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Letter to the Editor

Reply letter to the comment of Christmann V on 2018 ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: Calcium, phosphorus and magnesium

Dear Editor,

Chirstmann V. highlights important points with regard to the ESPGHAN/ESPEN/ESPR/CSPEN guideline on pediatric parenteral nutrition (PN): Calcium, phosphorus and magnesium. Her physiological approach is very stimulating and it is great to see the interest of our colleagues for this important topic.

1. Separate guidelines for ELBW infants

The guidelines were based on the available evidence. Increasing future evidence for different and specific nutritional requirements for subgroups of infants may justify separate guidelines for these subgroups in future updates. Maturity of organ function may indeed be far more important than birth weight.

2. Target plasma phosphate concentration

Definition of the target plasma phosphate (P) concentration requires a clear definition of the desired outcome (e.g. glucose homeostasis, sepsis prevention, lean body mass accretion, bone mineralization, neurodevelopment, and last not least prevention of non-communicable diseases, …). For plasma P in preterm infants a reference range of 1.6–2.9 mmol/l has been suggested [1]. In the clinical setting it is quite common to define concentrations below 1.6 mmol/l as hypophosphatemia and concentrations above 2.9 mmol/l as hyperphosphatemia [2]. However, the optimum target plasma P concentration still needs to be defined. Therefore, the guideline only mentioned the lower limit of the reference range (1.6 mmol/l) in order to highlight that adult reference ranges (lower limit 1.1 mmol/l) are not suitable for preterm infants [3]. Christman V suggests a target plasma concentration of 2.0 mmol/l which appears quite reasonable. Physiology may even suggest higher target plasma concentrations in very immature preterm infants. In preterm infants the renal phosphate threshold decreases with increasing post-menstrual age. In infants less than 30 weeks of gestation a median renal P threshold of 2.13 (1.95–2.33) mmol/l has been found, suggesting that the optimum plasma P concentration may even be higher than 2.0 mmol/l [4].

3. Monitoring of parenteral mineral supply

Due to the lack of evidence, for monitoring of the adequacy of mineral intake, the guideline provides a clear strong consensus recommendation based on low level of evidence.

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) [3].

Especially in infants and children with more extended periods of PN, less invasive monitoring and information on the mineral balance is desirable. Therefore, the following weak (conditional) second monitoring recommendation, based on extrapolated evidence from enteral nutrition studies, was given [3].

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).

As pointed out by Christmann V. and repeatedly discussed in the literature, this approach has limitations and requires knowledge of the plasma concentrations (for estimation of the renal phosphorus threshold) [5–8]. Otherwise e.g. phosphate loosing tubulopathy may be misinterpreted as P sufficiency.

4. Phosphorus requirement

Meeting P requirements of very preterm infants may be sometimes challenging, especially in ELBW infant and when not considering physiological needs and early metabolic balance studies. Unfortunately, the previous 2005 Pediatric PN guidelines did not include some of these aspects and advised lower P intakes. Some clinicians have only looked at these guidelines when trying to optimized their nutritional strategy in preterm infants. That is probably one of the reasons several authors described frequent and important hypophosphatemia when providing PN with high Ca:P ratio and high amino acid intake.

The guideline suggests the following model to estimate the P requirements [3]:

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

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Within physiological limits for compounding of PN the previously introduced equation may be used for estimation of the Ca:P ratio in PN [3].

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

Therefore, P intake needs to compensate for bone mineralization and more importantly for protein accretion. In addition, P intake needs to compensate for renal tubular phosphate losses as well.

Two important recommendations addressed early PN during the first days of life.

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 (LoE 2, RG B, conditional recommendation, strong consensus).

R 8.12 In early PN when calcium and phosphorus intakes are low 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).

In Viola Christmann et al., 2014 study [9], the authors described the consequences of insufficient P intakes when providing PN with a Ca:P ratio of 1.6. Such a ratio similar to the bone Ca:P ratio did not consider that some P is also required for cell metabolism and lean body mass accretion. As described in the new 2018 ESPGHAN/ESPEN/ESPR/CSPEN Pediatric PN guidelines, P intake needs to consider the need for both bone mineralization and lean body mass accretion. Insufficient intake has been associated with several adverse outcomes that are discussed in the guidelines. In their 2014 study, 0.5–1 mmol/kg/d additional P intake was required from day 3–4 to compensate early insufficient intake from PN. These additions decreased the Ca:P ratio down to 0.75–1.0 during the first days of life which has been recommended in the current guidelines.

In the Christmann V. et al., 2016 article [10], the PN solution contained 2.5 mmol/dl Ca, 1.6 mmol/dl P and 2.25 g/dl amino acids (Ca:P ratio of 1.6). Given the above-mentioned equation and recommendations R 8.11 and R 8.12, by compounding the solution carries a high risk of hypophosphatemia, and that's what actually happened. The Phosphate concentration of the solution did not compensate for Phosphate required for protein accretion, metabolism and tubular losses.

The estimation of Christmann V. that every g/kg of amino acids/protein should be accompanied by 1 mmol/kg of additional P requires confirmation in a clinical study. The mixed model analysis used to deduce this estimation needs to be questioned [10]. All infants had received the standard PN solution and increasing enteral milk (enteral nutrition, EN) intake. Therefore, Ca, P, and amino acid intake are intrinsically confounded and not independent. A residual plot has not been provided. Second, total Ca and P intakes cannot be included and discussed in any analysis without considering how much come from PN and EN. Ca and P intestinal absorption are different, around 40 and 90 percent of EN intake respectively. When only total Ca and P intakes are considered, nobody could assess how much intake really reach the blood compartment. Unfortunately, this was not considered in their 2016 article that only included in the analysis total Ca and P intake without considering the proportion from PN and EN. Thus, it is very difficult to really analyze the impact of Ca and P intake in this study on blood homeostasis and urine excretion. Finally, the paper states that “using manual backward selection, variables were kept in the model when they contributed statistically significantly with a p-value < 0.1”[10]. However, in several presented models Ca intake turned out to be insignificant ($p >> 0.1$) and was not removed.

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