN (LOE 2– and 4, RG 0, strong recommendation for, strong consensus)**

The fluid and electrolyte composition of the PN regimen should reflect fluid losses and deficits that may result from medical therapy. Digestive tract losses due to diarrhoea or from stomata should be measured (volume and sodium concentration) and replaced. Adjustments may be required frequently depending on the clinical situation. The patient should be on a stable regimen before starting a home PN programme.

7.2. Vitamins and trace elements

The PN infusion should provide vitamins and trace elements (TE), according to the patient's age, weight and specific needs. Certain conditions may predispose to deficiencies of fat-soluble vitamins by interrupting the entero-hepatic circulation: extensive resection of terminal ileum, bacterial overgrowth, which may lead to deconjugation of bile salts and increased inflammation with further small intestinal injury, and PN-associated cholestasis from prolonged PN [21,22]. Oxygen is the principal agent responsible for degradation of vitamins and originates from PN ingredients, the filling process, air remaining in the bag after filling, and oxygen permeation through the bag wall. Therefore, multilayered bags with reduced gas permeability should be used, and careful oxygen monitoring during the filling process is mandatory [23]. Exposure to light may degrade vitamins (especially vitamin A) and is associated with increased production of peroxides. Light protection should be considered for Home PN that is exposed to strong direct day light (see chapter "Vitamins"). Supplying vitamins in a lipid emulsion can be an additional way to reduce losses due to adsorption onto the tubing materials [24]. Vitamin and trace element (TE) doses in Home PN should be adjusted based on regular monitoring. In long-term PN patients, a restriction of manganese supplementation is needed to avoid accumulation [25,26]. In certain circumstances, e.g. patient weaning from PN, vitamins and minerals may be given orally/enterally.

7.3. Nutrition mixtures for paediatric home PN

R 12.9	**PN solutions should be compounded according to the individual patient's macro- and micronutrients needs (LOE 2– and 4, RG 0, strong recommendation for, strong consensus)**

Binary mixtures including glucose, amino acids, electrolytes, trace elements and vitamins (lipids being administered separately on a Y-line) or, ideally, all-in-one mixtures are provided to children on Home PN. Mixtures may be manufactured and delivered to patients with complimentary equipment weekly,

fortnightly or monthly. Vitamins or drugs added to nutrient mixtures might impair their stability whilst, the availability of drugs and vitamins might be reduced when introduced into PN mixtures [27]. Thus, depending on these limiting factors, the "safe" duration of PN bag storage varies from about 14 to up to 21 days. Bags should be stored at 4 °C from the time of their production to their administration to the patient without any discontinuity. The families should receive a dedicated refrigerator for PN bag storage.

Special PN mixtures should be prepared according to individual requirements. The so-called standard PN mixtures compounded by pharmaceutical companies, meant only for adult patients on short-term and/or complementary PN, cannot meet children's nutritional requirements and are free of vitamins and trace elements. They may be suitable for some adolescents on supplemental PN only. Their use in children at home can lead to metabolic complications with severe electrolyte imbalances. Currently, no pediatric standard formulas are suitable for children on PN at home.

8. Complications

Any complications that can develop in children receiving hospital PN may occur but are less frequent at home. The more common complications of long-term/home PN include infection, disturbances of fluid balance and occasionally renal disease, CVC related thrombosis and abnormalities of growth, bone density and body composition. IFALD is uncommon at home. Initial management of inter-current problems should be started by the parents with support of the community nurse/professional. If urgent medical care is needed the child should be taken to the nearest hospital.

Parents should have a hand held plan for how to manage complications.

The two most common infections are those involving the skin and sub-cutaneous tissue around the catheter exit site and CRBSI. If inflammation develops at the exit site, a swab should be taken and antibiotic treatment commenced. A topical antibiotic can be used initially and, if the infection fails to respond, a systemic antibiotic. Most patients with IF can absorb an oral/enteral antibiotic sufficiently well, but in more severe cases with no oral tolerance intravenous treatment may be necessary.

In order to avoid serious life-threatening complications of septicaemia if the child develops a fever >38.5°C or is unwell with rigors/other symptoms suggestive of infection, s/he should be taken to the nearest hospital with in-patient paediatric facilities. A blood culture should be taken via the CVC and at least two antibiotics to cover both gram-positive and gram-negative infections commenced. Antibiotics should be adjusted according to sensitivities once available. Treatment may be continued at home with antibiotics either given by the parents (after training) or a community nurse, providing the child is stable. Taurolidine and 70% ethanol line locks have been successfully used to reduce the incidence of infection when PN is cycled: see chapter "venous access" for recommendations [28,29].

In children with excessive fluid losses, e.g. those with intestinal dysmotility or pseudo-obstruction, there should be a plan for managing increasing fluid losses at home in the first instance. In most cases the volume of PN infused can be increased, with a plan for hospital admission if losses exceed a certain volume or the child is clinically unwell. By increasing PN volume, fluid and electrolyte replacement will be given. Children will often have reduced appetite when losses increase (if on partial PN) and will also benefit from the increased calories.

Growth on PN can be poor [30]. In order to promote growth protein/nitrogen intake may be increased. When nitrogen intake is increased, the amount of glucose has to be increased as well. If the child's height gain does not improve s/he may gain excessive fat. If this starts to occur with the weight centile increasing above the height centile, the carbohydrate and protein should be reduced again.

Low bone density is a risk of long-term PN [30]. Monitoring of vitamin D and a DXA scan should be done on an annual basis. Other relevant investigations include parathyroid hormone (PTH), calcium, phosphate and urinary calcium. If vitamin D is low, oral or intra-muscular supplements may be needed in addition to that in the PN.

Catheter-related venous thrombosis is a potential risk and pulmonary emboli may develop [15,31]. Long-term anti-coagulation treatment may be required.

Children are at risk of increased fat mass and low lean body mass [14]. Measurement of body composition using Dual X-ray absorptiometry (DXA) should be considered on a 2–3 yearly basis or annually if previously abnormal.

Hepatobiliary disease is a less of a risk in long-term stable patients at home compared to in hospital. If present on discharge liver function usually improves with time and should be monitored appropriately. There is an increased risk of gallstones. Annual ultrasound examination is recommended and gallstones treated as needed [32].

Episodes of dehydration and possible pre-renal failure when there are excessive fluid losses can predispose to renal disease. Monitoring includes 3-monthly urea and creatinine blood levels and annual renal ultrasound.

9. Quality of life

R 12.10	**The aim of home PN should be survival into adult life with the best possible growth and psychosocial development, school attendance and participation in other activities, e.g. sport, swimming, family holidays (LOE 4, RG 0, strong recommendation for, strong consensus)**

The aim of PN at home is to give the best possible quality of life to the child and family. It should be recognised that some children may need to stay on treatment throughout childhood and into adult life. It is important to set up the PN so that the child can have the most normal life possible for weeks, months and years. If set up in the simplest manner possible the PN is incorporated into daily life and any symptoms related to underlying disease are more troublesome than PN itself [18]. It is possible for children on PN at home to have a similar quality to healthy children [33]. Children can attend regular school, participate in non-contact sport and swim and go on family holidays [34]. In many countries there are patient support groups for home PN patients. Support groups can advise on foreign travel, including health insurance amongst other issues. Quality of life and survival on long-term/home PN can be maximised when the child is cared for by a multi-disciplinary team that uses the existing evidence-based guidelines. A portable infusion pump should be used and the specialist centre should facilitate care close to home whenever possible.

In children with other major organ failure, e.g. severe developmental delay without the ability to live an independent life, or those who need palliative care, home PN may prolong suffering rather than improve quality of life. In such cases an ethical review may be needed.

10. Home PN long-term outcome: importance of centralised home PN expert centers and the role of small bowel transplantation

R 12.11	**Early referral of long-term PN patients to an expert center may reduce PN-associated complications (LOE 2−, RG 0, strong recommendation for, strong consensus)**
R 12.12	**Early referral to a centre for intestinal transplantation can minimise mortality from Home PN related complications whilst on the waiting list (LOE 2−, RG 0, conditional recommendation for, strong consensus)**
R 12.13	**Home PN expert centres should provide 24-h phone support and support weaning off PN at the earliest opportunity (LOE 4, RG 0, strong recommendation for, strong consensus)**

Large, long-term pediatric surveys reported a mean Home PN duration of about 2 years with an upper duration longer than 15 years [7,35]. About 40–70% of pediatric patients can be weaned from long-term Home PN depending on their underlying disease and medical condition, the prognosis being better for inflammatory bowel diseases and short bowel syndrome than for other indications [7,36,37]. Patients with motility disorders and structural enterocyte defects have an increased risk for permanent PN dependency [36,38].

Survival rates of long-term Home PN patients vary between 62 and 94% depending on cohort and observation period [7,39]. Mortality during the early years of Home PN is mainly attributable to the underlying disease, whereas in long-term patients PN-related complications predominate [40]. Children on Home PN have better survival rates and greater likelihood of resuming full enteral nutrition than adult patients [7].

However, a subgroup of children receiving Home PN have irreversible intestinal failure and cannot be weaned from PN [38]. In these patients small bowel transplantation might be an alternative to lifelong Home PN, depending on the individual situation (complications of long-term PN, tolerance of the family). Only a small percentage of patients require immediate transplantation for life threatening conditions. When irreversible intestinal failure is diagnosed, patients should be considered to be listed for intestinal transplantation in accordance with the criteria of the American Society of Transplantation [41]. Nevertheless, Home PN can be used for an indefinite period of time without intestinal transplantation, if long-term PN is effective and well tolerated. Some children are now growing up on PN and transitioning to adult care. Careful support is needed to ensure that the young adult engages with their new team and takes on appropriate responsibility for their future health. Since the first isolated small bowel transplantations, major advances resulted from the use of new immunosuppressive treatments [2]. When liver structure and function are impaired by long-term PN, a combined small bowel and liver transplantation should be considered. However, timing of referral and criteria for isolated intestinal or combined transplantation are still a matter of debate [40,41]. Earlier referral may be a contributory factor to improved survival [2]. Home PN expert centers should provide a 24-h phone support and support weaning off PN at earliest opportunity. Early referral of long-term PN patients, especially before irreversible liver failure occurs, can increase their quality of life and survival and reduce the cost of care [2].

Conflict of interest

None declared.

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Clinical Nutrition 37 (2018) 2409–2417

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Standard versus individualized parenteral nutrition

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ARTICLE INFO

Article history:
Received 29 May 2018
Accepted 29 May 2018

1. Methods

Literature search

Timeframe: New publications from 2004 until December 2014 were included. Relevant "older" historic references related to these were also considered. A second literature search for RCTs and significant publications was conducted until the end of November 2016.

Type of publications: Randomized trials, observational studies (case-controls, prospective cohort studies, time series, and retrospective data), meta-analyses, and systematic reviews.

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https://doi.org/10.1016/j.clnu.2018.06.955
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Table: Recommendations for standardized versus individualized parenteral nutrition (PN)

R 13.1	Standard PN solutions should generally be used over individualized PN solutions in the majority of pediatric and newborn patients, including VLBW premature infants (LOE 2 in premature infants and LOE 3 in children, RG 0, Conditional recommendation for)
R 13.2	Individually tailored PN solution should generally be used when the nutritional requirements cannot be met by the available range of standard PN formulations (i.e. in very sick and metabolically unstable patients such as those with abnormal fluid and electrolyte losses; and in infants and children requiring PN for prolonged periods such as those with short bowel syndrome (LoE 2, RG B, Strong recommendation for)
R 13.3	Computerized prescription, whether standardized or individualized, should be used in the ordering process of PN when possible (LoE 2+, RG B, Strong recommendation for)

Key words: Standard parenteral nutrition, individualized parenteral nutrition, individually-tailored or prescribed parenteral nutrition, computerized prescription, premature or preterm infants, very-low-birthweight infants, pediatric patients, infants, children.

Language: English

Search: Searches were performed in three stages. First, all the titles on the relevant key words were retrieved. 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.

2. Introduction

PN can be provided as a standard, usually commercial, formulation that is designed to meet the nutritional needs of most patients of the same age group with a similar condition. The aim of standardizing parenteral nutrition (PN) is to improve patient safety (minimize procedural incidents) and optimize resource efficiency at the same time as providing clinically appropriate nutrition (meeting individual patient requirements) [1].

Alternatively, an individually tailored PN formulation, adapted to the individual patient's nutritional needs, can be prescribed. Both types of PN preparations have advantages and disadvantages. Stability of the final product, time pressures on the pharmacy, quality control and cost benefit considerations make the use of standard solutions an attractive option. These standard formulas do not necessarily meet all the requirements of newborns, infants and children [2,3], although even in those units that rely on individualized prescribing, there is some scope for their use in stable patients [4].

The following questions were addressed regarding standardized versus individualized PN:

- Can Standard PN cover the needs of all paediatric patients?
- Is it essential to use computerized prescription?
- Should Standard PN be preferred over individualized PN?
- Can Standard PN be ordered for long periods of time?

Table 1 summarizes studies comparing standardized vs. individualized PN in neonates, infants and children based on their level of evidence. In general, there are very few randomized controlled studies, and unfortunately these are relatively small or methodologically problematic. Overall the level of evidence is low and this is reflected in the strength of our statements and recommendations.

3. Individually prescribed parenteral solutions

The main advantage of individually prescribed PN solutions is that these are tailored to suit a specific patient, and to provide optimal nutrition, assuming that all nutrients are delivered in a safe and bioavailable manner. The prescription can be changed on a daily basis, reflecting the patient's medical condition and most recent laboratory tests [4]. In contrast to individualized prescriptions, standardization carries the risk of turning into "cookbook medicine" that lacks continuous clinical judgment of the patients' changing nutritional requirements. This risk may be increased when the patient is a tiny fragile very-low-birth-weight (VLBW) premature infant with very high nutritional requirements and at risk of developing significant nutrient deficits and sometimes life-threatening, metabolic disturbances (e.g. hypo- or hyperglycemia, hypo- or hypernatremia, hypo- or hyperkalemia). Studies in VLBW infants as well as in pediatric patients suggest that compared to infants on standard PN, infants given individually tailored PN received more optimal nutrition, achieved better growth without clinical or laboratory complications, had a shorter period of exclusive PN and required fewer electrolyte corrections [5–7]. A randomized controlled study comparing individualized versus standard PN formulation in premature infants demonstrated higher intakes of amino acids, lipids and energy, with greater weight gain in the group receiving individualized PN [6]. However, the difference in caloric intake and weight gain may not have been attributable to the administration of standard solutions per se, but to the more intensive monitoring assisted by pharmacists in the group receiving individualized PN. Some authors have suggested that individualized PN preparations are more optimal for the current more aggressive nutritional approach to PN in VLBW infants [7]. Yet, these authors admit that the currently available standardized PN admixtures with adequate nutritional composition should be considered as appropriate alternatives. This is in contrast to "historical" standardized PN solutions that did not meet all the nutritional requirements of neonates, and could have resulted in inadequate nutrition and poor growth if used for longer periods [2].

4. Standard parenteral solutions

R 13.1	**Standard PN solutions should generally be used over individualized PN solutions in the majority of pediatric and newborn patients, including VLBW premature infants (LOE 2 in premature infants and LOE 3 in children, RG 0, conditional recommendation for, strong consensus)**
R 13.2	**Individually tailored PN solution should generally be used when the nutritional requirements cannot be met by the available range of standard PN formulations (i.e. in very sick and metabolically unstable patients such as those with abnormal fluid and electrolyte losses; and in infants and children requiring PN for prolonged periods such as those with short bowel syndrome (LoE 2, RG B, strong recommendation for, strong consensus)**

A study comparing short term standard solution (fixed amino acid/glucose ratio) with a computer generated individualized prescription, taking enteral intake and additional fluids into account, did not find any differences in the weight gain of premature infants [8]. Furthermore, in a study that evaluated the use of standard PN solutions in a pediatric intensive care unit, it was found that standard PN orders could be used in the majority of the patients. These solutions were usually nutritionally adequate and the intake of most macronutrients and electrolytes was similar to

Table 1
Summary of studies on standardized and individualized PN in neonates, infants and children. Following the methodology of previous reviews [1,18,38]. Adapted for the pediatric population and updated − December 2014.

Author (year)	Patients	Intervention	Design	Results	Comments
LOE 1 + or 1++: Large randomized trials or systematic reviews with clear-cut results					
None					
LOE 1−: Small or large randomized trials or systematic reviews with uncertain results or flaws in study design					
Cade (1997) [8]	Premature infants − median GA 29 wks	STD (n = 25) vs. IND (n = 27). IND was computer-assisted regime	Prospective RCT	There were no differences in daily weight gain; biochemical stability (as indicated by plasma Na and P); or PN solution wastage	Both regimes prescribed electrolytes as per kg/day
Level 2+: Nonrandomized, contemporaneous controls					
Mutchie (1979) [5]	Pediatric hospital patients	STD solutions (n = 26) vs. IND (n = 26). IND was individualized by use of minicomputer and monitored by a pharmacist. Six patients in each group were neonates ≤35 days on PN only for 8−20 days	Nonrandomized contemporaneous controls	IND longer PN duration and rate of use (+31%), but lower costs (−44.10$ per TPN course). IND better weight gain (17 g/day vs. 4 g/day in STD) (p < 0.05) for the 6 neonates	Pharmacist monitoring of TPN only in IND group
Dice (1981) [6]	Premature infants − mean GA 31 wks	STD (1 formula) (n = 14) vs. IND (n = 14)	Nonrandomized contemporaneous controls (patients assigned alternatively to groups)	IND better weight gain (11.8 vs. 4.9 g/day) (p < 0.02) IND better intake of: (1) protein (2.2 vs. 1.9 g/kg/day) (p < 0.01); (2) Calories (62 vs. 52 kcal/kg/day) (p < 0.001); (3) Lipids (2.0 vs. 1.5 g/kg/day) (p < 0.001) But, in IND also greater costs	STD PN facility developed. IND both individualized and pharmacist-monitored
Krohn (2005) [9]	Pediatric ICU − ages 3 months to 18 years (n = 46). (Lack of demographic data)	STD (8 formulas) (226 prescriptions) (68%) vs. IND (111 prescriptions) (32%)	Observational study (8 months) based on record review. Descriptive results. No statistical analysis	54% of patients receiving STD PN required nutrient modifications Na, Ca and P lower but AA higher in IND vs. STD in patients <10 kg P not given in 20 of 57 IND PN More electrolytes imbalances in IND vs. STD (34% vs. 26%)	STD PN originally prepared in the hospital pharmacy, but modifications were performed by nurses under laminar flow hood on the ward. IND formulations were prepared by nurses under laminar flow hood on the ward area
Skouroliakou (2009) [13]	Preterm neonates (28−36 weeks) − mean GA − 33.9, mean BW − 2100 g − with respiratory failure	STD (computer-based) (n = 30) vs. IND (manually calculated by neonatologists) protocols	Nonrandomized contemporaneous controls (patients were pair-matched by GA and clinical condition)	STD protocols provided more: energy (111 vs. 89 kcal/kg/day) (p = 0.05); protein (AA 1.70 vs. 1.33 g/kg/day) (p = 0.023); and calcium (2.02 vs. 1.01 mEq/kg/day) (p < 0.001) Infants in STD group gained weight better during PN (+44 g) vs. IND (−53 g) (p = 0.002) At the end of PN, STD infants had some better CBC values (MCV & MPV)	Four STD protocols based on ASPEN guidelines (1993−7) prepared by automatic compounder supervised by pharmacist. IND manually calculated and prepared under pharmacist supervision
LOE 2−: Nonrandomized, historical controls					
Yeung (2003) [10]	Premature neonates GA < 33 wks	STD (2 formulas) (n = 27) (2000−1) vs. IND (n = 31) (1999−2000)	Retrospective observational study (nonrandomized historical controls)	Intake of protein better in STD in each of the days (2−7) and cumulative for the first week (13.6 vs. 9.6 g/kg/wk) (p < 0.05) STD received more Ca (1.25 vs. 0.95 mmol/kg) and P (1.25 vs. 0.95 mmol/kg) on days 4−7 (p < 0.02), but less Mg Significant cost reduction STD 88 vs. IND 130 AUD per bag	STD PN commercially batched produced. IND prepared in the pharmacy
Lenclen (2006) [11]	Premature neonates GA < 32 wks	STD (3 formulas) (n = 20) (2003) vs. IND (n = 20) (2001)	Retrospective observational study (nonrandomized historical controls)	Intakes better in STD on Day 3: (1) AA (1.5 vs. 0.9 g/kg/day) (p = 0.0001); (2) CHO (10.7 vs. 9.6 g/kg/day) (p = 0.002); (3) Ca:P ratios better balanced (p = 0.0001)	STD PN prepared in sterile isolator in pharmacy. IND prepared by nursing staff under laminar airflow hood

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Table 1 (*continued*)

Author (year)	Patients	Intervention	Design	Results	Comments
				Cumulative intake of AA at first week better in STD (13.6 vs. 11.1 g/kg/wk (p = 0.0003)	
Smolkin (2010) [7]	Premature VLBW (BW ≤ 1500 g) neonates	STD (n = 70 cohort in 2000–1) vs. INS (n = 70 cohort in 2006–7). (5 STD formulations)	Retrospective observational study (GA-matched historic controls)	IND group showed significantly greater daily weight gain during NICU stay (23.76 vs. 20.27 g/day) (p < 0.0001). IND group showed significantly greater weight gain SDS (standard deviation scores) at 1st week (p = 0.036) and over the 1st month of life (p = 0.0004); and had higher discharge weights (2627 vs. 2434 g) (p = 0.001) and discharge weight SDS (p = 0.012). IND had also better FOC SDS at discharge (p = 0.006) IND infants received higher mean daily caloric intakes (75 vs. 53 kcal/kg/day) (p < 0.0001), as well as higher mean daily protein, glucose and fat intakes (p < 0.0001 for all intakes) compared to STD PN IND had significantly shorter durations of exclusive PN (5.6 vs. 7.9 days) (p = 0.007) and needed less electrolyte corrections (p = 0.003)	IND infants had significantly lower mean BW All intakes (energy, AA, CHO and fat) were significantly lower with STD formulations. STD data reflects nutritional practices 6 years earlier. Authors admit that IND PN was in accordance with the current more aggressive nutritional approach to VLBW infants, and that STD PN with adequate compositions (as opposed to their STD formulations) may offer appropriate alternative to IND PN in VLBW
Iacobelli (2010) [12]	Premature neonates GA < 33 wks	STD (n = 67 cohort in 2006–7) vs. IND (n = 40 cohort in 2006). (8 STD formulations for days 1–7)	Prospective observational study (non-randomized historic controls)	STD group received during the 1st wk of life significantly more: energy (64 vs. 56 kcal/kg/day) (p < 0.001); AA (2.2 vs. 1.8 g/kg/day) (p < 0.001); glucose (10.4 vs. 9.8 g/kg/day) (p < 0.01); lipids (1.7 vs. 1.3 g/kg/day) (p < 0.001); Na (1.48 vs. 0.93 mmol/kg/day); and less volume/water (125 vs. 131 ml/kg/day) (p < 0.05) compared to IND. Nonoliguric hyperkalemia was significantly less frequent in STD compared to IND (2.9% vs. 20.0%) Weight loss (% of BW) at DOL # 7 was significantly reduced in STD (4.2%) vs. IND (7.7%)	IND prescriptions prepared with the help of computer system. STD orders based on ESPEN/ESPGHAN guidelines 2005. STD bags prepared by a commercial manufacturer
Caba Porras (2010) [14]	Children > 1 yr, or > 10 kg; Mean age 6.8 yrs (1–14), weight 26.6 kg (9–50) (From 2006 to 2008)	N = 47 children, 539 units of PN STD (83%): n = 39, 437 units IND: n = 8, 102 units	Retrospective observational	STD: Total energy requirements reached within 1–3 days using 1–3 types of formulas. Only 4% (22) modified with easily feasible changes: volume increase (16), glucose lowering (3), K increase (3) IND: The same trends, but caloric intake lower than 33% of recommended	STD PN meet nutritional requirements in most patients with adaptability and versatility to morbidity. STD eased prescription-validation and preparation and improved efficiency
Doublet (2013) [15]	Newborns admitted to NICU on DOL#1 and required TPN	3500 PN prescriptions evaluated	Retrospective observational study comparing two one-year periods before and after move from individualized to standardized formulations	The TPN goals for newborns in the first 2 wks of life (as defined and written in the NICU policy) were better full filled with STD PN compared to IND (44.0% vs. 9.4% of the prescriptions). Differences appeared as early as DOL#3 and remained during the first 15 days on PN	Goals defined by TPN goals for newborn of this university hospital unit
Bolisetty (2014) [39]	Preterm neonates GA < 32 wks N = 153 divided into pre (N = 68) & post-consensus (N = 85) groups	New STD PN formulations implemented in July 2011 [17]	Before-after intervention study	New consensus STD PN solutions provided better protein intake in the first 7 days and were associated with greater weight gain in the first 4 weeks Post-consensus group in comparison to pre-consensus cohort: • Commenced PN earlier (6 vs. 11 h, p = 0.005);	Before and after study, old vs. new STD solutions, in a small population (n = 153) Comparison to either IND PN solutions and/or each NICU's own STD PN solutions Some of the results might have been attributed to the change in

				• Had higher protein intake on days 1–7 (up to 3.55 vs. 2.35 g/kg/day, $p < 0.001$); • Had higher caloric intake on days 1–3 ($p = 0.03$); • Had less daily fluid intake on days 3–7 ($p = 0.02$); • Had reduced duration of lipid therapy ($p = 0.01$); • Had a significantly greater weight gain in the first 4 weeks ($p = 0.003$). Protein intake on DOL#1 was below the consensus goal of 2 g/kg/day Safety – OK	PN practices dictated by the new consensus guidelines More SGA infants in post-consensus group (with twice more SGA infants in the "Before" group) Effect of enteral and PN nutrition pooled together, along with limitations related to the lack of complete enteral and PN intake data from birth to discharge to determine any improvements or variation between the cohorts Significant increase of protein and energy intake without real clinical benefit
LoE 3: Case series, uncontrolled studies, surveys					
Devlieger (1993) [40]	VLBW Neonates (≤1500 g)	STD (a single PN formulation with fixed amount of nutrients in four dilutions with water to a fluid load of 90, 110, 130 or 170 ml/kg/day). Multivitamins and fat emulsions given separately	Observational	Weight gain similar to the normal fetal weight gain in utero. STD presents advantages in terms of safety, availability, ease of application, and lower production costs. No significant complications recorded	No comparison to control patients on IND PN
Beercroft (1999) [4]	Neonates – Median GA 29 wks, median BW 1080 g	148 IND PN prescriptions over 4-wks period were compared to computer-recommended STD protocols	Observational	82% of PN prescriptions deviated from protocol (in relation to nutrients: CHO 61%, AA 7%, fat 0, Na 52%, K 9%, P 53% and Ca 24%); But only 44% of these changes were prompted by abnormal lab results (Na13%, K 53%, Ca 4%, P 69%) Authors estimated that up to 2/3 of PN orders could be given as a range of STD PN solutions	Only comparison of IND vs. STD PN formulations recommended via a single specific computer program. Authors conclude that a higher proportion of PN solutions could be standardized if the computer regimes were modified to reflect current practices in the NICU
Bethune (2001) [2]	Neonates, infants and children	Comparison of STD PN formulations to recommended intakes (in neonates and infants 2 leading university hospitals' standards; and in children 2 commercially available standards)	Survey of STD PN solutions in the UK	With adequate nutritional monitoring commercially available STD can be used safely for children > 1 yr for short periods if biochemical deficiencies corrected by addition of electrolytes No commercially available STD for PN in neonates and infants, commonly resulting in inadequate provision of nutrition to these patients with potentially serious consequences	Recommendations: Increase training in PN compounding and clinical nutrition Preparation of commercially available, licensed STD bags suitable for neonates and infants, as well as next-day service for IND formulations from a small number of specialist centers for those in need
Lapillonne (2009) [41]	National survey in France in 296 neonatal departments	STD PN were used in 66% of units and accounted for 45% of PN prescriptions. Significantly more in Level II than Level III (68% vs. 24%) ($p < 0.0001$)	Survey	13 of the 40 STD PN solutions for neonates did not contain AA The addition of macro- and/or micronutrients was very frequent	Great heterogeneity in PN practices Large number of STD PN solutions were not appropriate for the nutrition of full-term and/or preterm infants
Rigo (2013) [16]	1. Single center – cohort of VLBW neonates – Mean GA 28.5 wks, mean BW 1005 g 2. Multi-center (phase III) non-comparative study of preterm (<37 wks) neonates – Mean GA 31.2 wks, mean BW 1382 g	Binary premixed RTU STD PN solution from pharmacy hospital (n = 102) Commercially premixed 3-chamber STD PN bag (n = 97)	Observational	1. Nutritional intake was in line with the most recent updated recommendations for AA and energy intakes (2.5 and 45 on Day 1 increasing to > 3.5 g/kg/day and >100 kcal/kg/day at the end of the 1st week). Postnatal weight loss ≤6% limited to 1st 3 days with mean return to BW by 7 days	Cumulative nutritional deficit and postnatal growth restriction can be abolished, even in ELBW infants, by using STD premixed RTU PN solutions STD PN formulations give answer to the need for well-

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Table 1 (*continued*)

Author (year)	Patients	Intervention	Design	Results	Comments
				2.10 infants required additional AA in the 1st 2 days. & infants received additional glucose. 65 required additional electrolytes (Mainly Na) and minerals. Mean protein & energy were in the range of recommendations. Weight gain during PN was positive especially in those included early, close to birth	balanced PN with high AA from the 1st day of life in VLBW infants Commercial premixed 3-chamber STD PN bags (with possibility to activate also the lipid component in the same bag) are easy to use, practical for handling and well-accepted by nurses, pharmacists and neonatologists, compared to RTU compounded bags and tailored premixes without any serious adverse events
McCarthy (2016) [42]	VLBW infants	Over 5 months all IND PN prescriptions for VLBW infants $\leq$ 31 weeks from DOL#2 on were compared to the STD appropriate for use on the day in question	Observational	VLBW infants prescribed IND PN received significantly more AA (28%), glucose (6%), energy (11%) and calcium (8%) from the aqueous phase of PN than they would have received if given a similar volume of STD PN. These benefits were seen over all the days for which PN was administered	Modifications of the STD PN formulations that have been used for comparison to IND PN in this study would probably result in better STD PN formulations that could change the conclusions of this study
Kriessl (2016) [43]	VLBW ($\leq$1500 g) preterm infants (N = 71)	Observational study	Comparison of IND (using the new prescription software catoPAN, Cato Software Solutions) vs. STD (Numeta, "ready-to-use" triple-chamber container, Baxter) PN prescriptions	Protein intake in STD PN was significantly lower than in IND prescribed PN solutions, and below the recommendations for daily supply during the first days of life Energy intake was significantly higher with Numeta, but energy, carbohydrate, and fat intakes were satisfying The protein-energy relation in Numeta is not well balanced Numeta provided inadequate high intake of electrolytes for the first day of life and also during the transition phase Numeta as a STD commercial PN save human resources (shorter preparation time), but bags of this STD PN cost higher than STD	Single center Small sample: 374 prescriptions in a small population (n = 71) Most prescriptions studied were for preterm infants with BW > 1000 g (n = 333) (BW $\leq$ 1000 g [n = 41]) The conclusion of the authors was that Numeta is an alternative to IND PN in infants with BW > 1000 g and an enteral feeding volume of approximately $^{1}/_{3}$ of the total daily intake

AA = amino acids; BW = birth-weight; CHO = carbohydrates; DOL = day of life; ELBW = extremely-low-birth-weight (BW $\leq$ 1000 g); FOC = fronto-occipital circumference (head circumference); GA = gestational age; ICU = intensive care unit; IND = individualized; NICU = neonatal ICU; PN = parenteral nutrition; RCT = randomized controlled study; RTU = ready to use; SDS = standard score deviations; STD = standardized; TPN = total PN; VLBW = very-low-birth-weight (BW $\leq$ 1500 g).

those from individually prescribed PN [9]. In fact, calcium and phosphate intakes were better with standard PN compared to the individualized PN, and electrolyte imbalances occurred less frequently [9]. Another study retrospectively evaluated the difference in nutrient intakes and biochemical responses in premature infants who received standardized versus individualized PN between days 2–7 of life. In that study, there was no clinical advantage or improved biochemical control with individualized PN regimes [10]. An increase in protein intake was observed in the standardized PN group, accompanied by proportional increases in the intakes of glucose, electrolytes and acetate. It was also found that in infants who were on standardized PN, the cumulative deficit in protein intake by the end of the first week was 35% less compared to those who were on the individualized regimes. Infants on standardized PN also had higher intakes of calcium and phosphate, resulting in less cumulative deficits and better bone mineralization [10]. Lenclen et al. also showed that in premature infants standardized PN formulations provided higher early intakes of amino acids and glucose, and better calcium phosphate ratio during the first week of life, while maintaining the same biochemical parameters [11]. More recently, studies in preterm infants have shown that PN using standardized formulations resulted in better intakes of protein, energy, glucose and calcium with less water intake and decreased incidence of significant electrolyte disturbances [12,13]. Furthermore, nutritional goals of preterm infants and children could be successfully met using standardized PN formulations [14–16]. Recently, the Australasian Neonatal Parenteral Nutrition Consensus Group agreed that standardized PN offers advantages over routine individualized PN in terms of providing adequate nutrition for the majority of neonates in neonatal intensive care units without significant alteration in biochemical responses, and with the potential for reduced cost and prescription error. These conclusions are based on five different ready-to-use binary solutions for preterm infants and one for term neonates [17].

Based on the above, it is suggested that a standardization strategy should be considered as part of the approach for improving quality control and good professional practice for the preparation of PN solutions. Batch-produced standardized PN bags can be readily available as ward stock in neonatal intensive care units, thus allowing initiation of PN immediately after the delivery of a premature infant [16]. Overall, readily available standardized PN solutions are advantageous compared to individualized prescriptions, by providing higher nutrient intakes that are associated with better weight gain and less nutritional deficits [18]. Commercially prepared standard PN bags decrease the risk of ordering errors, as well as the risk of compounding errors in the hospital pharmacy that has to deal with many different PN prescriptions on a daily basis. Large-scale commercial production of standard PN bags can be further facilitated by using automated compounding technology that can assure better pharmaceutical control of the physicochemical stability and compatibility of PN admixtures. This can decrease the risk of potentially adverse outcomes from infusion of incompatible nutrient admixtures (e.g. precipitated calcium phosphate) [19–21]. Large-scale commercial production of standard PN bags can also offer better aseptic manufacturing conditions than the average hospital pharmacy, thus decreasing the risk of PN-associated infections [2]. Commercially batch-produced standardized PN bags may also reduce the large costs of individualized PN production [22]. The need to add the parenteral multi-vitamins to the standard PN bag shortly before infusion is a limitation that requires proper handling to assure aseptic conditions and avoid errors. Also, the inclusion of various trace elements may shorten the shelf life of the standard bag.

5. Computer assisted prescribing

R 13.3	**Computerized prescription, whether standardized or individualized, should be used in the ordering process of PN when possible (LoE 2+, RG B, strong recommendation for, strong consensus)**

PN is an intravenous medication, with more than 50 ingredients and additives, and as such is liable to medication errors, especially in pediatric patients where all the calculations are weight-based [23]. The ordering process is time consuming, necessitates knowledge and experience, and involves the risk of fatal errors [23,24]. Development of an optimal PN order form, including age and weight-specific nutrient requirements with guidelines for advancing substrates may help the clinician especially if inexperienced, facilitating PN prescription and decreasing prescribing errors [25,26]. Computerized prescription may aid in maintaining stability and compatibility of PN solutions, which are safety issues of great concern [23]. The most significant pharmaceutical issues involve the stability of intravenous lipid emulsions and the compatibility of calcium and phosphate salts to avoid precipitates. The existence of a hospital nutrition support team, well-established communication channels between the prescribing clinicians and the pharmacy team dedicated to PN preparation, and the use of compounding devices decrease these risks, but does not abolish them [19–21,27].

Recent technology has enabled the development of advanced computerized PN ordering systems where the software is based on guidelines [28]. Such computerized nutritional software provides a low cost and easy to use method for correctly calculating nutrient dosages. Indeed, the use of a computerized prescription results in better growth and better biochemical control in newborn studies [23]. In addition, electronic ordering systems can still allow individualization of PN prescription, thus improving biochemical control and decreasing wastage. Computer assisted PN prescribing programs are a valuable educational tool for the junior clinician who is not experienced in clinical nutrition. These tools also facilitate communication between the prescribing clinical team and the pharmacy department [4]. Computer programs for ordering PN are widely used [23,24,29]. One such program reduced the time needed to calculate a nutrition plan from a mean of 7.1 min to 2.4 min, with errors in calculation being corrected interactively and reduced from 56% to 22% [24]. In another study it was found that automating the process of writing and delivering PN orders saved time and resulted in improved nutrient content of the PN solutions [30]. The time required to write and deliver PN orders was significantly lower using computer rather than manual methods (1.4 ± 0.2 vs. 4.5 ± 0.5 min; $P = 0.0001$), and the use of computer ordering lead to significant improvements in weight gain [31] and the nutrient composition of the PN for energy, protein, calcium, and phosphate [23,32]. In addition, alkaline phosphatase concentrations improved. This helped achieve caloric and protein intake goals earlier and improved mineral status in premature infants compared with the manual method of ordering [30]. Available programs can rapidly generate a nutrition plan with reduced likelihood of providing excessive glucose and energy [33].

However, in practice it has not been possible to confirm all the proposed advantages of individualized computer-assisted prescriptions in premature infants [8]. A possible disadvantage of a computer-based prescription program is that it might encourage trivial adjustments in PN prescriptions, based on laboratory results that in clinical practice are irrelevant [4]. Based on these

observations, it was suggested that a higher proportion of PN could be standardized, if modified to reflect the practice guidelines.

6. All-in-one multi-chamber standardized PN solutions

When standardizing PN solutions, the stock solutions may be two in one (proteins and dextrose while lipids are given separately) or all in one (bag containing protein dextrose and lipids). A recent study evaluated four all-in-one (AIO) standard pediatric PN solutions and found that their use was feasible and safe, although some may require electrolyte changes and a few patients still require individualized PN, especially for longer periods [34]. Other recent studies evaluated the efficacy, safety, flexibility, and ease of use of an industrially manufactured ready-to-use multi-chamber PN bag system containing three sterilized macro-nutrient solution chambers (for amino acids, glucose and optional lipid bag activation system) specially designed for administration not only to children [35] but also to preterm infants [16,18,36]. This technologically advanced multi-chamber PN bag system was easy-to-use, guaranteed sterility and longer shelf life, and provided well-balanced and safe nutritional support. Nutritional intakes and weight gain were within the recent PN recommendations for preterm infants.

7. Conclusions

Computer assisted prescribing software for PN should become readily available, as these programs can save time, decrease prescription and compounding errors, and improve the quality of nutritional care. Such computerized programs should guide the physician to the most adequate standardized solution and optimize the use of individualized solutions. The combination of computerized prescription and the use of multi-chamber PN bags may enhance the ability to rely on standardized PN with minimal usage of individualized prescriptions. Computerized prescription, whether standardized or individualized, should be used in the ordering process of PN where possible.

Standard PN solutions can be used safely in most pediatric and newborn patients, including VLBW premature infants, certainly for the short periods (up to 2–3 weeks) needed for most infants [18,37]. Standard PN solutions should generally be chosen over individualized PN solutions in the majority of pediatric and newborn patients, including VLBW premature infants.

A range of standard regimens to suit different clinical conditions should always be available. Adequate monitoring of the metabolic and nutritional status of an infant on standardized PN should be assured, and the most suitable available standard PN formulation for the infant's condition should be ordered at least once daily. Individually tailored PN solution should generally be used when the nutritional needs cannot be met by the available range of standard PN formulations (i.e. in very sick and metabolically unstable patients (such as those with abnormal fluid and electrolyte losses); and in infants and children requiring PN for prolonged periods (such as those with short bowel syndrome)). Uncritical use of standard formulations in such patients, particularly over longer periods of time, may be less than optimal for growth and development.

Conflict of interest

None declared.

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Clinical Nutrition 37 (2018) 2418–2429

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

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

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ARTICLE INFO

Article history:
Received 12 June 2018
Accepted 12 June 2018

1. Methods

Literature search

Timeframe: publications from 2004 until December 2014 were reviewed

Type of publications: The search was restricted to infants and children (0–18 years) but not limited by publication form or language.

Key words: The search was conducted in Ovid Medline using both MeSH terms and text words for “parenteral nutrition

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https://doi.org/10.1016/j.clnu.2018.06.956
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complications". In parallel an expert search was conducted focusing on specific subtopics of parenteral nutrition complications.

Titles and abstracts retrieved by electronic and expert searches were first screened by a collaborator of Cochrane Hungary and clearly irrelevant abstracts were removed. Subsequently, members of the Working Group screened titles and abstracts for eligibility. Full texts of all potentially relevant manuscripts were retrieved and assessed.

damage; 2) admixture stability; 3) interactions between PN and medications; 4) metabolic bone disease; 5) hepatobiliary complications; and 6) effects of PN on growth parameters.

Other types of complications (e.g. metabolic or nutritional complications, Refeeding syndrome) are described in other chapters of this Guideline.

Table 14.1: Recommendations for the prevention of complications

R 14.1	Any child with IF and an indwelling CVC is at significant risk for CRBSI and, accordingly, any fever (temperature >38.5 or rise >1 °C), or change in clinical or laboratory parameters should raise the suspicion of CLABSI until proven otherwise (LOE 2+, RG B, strong recommendation)
R 14.2	Paired quantitative blood cultures taken simultaneously from both the CVC and a peripheral vein should ideally be obtained when a CRBSI is suspected and before the start of antibiotic therapy (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation)
R 14.3	The most readily available technique to confirm CRBSI without catheter removal is the calculation of DTP (differential time to diagnosis) between blood cultures drawn from the catheter and from a peripheral vein or separate lumen (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation)
R 14.4	Empirical antibiotic therapy for CRBSI should usually include coverage for Gram-positive coagulase-negative or −positive staphylococci and Gram-negative bacilli (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation)
R 14.5	The duration of antimicrobial therapy for CRBSI with retained catheter is generally 10−14-days, assuming clinical and microbiological response within 48 −72 h and no evidence of complications (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation).
R 14.6	Removal of the CVC is recommended in the presence of clinical deterioration or persisting or relapsing bacteremia, presence of suppurative complications or for particular infectious agents (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation)
R 14.7	Thrombotic catheter occlusion and CVC related thrombosis require thorough investigation and treatment as they may be associated with significant morbidity (LOE 2−, RG B, strong recommendation)
R 14.8	Fibrinolytics are the drug class of choice for treating thrombus-occluded catheters. Tissue plasminogen activator (tPA, alteplase) is currently the recommended agent; however, urokinase and recombinant urokinase (rUK) can also be used (LOE 2+, RG B, strong recommendation)
R 14.9	The recommended management of acute and symptomatic CVC-related thrombosis depends on the requirement for the CVC and usually requires antithrombotic medication (LOE 2+, RG B, strong recommendation)
R 14.10	Proper positioning of the catheter tip and immediate investigation when catheter breakage or fluid extravasation are suspected should be implemented in order to prevent the occurrence of significant morbidity (LOE 4, RG 0, strong recommendation)
R 14.11	Appropriate measures to secure the catheter in place and education for users on correct maintenance and safety of the catheter are strongly recommended (GPP, strong recommendation
R 14.12	PN should be administered wherever possible using an admixture formulation validated by a licensed manufacturer or suitably qualified institution (GPP, strong recommendation)
R 14.13	A matrix table should be sought from the supplier of the formulation detailing permissible limits for additions of electrolytes and other additives (GPP, strong recommendation)
R 14.14	Alternative ingredients should not be substituted without expert advice or repeat validation (GPP, strong recommendation)
R 14.15	Phosphate should be added in an organic-bound form to prevent the risk of calcium-phosphate precipitation (GPP, strong recommendation)
R 14.16	If inorganic phosphate is used, stability matrices and order of mixing must be strictly adhered to (GPP, strong recommendation)
R 14.17	When '2 in 1' admixtures with Y-site lipids added are used, addition of lipids should be fully validated by the manufacturer or accredited laboratory, or the lipid infused through an alternative line (GPP, strong recommendation)
R 14.18	Mixing of medications with PN in administration lines should be avoided unless validated by the manufacturer or accredited laboratory (GPP, strong recommendation)
R 14.19	Multi-layer bags which are impermeable to oxygen are recommended for PN administration (GPP, strong recommendation)
R 14.20	Light protection is recommended for both PN bags and administration sets (LOE 3, RG 0, strong recommendation)
R 14.21	The recommended delivery site for PN is via a central line; however peripheral PN can also be given for short periods (LOE 3; RG 0, strong recommendation)
R 14.22	The osmolarity of peripheral PN solution should be kept less than 900 mosmol/l (LOE 3; RG 0, conditional recommendation)
R 14.23	In children on home PN, regular measurements of urinary calcium, plasma calcium, phosphorus, parathyroid hormone and 25-OH vitamin D concentrations and serum alkaline phosphatase activity should be performed (LOE 2+, RG B, strong recommendation)
R 14.24	Ingredients with the lowest amount of aluminum are advocated for the preparation of parenteral nutrition solutions provided to patients receiving PN (LOE 2++, RG B, strong recommendation)
R 14.25	Regular assessment of bone mineralization should be performed (LOE 2−, RG B, strong recommendation)
R 14.26	The risk of liver disease may be decreased by reducing patient-related and PN-related risk factors (LOE 2+, RG B, strong recommendation)
R 14.27	In patients with intestinal failure-associated liver disease, maximizing enteral intake as tolerated may improve liver disease outcome (GPP, strong recommendation)
R 14.28	In patients on long-term and home PN, cyclic of PN infusion is recommended as soon as metabolic and fluid status allows (LOE 3, RG 0, strong recommendation)
R 14.29	Pure soybean-based lipid emulsions should be avoided in the presence of cholestasis (LOE 3, RG 0, strong recommendation)
R 14.30	The use of mixed LEs may be encouraged in IF patients for long term PN (LOE 3, RG 0, conditional recommendation)
R 14.31	The initiation of ursodeoxycholic acid may be considered in the presence of biochemical signs of cholestasis (LOE 3, RG 0, conditional recommendation)
R 14.32	Early referral to an experienced pediatric intestinal failure rehabilitation/transplantation centre is recommended in infants/children with intestinal failure-associated liver disease (GPP, strong recommendation)
R 14.33	All patients on long term PN require regular monitoring of growth and body composition (LOE 2−, RG B, strong recommendation)

2. Introduction

This chapter handles the following main areas where complications during parenteral nutrition may arise: 1) CVC related complications including infection, occlusion, central venous thrombosis, pulmonary embolism and accidental removal or

3. Complications of central venous catheters

3.1. Infections

Central line−associated bloodstream infections (CLABSIs) are the most common, serious complication associated with central

venous catheters (CVC) use. CLABSIs are a significant cause of morbidity and mortality in pediatric patients with intestinal failure (IF) who are parenteral nutrition (PN) dependent. Intravenous access is a lifeline for these patients, and the loss of vascular sites is an indication for intestinal transplantation [1,2] (LOE 2−). Furthermore, recurrent sepsis is also a major cause of IF-associated liver disease (IFALD) [3–5] (LOE 2−). Unless an alternative source is identified, all bloodstream infections in patients with a CVC are classified as CLABSI. When evidence confirms that the colonized device is the true source of infection, the more specific diagnosis of catheter related blood stream infection (CRBSI) is used [6] (LOE 2+).

The reported incidence of CRBSI in the pediatric literature is between 3.8 and 11.3 infections per 1000 catheter days, depending on patient and catheter variables [7] (LOE 2+). In children with IF the range of CRBSI is very similar, 1.2–10.2 ± 6.2 per 1000 catheter days [8–10] (LOE 3). The estimated reported frequency of CRBSI in home PN (HPN) patients in the literature varies between 0.34 and 3.94 episodes per catheter year [10–13] (LOE 3). Prevention focused protocols can reduce this rate to less than 1 per 1000 catheter-days [14] (LOE 2+). The major pathogens isolated are Gram-positive coagulase-negative (30–40%) or −positive (7.7–15%) staphylococci, Gram-negative bacteria (30–40%), fungi (4.6–6%) or polymicrobial flora (12%) [9,10,15] (LOE 3).

Risk factors that have been associated with an increased rate of CRBSI include prematurity, malignancy, previous abdominal surgery, small bowel length, presence of an enterostomy, lack of enteral nutrition, use of catheter for PN and duration of PN and use of antacids [16] (LOE 2+) [17]; (LOE 3) [18]; (LOE 2+). Medicard insurance and age <1 year were also associated with increased risk for CRBSI (odds ratio [OR], 4.4 [95% CI, 1.13–16.99] and 6.6 [1.50–28.49], respectively; $P < .05$) in children on HPN [19] (LOE 3).

3.1.1. Diagnosis of CRBSI

R 14.1	**Any child with IF and an indwelling CVC is at significant risk for CRBSI and, accordingly, any fever (temperature >38.5 or rise >1 °C), or change in clinical or laboratory parameters should rise the suspicion of CLABSI until proven otherwise (LOE 2+; RG B, strong recommendation, strong consensus)**
R 14.2	**Paired quantitative blood cultures taken simultaneously from both the CVC and a peripheral vein should ideally be obtained when a CRBSI is suspected and before the start of antibiotic therapy (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**
R 14.3	**The most readily available technique to confirm CRBSI without catheter removal is the calculation of DTP (differential time to diagnosis) between blood cultures drawn from the catheter and from a peripheral vein or separate lumen (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**

Any child with IF and an indwelling CVC is at significant risk for CLABSI and, accordingly, any fever (temperature >38.5 or rise >1 °C), lethargy, metabolic acidosis, hypoglycemia, thrombocytopenia or ileus in an IF patient must be presumed to be due to a CLABSI until proven otherwise [6,20] (LOE 2+). The US Center for Disease Control and Prevention has published guidelines for the diagnosis of CRBSI, mainly involving matching peripheral blood cultures with catheter blood or tip cultures [6,20]. However, few studies exist to validate these criteria in children and modified diagnostic criteria are often applied for practical purposes. A definitive diagnosis of a CVC-related infection can be challenging, especially in children. Standard qualitative peripheral blood culture remains the most commonly performed investigation for CRBSI, but does not indicate the source or quantity of organisms and is subject to contamination. In contrast, paired quantitative blood cultures taken simultaneously from both the CVC and a peripheral vein represent a considerable improvement, and should be obtained before initiation of antimicrobial therapy [6,20] (LOE 2++ in adults).

Confirmatory tests for the diagnosis of CRBSI include: culture of the same organism from at least 1 percutaneous blood culture and from a culture of the catheter tip when the catheter is removed, or 2 positive blood samples, one from the CVC and the other from a peripheral vein, that meet CRBSI criteria for quantitative blood cultures or differential time to positivity (DTP). For quantitative blood cultures, a colony count of microbes grown from blood obtained through the catheter hub that is at least 3-fold greater than the colony count from blood obtained from a peripheral vein best defines CRBSI. The most readily available technique to confirm CRBSI without catheter removal is the calculation of DTP between blood cultures drawn from the catheter and from a peripheral vein or separate lumen. For DTP, growth of microbes from a blood sample drawn from a catheter hub at least 2 h before microbial growth is detected in a blood sample obtained from a peripheral vein best defines CRBSI [6,20] (LOE 2++ in adults). In a recent retrospective study in the NICU, optimal DTP cutoff for the diagnosis of CRBSI was >1 h, with a sensitivity of 94%, specificity of 71%, positive predictive value of 88%, and negative predictive value of 83%, suggesting that DTP of paired blood cultures may have some potential in the diagnosis of catheter related infections in this setting [21] (LOE 3). Cultures of blood from the catheter and when appropriate of soft tissues at the entrance-exit sites or tunnel should be obtained before the initiation of antibiotic therapy.

3.1.2. Therapy of CRBSI

R 14.4	**Empirical antibiotic therapy for CRBSI should usually include coverage for Gram-positive coagulase-negative or −positive staphylococci and Gram-negative bacilli (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**
R 14.5	**The duration of antimicrobial therapy for CRBSI with a retained catheter is generally 10–14-day, assuming clinical and microbiological response within 48–72 h and no evidence of complications (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**
R 14.6	**Removal of the CVC is recommended in the presence of clinical deterioration or persisting or relapsing bacteremia, presence of suppurative complications or for particular agents (extrapolated from adult studies rated as LOE 2++, RG B, strong recommendation, strong consensus)**

In the 2009 update by the Infectious Diseases Society of America, the authors outline approaches to the management of CRBSI in patients with short- and long-term CVCs, in adults and children [6,20]. Empirical antibiotic therapy for CRBSI should usually include coverage for Gram-positive coagulase-negative or −positive staphylococci and Gram-negative bacilli (LOE 2++ in adults). The choice of antibiotics must be based on patient risk factors, severity of infection and local resistance pattern and changed to a narrower-spectrum therapy once the infecting organism has been identified. The duration of systemic antimicrobial therapy after a CRBSI diagnosis depends on several factors including: catheter removal or retention, response to antimicrobial therapy within the first 48–72 h (resolution of fever and bacteremia), and the development of other complications (embolic tissue infection, septic thrombosis, or endocarditis) (LOE2++ in adults). There are no compelling data to support specific recommendations for the duration of therapy for device-related infection. The optimal duration of therapy for treating CRBSI in children with or without catheter removal has not been

established. Therefore, recommendations regarding the duration of therapy for pediatric patients with CRBSI mirror adult recommendations. In general, if the catheter is retained a 10–14-day course of systemic antimicrobial therapy is adequate, assuming a response to antimicrobial therapy within 48–72 h and no evidence of complications (defined as persistent bacteremia 72 h after appropriate treatment initiation, suppurative thrombophlebitis, endocarditis, osteomyelitis, or possible metastatic seeding) (LOE 2+).

Because of vascular access difficulties in children, it is often necessary to attempt CRBSI treatment without catheter removal. Several studies have reported successful CRBSI management among children without catheter removal [18] (LOE 2+) [22]; (LOE 3). In 52 children with SBS, of the 181 episodes in which the catheters were not promptly removed, renal insufficiency occurred in 12 (7%) cases, disseminated infection in 7 (4%), hypotension in 13 (7%), and mechanical ventilation in 10 (6%). Complications also occurred in 4 of the 14 episodes in which the catheter was promptly removed. Although there was no catheter management-dependent difference in time required to clear infection for Gram-positive and Gram-negative organisms, the time required to clear infection was significantly longer in episodes of infection caused by fungal organisms when the catheter was not removed promptly. Twelve patients died prior to hospital discharge, 5 from complications of their infections (n = 2 coagulase-positive staphylococci, n = 1 *Candida albicans*, n = 1 *Enterococcus faecalis*, n = 1 *Eschericia coli*). In all 5 of these patients, the catheter was not promptly removed [22].

Removal of the CVC is required if there is clinical deterioration or persisting or relapsing bacteremia, severe sepsis, suppurative thrombophlebitis, endocarditis or bloodstream infection that continues despite 72 h of antimicrobial therapy to which the infecting microbes are susceptible [6,20] (LOE 2++ in adults). Patients with a long-term CVC and an uncomplicated CRBSI with *Staphylococcus* aureus, *Pseudomonas* species or Candida require immediate removal of the infected CVC and a defined course of systemic antibiotic therapy, except in rare circumstances when no alternate venous access is available (LOE 2++ in adults). Treatment of catheter-associated fungemia without removal of the catheter has a low success rate and is associated with higher mortality (LOE 2++ in adults). Recent reports involving children with *Candida* CRBSI found that the addition of antifungal lock therapy led to a high cure rate without catheter removal, but there are insufficient data to recommend routine catheter salvage using this approach for this infection unless there are unusual extenuating circumstances [23,24] (LOE 3). Replacing catheters can be difficult in patients with limited access, and surgical complications can arise. As such, the risks of catheter retention in the setting of infection must be weighed against those of surgery and general anesthesia, as well as the consumption of the limited anatomical sites that are suited for catheter placement. Children treated for CRBSI without catheter removal should be closely monitored with clinical evaluation, additional blood cultures, and use of antibiotic lock therapy combined with systemic therapy for catheter salvage [6,20] (LOE 2+).

Uncomplicated exit site infections (i.e., those without systemic signs of infection, positive blood culture results, or purulence) may be managed with topical antimicrobial agents on the basis of the exit site culture results (LOE 2+). Catheter removal and systemic antibiotic therapy is recommended for patients with an apparent tunnel or port-site infection (LOE 2+) [6,20].

Antibiotic lock therapy has been recommended for the treatment of adults with CRBSI, always used in conjunction with systemic antibiotic therapy (LOE 2+). It involves installing a high concentration of an antibiotic to which the causative microbe is susceptible in the catheter lumen. Data on ethanol and antibiotic locks use as adjuncts to systemic antibiotic treatment in children with CRBSI is sparse and this therapy is not routinely recommended (LOE 3).

Contaminated PN and intravenous fluid have been reported to cause sepsis outbreaks. The contamination may have taken place during compounding of PN in the pharmacy or during handling of the solutions in the ward. Gram positive and –negative bacteria and Candida albicans were found to be the species most likely to contaminate PN during preparation or administration and have been implicated in more than 95% of all outbreaks and sporadic cases of nosocomial bloodstream infections related to contaminated parenteral admixtures [25–27] (LOE 3).

3.2. Mechanical complications

Mechanical events such as occlusion, leakage and dislodgement are commonly seen. The reported incidence of CVC mechanical complications in different series is 3.37 per 1000 days-catheter (95% CI: 2.76–4.12) [9] (LOE 3).

3.3. Occlusion

Catheter occlusions, in which blood cannot be drawn nor solutions infused, can occur from mechanical causes, precipitation of a medication or PN, or as the result of a thrombotic process. Recognition of the probable cause is critical to appropriate intervention and salvage of the catheter. Catheter occlusion can occur suddenly (usually caused by an intraluminal precipitate) or can develop over several days (usually clots).

3.3.1. Nonthrombotic occlusions

PN components (lipids or calcium–phosphorus complex) and, less frequently, incompatible drugs may precipitate and cause occlusion. Medication crystallization and precipitation within CVC usually occur when incompatible medications are administered. Adding a solution that returns the pH of the crystallized medication back into the normal range may dissolve the precipitate. When medications with a normally high pH (eg, phenytoin) crystallize in a central vascular device, sodium bicarbonate can be infused to raise the pH and the medication may revert to its liquid state. When low pH medications (eg, vancomycin) crystallize in a CVC, hydrochloric acid can be used to lower the pH and dissolve the precipitate occlusion [28,29] (LOE 3). Lipid occlusions may also occur and are more prevalent with silicone catheters because lipid emulsions adhere to silicone. Ethyl alcohol at a 70% solution may be used to dissolve lipid occlusions [30] (LOE 3).

Catheter kinking along the path of the CVC and tip positions against the vessel wall may create mechanical occlusions that prevent or reduce flow through catheter. Proper positioning of CVC catheters may prevent this complication which often occurs with shorter catheters with tips high in the superior vena cava [31] (LOE 3). Catheter “pinch-off” and “pinch-off syndrome” are terms used to describe the compression of a CVC between the clavicle and first rib. Over time, repeated compression (caused by shoulder and arm movement) can cause a mechanical obstruction, catheter injury with infusate leak or rupture. A contrast study or chest x-ray can be used to confirm or rule out catheter pinch-off [32] (LOE 3).

3.3.2. Thrombotic occlusion and CVC related thrombosis

R 14.7	**Thrombotic catheter occlusion and CVC related thrombosis require thorough investigation and treatment as they may be associated with significant morbidity (LOE 2–, RG B, strong recommendation, strong consensus)**

Thrombosis associated with a CVC can involve the catheter tip, the length of the catheter, or the catheterized vessel. The reported prevalence of CVC-related thrombosis in children varies, depending on the underlying diagnoses, diagnostic tests and index of suspicion/presence of symptoms. In the Canadian registry the incidence of CVC-related thrombosis in children with different diseases was 3.5 per 100,000 hospital admissions [33] (LOE 2++). In children receiving HPN, the incidence of CVC-related thrombosis was reported to range from 1 to 80%, with the lowest frequencies reflecting the clinical diagnosis of thrombosis and the highest frequencies reflecting venographic evidence of thrombosis [34] (LOE 2−).

The majority of CVC related thromboses are asymptomatic. Otherwise, the initial symptoms of line thrombosis in children receiving PN through CVC include mainly difficulty in flushing or obtaining blood from the catheter. Symptoms associated with superior vena cava (SVC) and inferior vena cava (IVC) occlusion also include head and neck swelling, pleural effusion, chemosis and plethora, and lower limb edema, respectively [35,36] (LOE 2−). Symptoms attributed to pulmonary emboli (PE) include dyspnea, stridor, hoarse cry and airway occlusion, and chest pain in older children [37] (LOE 2−).

A combination of ultrasound and venography imaging seem to be required for accurate diagnosis of CVC-related thrombosis in the upper venous system [38] (LOE 2+). Ultrasonography may be adequate for jugular thrombosis but inadequate for diagnosis of subclavian or SVC thrombosis. Nevertheless, one can start with this method, as it is non-invasive and easy to perform. If the result is negative and clinical suspicion is high, venography is the method of choice. In the future, magnetic resonance imaging may become a noninvasive alternative for invasive venography for the detection of CVC-related thrombosis [39] (LOE 2−).

Morbidity and mortality from thrombotic events are clinically significant and include loss of subsequent intravenous access, recurrent thrombosis, PE, postthrombotic syndrome and death.

The incidence of CVC-related thrombotic events in children receiving long-term PN varies from 1% based on clinical diagnosis to 35% based on ventilation perfusion scans or echocardiography to 75% based on venography [37,40–42]. (LOE 3). Specific thrombus-related mortality is however extremely low, with most studies of children receiving long-term PN reporting a mortality rate of 0% [40,41,43] (LOE 3).

3.3.2.1. Treatment of thrombotic catheter occlusion.

R 14.8 **Fibrinolytics are the drug class of choice used to treat thrombus-occluded catheters. Tissue plasminogen activator (tPA, alteplase) is currently the recommended agent; however, urokinase and recombinant urokinase (rUK) can also be used (LOE 2+, RG B, strong recommendation, strong consensus)**

Fibrinolytics are the drug class of choice used to treat thrombus-occluded catheters. Thrombolytic agents used to restore catheter patency are streptokinase, urokinase and tissue plasminogen activator (tPA). COOL (double blind placebo controlled, 149 patients) and COOL-2 (open label, 991 patients) (Cardiovascular Thrombolytic to Open Occluded Lines) have shown the role of alteplase, a recombinant fibrinolytic agent with a higher degree of fibrin selectivity, for restoration of patency of occluded venous catheters, without significant side effects [44,45] (LOE 2++). The populations in both trials consisted of adult and pediatric patients. Catheters' patency was restored to 74% in the alteplase arm and 17% in the placebo arm ($P < .0001$ compared to placebo). Alteplase doses of 0.5–2 mg have been instilled into the CVC lumen with dwell times ranging from 30 to more than 240 min. Overall efficacy ranged from approximately 50%–90%, with greater efficacy generally reported with larger doses and longer dwell times. The Cathflo Activase Pediatric Study which was performed in 310 children reported a cumulative rate of restoration of catheter function after serial administration of a maximum of two doses of alteplase, each with a maximum dwell time of 120 min, of 82.9% (95% CI, 78.2–86.9%). No intracranial or other major bleeding or thrombo-embolic events occurred [46] (LOE 2++). Repeated doses of alteplase may be necessary if patency is not restored, as recommended by both the manufacturer and the American College of Chest Physicians ACCP) [43] (LOE 2++). Limitations of current studies of alteplase for catheter occlusion in children include small study populations and relative lack of pediatric-specific prospective trials.

The latest American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic Therapy and Prevention of Thrombosis, 9th ed states: “In pediatric patients, tPA is the agent of choice”. Reasons for this preference include a previous US Food and Drug Administration warning regarding urokinase, experimental evidence of improved clot lysis in vitro compared with urokinase and streptokinase, fibrin specificity, and low immunogenicity [47].

A recent review of thrombolytic treatment for catheter obstruction (studies in adults and children with different disorders and catheter types) reported that alteplase, one of the current therapies, clears 52% of obstructed catheters within 30 min with 86% overall clearance (after 2 doses, where necessary). Recombinant urokinase cleared 60% of catheters at 30 min but only 73% of catheters after repeated doses. Newer medications such as reteplase, tenecteplase and alfimeprase may have higher efficacy or shorter time to clearance. Reteplase is a new recombinant tissue plasminogen activator similar to alteplase but it lacks several structural domains. Therefore, penetration into the thrombus is improved, allowing fibrinolysis throughout the thrombus. Reteplase was instilled into 15 clotted catheters in children in a dose escalation trial. The dose of reteplase was started at 0.1 units and increased with increments of 0.1 units to a maximum dose of 0.4 units. Attempts to access the catheter were made every 15 min for 1 h. Twelve of the 15 catheters (80%) were patent after a mean dwell time of 38 min. No adverse events occurred. Reteplase seems to be as efficient and safe as alteplase, but may need shorter dwell times [48] (LOE 3). Recombinant urokinase may also have a role in prevention of thrombotic catheter occlusion [49] (LOE 2+).

3.3.2.2. Treatment of catheter-related thrombosis.

R 14.9 **The recommended management of acute and symptomatic CVC-related thrombosis depends on the requirement for the CVC and usually requires antithrombotic medication (LOE 2+, RG B, strong recommendation, strong consensus)**

In patients with catheter-related venous thrombosis, and a catheter *in situ*, anticoagulation, including low-molecular-weight heparin (LMWH) subcutaneously or unfractionated heparin (UFH) intravenously, is the main initial therapy. The aims of initial anticoagulant therapy are to prevent thrombus extension and subsequent pulmonary embolization. After 3 months of full anticoagulant therapy, switching to prophylactic doses of anticoagulation therapy is recommended and this should be administered until the removal of the CVC [43] (LOE 2+).

Thrombolytic therapy is usually not recommended unless a major vessel occlusion is involved causing critical compromise of organs or limbs (LOE 2+). Thrombolytics stimulate thrombus resolution more rapidly than heparin anticoagulation, particularly if the clot is relatively acute, roughly less than 2 weeks old. However, this benefit must be weighed against the risk of major bleeding, which is greater than with anticoagulation alone. If thrombolysis is required, tPA is used rather than other lytic agents [49–52] (LOE

2+). Compared to urokinase and streptokinase, tPA has shown improved clot lysis in vitro, fibrin specificity and low immunogenicity [53,54] (LOE 3). The success rate of thrombolysis in pediatric patients varies. Reported rate of complete thrombus resolution is 53%, 43%, and 69%, respectively when using streptokinase, urokinase, or tPA [54,55] (LOE 3). The major drawback of thrombolytic therapy is the increased number of major bleeding complications. In retrospective case series these complications occurred in 0%–40% of the children treated with alteplase [50] (LOE 4). Alternatively, a successful combination of chemical thrombolysis and balloon angioplasty or endovascular recanalization for catheter salvage has been described in the literature [56,57] (LOE 5).

The recommended management of radiographically detected asymptomatic CVC-related thrombosis is less clear and based mainly on expert opinion and less on evidence-based data. Since asymptomatic CVC-related thrombosis is believed to have clinical significance in children, treatment with anticoagulation is recommended in the absence of contraindications [43] (LOE 2+). For children receiving long-term HPN thromboprophylaxis with vitamin K antagonists (VKAs) has been suggested [43] (LOE 2+).

A recent Cochrane systematic review which assessed the efficacy and safety of different interventions used to restore patency of occluded CVC lumens in adults and children, identified only 7 (2 in children) randomized or quasi-randomized controlled trials (RCTs) [58]. None of the included studies investigated chemical or surgical interventions for treating occluded CVCs. All 7 studies investigated different comparisons or strengths of thrombolytic or anticoagulant therapies for treating CVC occlusion caused by a thrombus. There was some evidence from 2 studies that investigated urokinase vs. placebo (RR 2.09, 95% CI 1.47 to 2.95) and alteplase 2 mg/2 ml vs placebo (2 studies, RR 4.19, 95% CI 2.44 to 7.20) that these two drug interventions may be effective in treating occlusion of CVC lumens caused by thrombosis [59,60] (LOE 2+).

3.4. Extravasation, breakage and migration

R 14.10	**Proper positioning of the catheter tip and immediate investigation when catheter breakage or fluid extravasation are suspected should be implemented in order to prevent the occurrence of significant morbidity (LOE 4, RG 0, strong recommendation, strong consensus)**
R 14.11	**Appropriate measures to secure the catheter in place and education for users about correct maintenance and safety of the catheter are strongly recommended (GPP, strong recommendation, strong consensus)**

Extravasation, the leakage of infusate from a vein into the subcutaneous space, is a relatively infrequent complication of central venous catheters. Life-threatening extravasation complications have occasionally been reported including pleural or pericardial effusion and cardiac tamponade [61,62]. Rarely reported sites of extravasation include the pulmonary parenchyma [63,64], renal pelvis [65], scrotum [66,67], retroperitoneal space [68], spinal epidural space [69] and subdural space [70] and even into pharynx causing oral aspiration of PN infusate [71] (LOE 4). Massive PN fluid extravasation into subcutaneous tissue has been treated with recombinant human hyaluronidase (rHuPH20) [72] (LOE 5). Approved by the United States Food and Drug Administration (FDA) as an adjuvant to increase the absorption and dispersion of other injected drugs in adults and children, rHuPH20 (Hylenex [Baxter International Inc., Deerfield, IL]) has been reported to be safe and well tolerated when used to facilitate the absorption of hydration fluids and subcutaneous drugs [73].

Catheters that loop at acute angles are at risk for fracture. The most common signs of a fractured catheter are local swelling, pain, or skin site leakage on injection. Other less common signs are resistance on injection, inability to withdraw, cough, and chest pain. In cases of suspected catheter fracture, it may be prudent to obtain radiographic studies encompassing the upper extremities and chest, even in the asymptomatic patient. The catheter tip can migrate to locations such as the internal jugular vein in the neck or contralateral brachiocephalic vein. Intravascular and intracardiac embolization of the catheter fragments is a severe and rare complication and accounts for <1% of all reported complications [74] (LOE 4). Giving the high mortality and the wide range of complications that may result, it is important to remove the catheter fragment immediately unless contraindicated. Percutaneous and open surgery are both options for the retrieval of catheter fragments. Retrieval of fragmented catheter emboli can now be safely and effectively accomplished percutaneously [75] (LOE 5).

Inadvertent device damage can occur during routine care and maintenance. Damage to tunneled catheters and PICCs is generally repaired by using a specially designed repair kit. Vascular erosion is a rare but life-threatening CVC complication. Improvements in catheter material properties have greatly decreased the incidence of vascular erosion. Any central vascular device catheter with its tip adjoining the vessel wall at a near perpendicular angle should be monitored closely, or preferably repositioned [76] (LOE 4).

3.5. Loss of vascular access

Careful management of vascular access in children with IF will allow for long-term access and prevent the development of access difficulties that can limit the ability to provide PN and lead to intestinal or multi-organ transplant. Finally, in patients that do develop significant thrombosis or occlusion of all of their central vessels, innovative methods of obtaining central venous access have been described, including transhepatic catheters, translumbar or percutaneous mammary catheters, and gonadal vein catheters [77] (LOE 4). Interventional radiology assistance is often helpful in these complex patients. Using these general guidelines, loss of central venous access should be an extremely rare indication for intestinal transplantation. Overall, 10% of IF patients referred for a small bowel transplant assessment had difficulty with placement of a central venous catheter for PN [78] (LOE 3).

4. Complications and considerations related to the composition of the PN solution

4.1. Stability

R 14.12	**PN should be administered wherever possible using an admixture formulation validated by a licensed manufacturer or suitably qualified institution (GPP, strong recommendation, strong consensus)**
R 14.13	**A matrix table should be sought from the supplier of the formulation detailing permissible limits for additions of electrolytes and other additives (GPP, strong recommendation, strong consensus)**
R 14.14	**Alternative ingredients should not be substituted without expert advice or repeat validation (GPP, strong recommendation, strong consensus)**
R 14.15	**Phosphate should be added in an organic-bound form to prevent the risk of calcium-phosphate precipitation (GPP, strong recommendation, strong consensus)**
R 14.16	**If inorganic phosphate is used, stability matrices and order of mixing must be strictly adhered to (GPP, strong recommendation, strong consensus)**
R 14.17	**When '2 in 1' admixtures with Y-site lipids added are used, addition of lipids should be fully validated by the manufacturer or accredited laboratory or the lipid infused through an alternative line (GPP, strong recommendation, strong consensus)**

Parenteral nutrition in paediatrics can be admixed into '2 in 1' or '3 in 1' admixtures. A '2 in 1' admixture is one that contains amino acids, carbohydrates and electrolytes in a single container with lipid emulsion kept in a separate container. A '3 in 1' admixture has all the components including lipid in a single container. With up to 100 chemical species present in an admixture, enormous potential for interaction exists. It is recommended that a formulation is used that has been thoroughly studied in the laboratory and is backed by a clear statement from an authoritative body such as a licensed manufacturer or an academic institution [79] (LOE 4). There may be variability through factors such as the variation in pH between different batches of glucose due to decomposition during autoclaving [79,80] (LOE 4) and changes in trace element profiles due to adsorption onto, or leaching from, admixture containers and tubing [81–83] (LOE 3).

A '3 in 1' admixture is administered through a single line and the emulsion stability has been confirmed for the formulation [79,84–86]. A '2 in 1' admixture validation generally excludes the lipid emulsion from any consideration during stability testing. The lipid emulsion is infused 'separately' but in practice this usually means into the same infusion line, through a 'Y' connector. This approach does not ensure stability [87–89] (LOE 3). As there are risks associated with instability of regimens, it has been recommended that PN admixtures be administered through a terminal filter [90] (LOE 3).

The use of organic-bound phosphates reduces the risk of calcium-phosphate precipitation and hence potential clinical risks [91]. Addition of heparin to admixtures, even where validated, carries a small risk of emulsion instability occurring with individual batches of heparin [92,93] (LOE 4).

4.2. Drug compatibility

R 14.18	**Mixing of medications with PN in administration lines should be avoided unless validated by the manufacturer or accredited laboratory (GPP, strong recommendation, strong consensus)**

Interactions between PN and medications occur in three main ways; physiological interactions that occur at all times, altered behaviour of medications owing to the complications of the presenting condition or sub-optimal nutritional support and direct chemical interaction in the tubing during administration [87] (LOE 3). There are many short reports in the literature looking at the physical and/or chemical stability of certain medications in specific PN admixtures. Extrapolation of these is difficult without expert advice. Medications are given in the form of a formulated product which frequently contains excipients (substances required for formulation of a drug which should be inactive) in addition to the active medication [94,95] (LOE 4). Studies must therefore be regarded as specific to the particular branded product(s) investigated. The pH of a PN admixture will generally be close to the pH of the amino acid mixture from which it was prepared [79] (LOE 4) but marketed products range from around pH 5.0 to pH 7.0. Drugs that ionise in aqueous solution are those most likely to cause precipitation. A drug that is largely unionised at pH 5.0 may be fully dissociated at pH 7.0 and vice versa so it is not possible to extrapolate findings between different admixtures.

The problem is further complicated because of the behaviour of fluids within infusion tubing, particularly at low flow rates. Sharp corners and hanging loops within the tubing can lead to 'non-circulating fluid spaces' where medications can pool, and not necessarily be cleared by flushing [96] (LOE 4). Adding medication into infusion sets can force a bolus of an equivalent volume of PN solution ahead of the medication. Also, depending upon where the drug is added to the set, it may delay delivery of all or part of the dose to the circulation if the dose volume is less than the residual volume of the tubing [96] (LOE 4). This means that any study of drug compatibility with PN can only be reliably applied to the particular product concentrations, flow rates tested and the precise equipment, tubing, connectors and adaptors used. Extrapolation should only be attempted by those with relevant expertise. Problems will frequently manifest as in-line precipitation or lipid droplet enlargement (or both). In-line filtration can prevent these reaching the patient [97,98] (LOE 3).

4.3. Peroxidation, light protection and vitamin stability

R 14.19	**Multi-layer bags which are impermeable to oxygen are recommended for PN administration (GPP, strong recommendation, strong consensus)**
R 14.20	**Light protection is recommended for both PN bags and administration sets (LOE 3, RG 0, strong recommendation, strong consensus)**

The use of PUFAs in PN increases the risk of peroxidation and is one of the potential factors in the development of IFALD. The contributing factors to peroxidation of lipid emulsions are exposure to oxygen within the bag, photo-degradation, and an increasing ambient temperature, the type of container used, trace elements in the formulation and the content of alpha-tocopherol within the bag [84,99]. Peroxidation can therefore be minimised by the use of multi-layer bags, which reduce the amount of oxygen in the bag, a formulation with sufficient amounts of anti-oxidant alpha-tocopherol, which acts as free radical scavenger and anti-oxidant ascorbic acid [83,100] (LOE 3).

Vitamins are prone to stability issues due to photo-degradation, oxidation and interactions with PN bags and administration sets [100]. Ascorbic acid is very susceptible to oxidation. This is important with respect to the formation of oxalic acid, a by-product of oxidation which can form calcium oxalate crystals with calcium salts in the formulation. Oxidation of ascorbic acid can be reduced by the use of multi-layer bags. The vitamins which are particularly susceptible to photo-degradation are retinol and riboflavin. The photo-degradation can be quite significant with a potential clinical impact to the patient. This effect is seen when the bags are exposed to daylight but also artificial ambient light on the ward. Lipid opacity is not sufficient to prevent photo-degradation therefore the bags and administration sets both need to be light protective [100] (LOE 3).

4.4. Osmolarity

RG 14.21	**The recommended delivery site for PN is via a central line; however peripheral PN can also be given for short periods (LOE 3; RG 0, strong recommendation, strong consensus)**
RG 14.22	**The osmolarity of peripheral PN solution should be kept less than 900 mosmol/l (LOE 3, RG 0, conditional recommendation, strong consensus)**

Parenteral nutrition should be infused via a central venous line to minimise the risks of thrombophlebitis and extravasation [101] (LOE 3). PN solutions are inherently acidic due to the glucose and amino acid solutions used but the osmolar load from the electrolytes also needs to be taken into account during the formulation

process. Lipid emulsions are isotonic and are therefore suitable for either peripheral or central use. Two recent retrospective studies have reported contradictory results with regard to adverse events of peripheral infused PN infusions with >1000 mOsm/l [105] or >900 mOsm [102] in neonates and older children. Dugan S reported increase rate of thromboflebitis events and infiltration in both neonates and older children given PPN with osmolarity >1000 mOsm/l [103]. By contrast, Cies et all found similar rates of adverse events in both neonates and children given either less or more than 900 mOsm/L PN solutions into peripheral sites [104]. In adults ASPEN recommends a less than 900 mOsm/l for PN solutions infused peripherally [104].

When peripheral PN is infused, solution' osmolarity of less than 900 mosmol/l reduces the risk of thromboflebitis [102–104] (LOE 3).

5. Metabolic complications of PN

5.1. Metabolic bone disease

R 14.23	**In children on home PN, regular measurements of urinary calcium, plasma calcium, phosphorus, parathyroid hormone and 25-OH vitamin D concentrations and serum alkaline phosphatase activity should be performed (LOE 2+, RG B, strong recommendation, strong consensus)**
R 14.24	**Ingredients with the lowest amount of aluminum are advocated for the preparation of parenteral nutrition solutions provided to patients receiving PN (LOE 2++, RG B, strong recommendation, strong consensus)**
R 14.25	**Regular assessment of bone mineralization should be performed (LOE 2−, RG B, strong recommendation, strong consensus)**

PN-related metabolic bone disease (MBD) with symptoms and signs of decrease in bone mineral density (BMD), osteoporosis, pain and fractures was reported not only in adults but in children on long-term parenteral nutrition as well [105–107] (LOE 2+). In children, increased risk of MBD was reported both during and after weaning from long-term PN [108–111] (LOE 2+). The cause of MBD is most probably multifactorial, including mechanisms related to both the underlying disease and PN: excess of vitamin D, phosphorus, nitrogen and amino acids intake as well as energy imbalance and aluminium contamination [112] (LOE 2−).

Pediatric patients receiving long-term PN are at risk for aluminium toxicity and consequential MBD even at present [113,114] (LOE 2++). Neonates who are exposed to parenteral aluminum intake may have reduced lumbar spine and hip bone mass during adolescence, which may predispose to osteoporosis and hip fracture later in life [115] (LOE 1−). Use of aluminium contaminated products should be kept to a minimum (e.g. by avoiding glass vials and certain mineral and trace element sources known to have high aluminium content). In order to practically achieve this goal, ingredients with measured and labelled aluminium content should be preferred for the preparation of pediatric PN solutions.

Regular measurements of urinary calcium, plasma calcium, phosphorus, parathyroid hormone and 25-OH vitamin D concentrations and serum alkaline phosphatase activity should be performed as part of the evaluation of MBD in patients on PN. Elevated serum alkaline phosphatase activity in infants on PN indicates bone rather than hepatic origin [116] (LOE 3). Diagnosis of bone disease relies primarily on the measurement of bone mineralization using validated imaging methods (e.g. dual energy X-ray absorptiometry). The International Society for Clinical Densitometry recommends a minimum interval of 6–12 months between DXA scans, depending on clinical presentation, taking into account the previous z-score results as well as previous occurrence of fractures [117].

Bone turnover markers (osteocalcin, c-telopeptide) may be useful indicators for identifying children on long-term PN at risk of MBD [118] (LOE 2−).

Very premature newborns have an increased risk of low bone mass and metabolic bone disease. Short-term decline in bone strength may be prevented by higher calcium and phosphorus intake via PN [119] (LOE 1−) or by early initiation of PN [120] (LOE 2+).

Bisphosphonate treatment was described to improve BMD in adults on PN; in infants, published experience of bisphosphonate use is very limited [121,122] (LOE 4).

5.2. Hepatobiliary complications of parenteral nutrition

R 14.26	**The risk of liver disease can be decreased by reducing patient-related and PN-related risk factors (LOE 2+, RG B, strong recommendation, strong consensus)**
R 14.27	**In patients with intestinal failure-associated liver disease, maximizing enteral intake as tolerated EN may improve liver disease outcome (GPP, strong recommendation, strong consensus)**
R 14.28	**In patients on long-term and home PN, cycling of PN infusion is recommended as soon as metabolic and fluid status allows (LOE 3, RG 0, strong recommendation, strong consensus)**
R 14.29	**Pure soybean-based lipid emulsions should be avoided in the presence of cholestasis (LOE 3, RG 0, strong recommendation, strong consensus)**
R 14.30	**The use of mixed LEs may be encouraged in IF patients for long term PN (LOE 3, RG 0, conditional recommendation, strong consensus)**
R 14.31	**The initiation of ursodeoxycholic acid may be considered in the presence of biochemical signs of cholestasis (LOE 3, RG 0, conditional recommendation, strong consensus)**
R 14.32	**Early referral to an experienced pediatric intestinal failure rehabilitation/transplantation centre is recommended in infants/children with intestinal failure-associated liver disease (GPP, strong recommendation, strong consensus)**

The liver and biliary tree have many essential roles including metabolism of carbohydrate and lipid; detoxification and elimination of endogenous and exogenous lipophilic compounds and heavy metals; and synthesis and secretion of albumin, bile acids, coagulation factors, cytokines and hormones. Most hepatobiliary complications of PN are moderate and reversible. In a few patients there may be more severe outcomes ranging from biliary sludge and gallstones to cirrhosis, hepatic decompensation and death.

The pathogenesis of PN associated liver disease is not completely understood [4,123] (LOE 2+). It probably results from the interaction of many factors related to the underlying disease, infectious episodes, surgery and components of the PN solution [4,123] (LOE 2+).

5.2.1. Patient and/or disease related factors

Children requiring long-term PN are at high risk of developing liver disease. Absence of oral feeding impairs bile flow and increases the risk of biliary sludge formation. Intestinal failure, especially intestinal atresia and gastrochisis, may be associated with disruption of bile acid enterohepatic circulation due to ileal resection, bacterial overgrowth due to bowel obstruction. These, as well as severe motility disorders and ileocaecal valve resection, are all factors thought to contribute to PN-associated liver diseases

[123,124] (LOE 2+) [125]; (LOE 2−). Recurrent septic episodes either catheter-related (gram positive bacteria) or digestive related (gram negative sepsis from intraluminal bacterial overgrowth) also contribute to liver injury. Prematurity is an associated factor especially when necrotizing enterocolitis or sepsis occur [4,126] (LOE 2+).

5.2.2. PN related factors

PN may have additional deleterious effects on the liver:

- It has been demonstrated that an excess of total energy delivered induces liver lesions, which are reversible when the energy supply is decreased [124] (LOE 2+) [127]; (LOE 2−).
- Excessive or inadequate amino acid supply [4,123] (LOE 2+) [128]; (LOE 2−).
- Continuous PN infusion and/or excessive glucose intake is associated with hyperinsulinism and subsequent steatosis [4,129] (LOE 2+) [130]; (LOE 2−), although it is not clear whether this is also associated with cholestatic liver disease.
- The role of excessive fat supply and subsequent lipoperoxidation has been suggested to contribute to PNALD [128,131,132] (LOE 2−). Phytosterols contained in lipid emulsions may contribute to liver dysfunction [133,134] (LOE 2−). The role of various lipid emulsions in the development and treatment of liver disease is detailed in the Lipid chapter.

5.2.3. Monitoring

Regular monitoring of hepatic function is extremely important during PN in order to minimize or correct factors responsible for liver disease. Elevation of plasma alkaline phosphatase and gamma-glutamyl transferase activities appears earlier than hyperbilirubinemia, but these are not specific laboratory markers. Clinical liver enlargement, confirmed by ultrasonography, may appear within a few days after PN onset. Liver biopsy is not indicated at the early stage of liver dysfunction. However, it was shown that steatosis is the first non-specific histological abnormality resulting from excessive glucose supply leading to lipogenesis, rather than from the deposition of exogenous IVFE. Cholestasis together with portal and periportal cell infiltration leads to fibrosis. This indicates severe liver disease, with possible progression to cirrhosis and liver failure unless digestive factors are corrected and PN is performed correctly.

Liver and intestinal transplant is recommended in infants and children with a poor prognosis (e.g. ultra short bowel<10 cm, congenital enteropathy, megacystis microcolon and disorders of uncertain natural history) [135] (LOE 2−).

5.2.4. Prevention and treatment of cholestasis

Some measures may limit or reverse liver disease including:

- Early referral to an experienced paediatric intestinal rehabilitation centre [136] (LOE 3).
- The stimulation of the entero-biliary axis by promoting oral or enteral feeding with breast milk or long-chain triglycerides containing formulae, even minimal feeding [123,124] (LOE 2+) [137], (LOE 2−).
- The reduction of intraluminal bacterial overgrowth caused by intestinal stasis by giving metronidazole or gentamicin [4,123] and/or by performing venting enterostomy or tapering enteroplasty [138] (LOE 2−) have been evaluated in few studies but no recommendations can be made based on these studies.
- The evidence for the use of ursodeoxycholic acid (UDCA) is limited to two randomized controlled studies for prevention of cholestasis and few other observational/retrospective studies that investigated UDCA as a therapeutic agent for the treatment of cholestasis. The studies included a heterogenous population of subjects. The prevention studies suggest that UDCA may be effective at reducing biochemical signs of liver cholestasis without significant infant intolerance to the treatment. No data on liver histology or liver disease outcomes are available [134,139] (LOE 2−) [140]; (LOE 3).
- Cyclic PN for most infants and children exception of very low birth weight infants [4,129] (LOE 2+).
- Reduction of total calorie intake and reduction of lipid dosage from PN [141] (LOE 1−) [142]; (LOE 2+).
- Fish-oil containing or based lipids may reverse PNALD [4,143] (LOE 2+) [144–147]; (LOE 2−) [148]; (LOE 3).

6. Growth retardation

R 14.33	**Pediatric patients on long term PN require regular monitoring of growth and body composition (LOE 2−, RG B, strong recommendation, strong consensus)**

A child dependent on PN must receive adequate nutrition not only to meet basic metabolic requirements but also to allow normal growth [149] (LOE 1).

Studies in children on long-term parenteral nutrition have reported high prevalence of growth deficits and abnormal body composition. Pichler et al. identified short stature (-2SD height for age) in half of their patients with short bowel and in 70% of children with different enteropathies [107]. Body composition abnormalities, including high/low body mass index and altered lean and fat mass were described in a group of children and adolescents aged 5–20 years [150]. Since abnormalities in body composition may have long-term metabolic consequences, growth and body composition monitoring are important parameters to investigate and monitor in these children.

Conflict of interest

None declared.

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