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

W. Mihatsch [a, *], M. Fewtrell [b], O. Goulet [c], C. Molgaard [d], J.-C. Picaud [e], T. Senterre [f], the ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition[1]

[a] Department of Pediatrics, Ulm University, Ulm, Germany
[b] Childhood Nutrition Research Centre, UCL Institute of Child Health, London, UK
[c] CHU Paris - Hôpital Necker-Enfants Malades, Paris, France
[d] Department of Nutrition, Exercise and Sports, University of Copenhagen, and Pediatric Nutrition Unit, Copenhagen University Hospital, Rigshospitalet, Denmark
[e] Service de Néonatologie et réanimation néonatale, Hôpital de la Croix-Rousse, and Dept. of Pediatrics, Claude Bernard University, Lyon, France
[f] Service Universitaire de Néonatologie, Centre Hospitalier Régional (CHR) de la Citadelle, and Centre Hospitalier Universitaire (CHU) de Liège, Liege University, Liège, Belgium

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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.

* Corresponding author. Klinik fuer Kinder- und Jugendliche, Helios Klinikum, Kanzlerstrasse 2-6, Pforzheim, Germany.
E-mail address: walter.mihatsch@gmx.de (W. Mihatsch).

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

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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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