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ESPEN Guideline

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

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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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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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