Guidelines for Neonatal Parenteral Nutrition: 2019 Update by the Portuguese Neonatal Society. Part II. Micronutrients, Ready-to-use Solutions and Particular Conditions

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Introduction

This update of the guidelines for neonatal parenteral nutrition (PN) prescription is divided into two parts:
- Part I, which is included in the same issue of the journal, wherein the general aspects and criteria for fluids, energy, and macronutrients prescriptions, particularly for very and extremely preterm infants, are reviewed.
- Part II, which is included herein, wherein the criteria for micronutrients prescription, recommendations for either using individualized prescription with hospital pharmacy compounding or commercial ready-to-use solutions, and PN recommendations in particular clinical conditions are reviewed.

Levels of evidence (LoE) and recommendation grades (RG) used in the updated guidelines of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), supported by the European Society of Paediatric Research (ESPR) together with the Chinese Society of Parenteral and Enteral Nutrition (CSPEN)[1] are adopted in this document and shown in the Appendix 1.

Appendix 2 provides a table for the rapid consulting of a complete PN prescription in preterm infants.

Keywords: Infant, Newborn; Infant Nutritional Physiological Phenomena; Infant, Premature; Micronutrients; Parenteral Nutrition Solutions; Parenteral Nutrition; Practice Guidelines as Topic

1. Individualized prescription

1.1. Sodium (Table 1)

Comments:

- Sodium (Na): 1 mmol = 1 mEq = 23 mg[3].
- In preterm infants, a physiological negative sodium balance should be allowed in the first postnatal days; otherwise, it may predispose to morbidity, including patent *ductus arteriosus* and bronchopulmonary dysplasia.[4,5] Some authors have reported that the administration of sodium from the first postnatal day is not associated with hypernatremia.[6-8] Nevertheless, most scientific societies[2,7,9] recommend that sodium should not be administered in the first postnatal day or not exceed 2 mEq/kg/day until 6% of birth weight is lost.[2,5] This interpretation will be biased if the weight loss results from the transepidermal loss of water (not from natriuresis) due to insufficient environment humidity provision[5,10-12] (Part I, sections 10.1 and 11.1).
- During the first postnatal week, serum sodium predominantly reflects the hydration status and subsequently it also indicates the sodium reserve.[3,5] Hypernatremia in the first postnatal days may result from dehydration secondary to excessive transepidermal water loss or inadequate sodium intake.[2] Hyponatremia may result from hemodilution secondary to oliguria, diuretics, and caffeine use, or sodium renal loss in very and extremely preterm infants.[2,7]
- When calculating the sodium intake, the amount carried by drug salts and saline infusion should be taken into account.[7,12]
- If the sodium requirements are much higher than

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APPENDIX 1 - Levels of evidence and recommendation grades[1]

Levels of Evidence (LoE)

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

Recommendation grades (RG) according to the level of evidence

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

RCT - randomized control trial.

APPENDIX 2 - Rapid consulting – Daily doses for preterm infants

	First postnatal day	Daily increase	Maximum
Fluids (mL/kg/d)	60-100 humidity 80%-90%	10-15	160-180
Energy (kcal/kg/day)	45-55	-	90-120
Glucose (mg/kg/min)	4-8	*qs* for glycemia 45-120 mg/dL	12
Amino acids (g/kg/day)	> 1.5	0.5-1	3.5
Lipids (g/kg/day)	1-2	0.5-1	4
Sodium (mEq/kg/day)	0-2 Initiate preferably after > 6% birthweight lost	-	3-5 (up to 7)
Chloride (mEq/kg/day)	Similar to sodium	-	Similar to sodium
Potassium (mEq/kg/day)	1-3 Initiate after urine output > 1 mL/kg/h	-	1-3
Calcium (mg/kg/day)	32-80	-	100-140 (alternative 88-90)
Phosphorus (mg/kg/day)	Divide calcium dose by 1.3	Divide calcium dose by 1.3	Divide calcium dose by 1.3
Magnesium (mEq/kg/day)	0.2-0.4	-	0.4-0.6
Water soluble vitamins (mL/kg/day) (Soluvit N Infant®)	1	-	1
Lipid soluble vitamins (mL/kg/day) (Vitalipid N Infant®)	1-2	1	4
Trace elements < 2 weeks of exclusive PN	Zinc 400-500 µg/kg/day	-	Zinc 400-500 µg/kg/day
> 2 weeks of exclusive PN	-	-	Peditrace® 1 mL/kg/day + Zinc (to make up 400-500 µg/kg/day)

PN - parenteral nutrition; *qs - quantum satis.*

recommended, the baseline intake should be provided by PN and the supplemental amount infused by an independent line through a Y-connection system with PN infusion using, for example, sodium chloride (NaCl)

20% (1 mL = 3.4 mEq); this method is convenient for adjusting the dose according to the serum sodium levels.

Parameters guiding the prescription:

- Serum sodium levels: Reference values 135-145 mEq/L.[3]
- Urinary sodium: A urine spot with Na < 20 mEq/L associated with hyponatremia, or a fractional excretion of sodium (FENa) < 3% in term infants or < 4% in preterm infants, may indicate volume depletion, whereas FENa > 3% in term infants and > 4% in preterm infants with renal insufficiency is more consistent with acute kidney injury.[13]

1.2. Chloride (Table 2)

Comments:

- Chloride (Cl): 1 mmol = 1 mEq = 35.5 mg.[3]
- The chloride intake usually parallels the sodium intake and the chloride dose should not exceed that of sodium and potassium to avoid hyperchloremic metabolic acidosis.[7]
- In preterm infants, excessive chloride intake is associated with hyperchloremic metabolic acidosis (Cl > 114 mEq/L).[2,9] This can be prevented or resolved by partially replacing chloride with acetate; for example, by administering the first 3 mmol/L of anion as chloride and the following 6 mmol/L as acetate; if more anion is necessary, chloride should be added again.[9] An alternative is administering 70% anion as chloride and 30% as acetate, although at the beginning very and extremely preterm infants may require all of the anion as acetate.[3]
- Prolonged use of loop diuretics may lead to hypochloremia.[14]
- Chloride excretion may occur in equilibrium with the bicarbonate levels; metabolic alkalosis may indicate chloride deficiency and acidosis may be associated with hyperchloremia.[9]

Parameters guiding the prescription:

- Serum chloride levels: Reference values 96-106 mEq/L.[3]
- Blood gases: For the surveillance of alkalosis and acidosis.[9]

1.3. Potassium (Table 3)

Comments:

- Potassium (K): 1 mmol = 1 mEq = 39 mg.[3]
- Although some authors have reported that the routine administration of potassium from the first postnatal day is not associated with hyperkalemia,[6] most scientific societies recommend that it should be started after the establishment of a diuresis ≥ 1 mL/kg/h and in the absence of hyperkalemia.[2,7,9] If these criteria are met in the first postnatal day, potassium can be started cautiously, especially in preterm infants.[2]
- In preterm infants, hyperkalemia may occur with or without oliguria; non-oliguric hyperkalemia can result from the absorption of hematoma, hemolysis, lack of administration of prenatal corticosteroids,[2] and in extremely preterm infants it results mostly from a postnatal intracellular to extracellular potassium shift.[15] In preterm infants, hypokalemia can result from an inadequate supply in the face of enhanced demands, renal losses, and diuretics or caffeine use.[2,14]
- In ventilated infants, sudden changes in serum potassium may be a consequence of changes in acid-base balance. Hyperkalemia results from metabolic acidosis with acidemia due to a net shift of potassium from the intracellular to the extracellular space, and hypokalemia results from metabolic alkalosis due to the cellular uptake of potassium.[16]
- When calculating the potassium intake, the amount infused as drug salts should be taken into account.[2]
- If potassium requirements are much higher than recommended, the baseline intake should be provided by PN and the supplemental amount infused by an independent line through a Y-connection system with PN infusion, using for example KCl 7.5% (1 mL = 1 mEq); this method is convenient for adjusting the intake according to the serum potassium levels.

Parameters guiding the prescription:

- Serum potassium levels: Reference values 3.5-4.5

Table 1. Daily intakes of sodium (mEq/kg) recommended by parenteral nutrition (LoE 4)[2]

Postnatal days	D1-3	D4-5	≥ D6
Term infants	0-2	1-3	2-3
Preterm infants > 1500 g	0-2*	2-5	3-5
Preterm infants < 1500 g	0-2*,†	2-5†	3-5†

D - day; LoE - level of evidence.
* Higher intakes may be necessary: 3 mEq/kg/day.
† Higher intakes may be necessary: 7 mEq/kg/day.

Table 2. Daily intakes of chloride (mEq/kg) recommended by parenteral nutrition (LoE 4)[2]

Postnatal days	D1-3	D4-5	≥ D6
Term and preterm infants	0-3	2-5	2-5

D - day; LoE - level of evidence.

mEq/L.[3]
- Urine output.[6]

Table 3. Daily intakes of potassium recommended by parenteral nutrition (LoE 4)[3,7,9]

- Onset: After the first postnatal day provided urine output is ≥ 1 mL/kg/h
- Requirements according to maturity and body weight: Term infants: 1-3 mEq/kg Preterm infants > 1,500 g: 1-3 mEq/kg Preterm infants < 1,500 g: 1-2 mEq/kg

LoE - level of evidence.

1.4. Calcium and phosphorus (Table 4)

Comments:
- Calcium (Ca): 1 mmol = 2 mEq = 40 mg.[3]
- Phosphorus (P): 1 mmol = 31 mg; the valency of phosphorus varies whether it is in the form of monobasic or dibasic phosphate.[3,18]
- In relation to the previous ESPGHAN recommendation,[19] much higher doses of calcium and phosphorus are currently proposed for growing preterm infants,[17] which raises concerns about its compatibility and stability in PN solutions and the risks of precipitation.[20]
- The use of organic salts of calcium and phosphorus and a pH < 7.1 in the final solution, which promotes the formation of dibasic calcium phosphate (60 times more compatible than monobasic), are the main determinants for good calcium and phosphorus compatibility in neonatal PN solutions.[17,18,20]
- Several studies have evaluated the compatibility of calcium and phosphorus in neonatal PN solutions,[20-23] although a good compatibility is not a guarantee of good bone deposition.[18] To date, only three trials have assessed the effect of different parenteral doses of calcium and phosphorus[24,25] and different Ca:P ratios[26] on bone mineralization relying on image methods. This insufficient information may explain why the parenteral doses suggested for preterm infants are relatively wide (Table 4).
- Using the previously recommended Ca:P ratio of mg:mg 1.7:1 (1.3:1 molar) for preterm infants,[19] hypercalcemia, hypophosphatemia, and hypokalemia frequently occurred in the presence of the recommended doses of amino acids (> 2.5 g/kg/day).[27,28] This was due to the cellular growth induced by a good supply of amino acids, leading to intracellular mobilization of potassium and phosphorus and consequent hypokalemia, hypophosphatemia, and bone calcium mobilization in response to hypophosphatemia.[27] A recent study in very preterm infants[29] showed that during the first postnatal week the use of a ratio Ca:P mg:mg of 1.3:1 (or equimolar 1:1) based on increased dose of phosphorus, solved the problem (LoE 2, RG B). In this study,[29] calcium, and phosphorus concentrations of 1.7 mmol/L in the final PN solution, corresponding to 68 mg/dL of calcium, and 52.7 mg/dL of phosphorus, were used.
- The lack or scarcity of studies testing both the mineral compatibility and stability in neonatal PN solutions and the impact on serum electrolytes balance of high calcium and phosphorus doses currently recommended by ESPGHAN/ESPEN/ESPR/CSPEN[17] (Table 4) is effectively a matter of concern. To ensure such safety, these studies need to control the principal factors interfering with mineral compatibility and stability, such as the organic or inorganic nature of the different calcium and phosphate salts available, Ca:P ratios, pH values in the final solution, amino acid concentrations, temperatures, and storage durations.[18]
- There is no robust evidence assuring the mineral compatibility and stability of the high mineral doses currently recommended,[17] using different available types and concentrations of amino acid solutions and phosphate salts, and different final pH of PN solutions.[30,31] Therefore, the suggested alternative is to use at least the following values[29]: calcium 88-90 mg/kg/day, phosphorus 68-70 mg/kg/day, with a molar Ca:P ratio of 1 (or 1.3:1 in mg). During the first postnatal days, the doses should not exceed the concentrations of calcium 68 mg/dL and phosphorus 52.7 mg/dL.[29]
- When choosing to administer phosphorus in the first postnatal day, it is necessary to consider the appreciable amount of sodium contained in most phosphorus salts (*e.g.* 2 mEq of sodium *per* 1 mL of sodium

Table 4. Daily intakes of calcium and phosphorus recommended by parenteral nutrition (LoE 2,3,4, RG 0)[17]

		Term infants	Preterm infants First postnatal week	Preterm infants After first postnatal week
Calcium	mg/kg	30-60	32-80	100-140
	mmol/kg	0.8-1.5	0.8-2.0	2.5-3.5
Phosphorus	mg/kg	20.40	31-62	77-108
	mmol/kg	0.7-1.3	1.0-2.0	2.5- 3.5
Ca:P ratio	mg:mg	1.3-1.7	1.3	1.3-1.7
	molar	1.0-1.3	1.0	1.0-1.3

Ca - calcium; LoE - level of evidence; P - phosphorus; RG - recommendation grade.

glycerophosphate).
- Solutions with high calcium concentrations should be administered by central venous catheter, due to the risk of tissue necrosis when extravasation occurs using the peripheral infusion.[32]
- Calcium gluconate should be packaged in polyethylene vials and not in glass vials because they are associated with aluminum contamination (LoE 3, RG B).[17]
Parameters guiding prescription:
- Serum phosphorus and alkaline phosphatase levels: A systematic review concluded that there are no reliable early biochemical markers for metabolic bone disease of prematurity.[33] Nevertheless, among the most commonly used, hypophosphatemia (< 5.5 mg/dL or < 1.8 mmol/L) and elevation of alkaline phosphatase (> 900 IU/L), particularly the combination of both, are the markers with higher sensitivity and specificity, whereas serum calcium level is a poor marker.[33,34]
- In very and extremely preterm infants, hypokalemia, hypophosphatemia, and hypercalcemia should be monitored when Ca:P ratios higher than 1.3:1 (or molar 1:1) are used.[27]

1.5. Magnesium (Table 5)

Comments:
- Magnesium (Mg): 1 mmol = 2 mEq = 24 mg.[3]
- Particularly in preterm infants in the first postnatal days, parenteral magnesium should only be initiated when serum magnesium levels are within normal limits,[3] due to limited renal capacity to excrete it and the possible prenatal exposure to magnesium sulfate used as tocolytic (LoE 2, RG B).[17]
Parameter guiding the prescription:
- Serum magnesium levels: reference values for term and preterm infants 0.7-1.5 mEq/L.[17]

1.6. Water-soluble vitamins (Table 6)

Comments:
- Although the optimal parenteral doses of most vitamins have not yet been determined in newborn infants, Table 6 indicates the recommended doses for water soluble vitamins[35]
- Vitamins should be administered daily (LoE 4, RG 0).[35]
- Following the manufacturer's instructions, the content of one vial of Soluvit® N (Fresenius Kabi) should be dissolved in 10 mL of water for injections or glucose solution for infusion (5%-50%).
- Water-soluble vitamins should be added to the lipid emulsion or to lipid-containing mixtures in order to increase their stability (LoE 4, RG 0).[35]
- Suggestion: Soluvit N® (Fresenius Kabi), daily dose of 1 mL/kg, 1 mL containing vitamin C 10.0 mg, thiamine 0.25 mg, riboflavin 0.36 mg, niacin 4.0 mg, pyridoxine 0.40 mg, vitamin B12 0.5 µg, pantothenic acid 1.50 mg, biotin 6.0 µg, and folic acid 40 µg. First, the lyophilisate powder of a Soluvit N® (Fresenius Kabi) vial content is reconstituted with 10 mL of water for injection or 5%-50% glucose solution for infusion; secondly, the prescribed volume of Soluvit N® (Fresenius Kabi) is withdrawn from the vial and mixed with the prescribed volume of Vitalipid N Infant® (Fresenius Kabi); finally, the mixture of both water- and fat-soluble vitamins is added directly to the lipid emulsion.

1.7. Lipid soluble vitamins (Table 7)

Comments:
- Vitamin A 1 µg = 3.33 UI; vitamin D 1 µg = 40 UI; vitamin E 1 mg = 1 UI.[36]
- Vitamins should be administered daily (LoE 4, RG 0).[35]
- The dose of vitamin K1 provided by fat soluble vitamin solutions for PN assumes that vitamin K1 has been administered on the first postnatal day to prevent the hemorrhagic disease of the newborn.[35]
- Fat soluble vitamins should be added to the lipid emulsion or to lipid-containing mixtures in order to increase their stability (LoE 4, RG 0).[35]
- Suggestion: Vitalipid N Infant® (Fresenius Kabi): If body weight < 2.5 kg, the daily dose is 4 mL/kg; if > 2.5 kg, the maximum daily dose is 10 mL. Each 1 mL of Vitalipid N Infant® (Fresenius Kabi) contains vitamin A 69 µg (230 IU), vitamin D2 1 µg (40 IU), vitamin E 0.64 mg (0.70 IU), and vitamin K1 20 µg.

1.8. Trace elements (Table 8)

Comments:
- The major transfer of trace elements to the fetus occurs in the third trimester. Although optimal parenteral doses of most trace elements have not yet been determined

Table 5. Daily intakes of magnesium recommended in parenteral nutrition (LoE 2,3,4, RG 0)[17]

		Term infants	Preterm infants First postnatal week	Preterm infants After first postnatal week
Magnesium	mg/kg	2.4-5.0	2.0-5.0	5.0-7.5
	mmol/kg	0.1-0.2	0.1-0.2	0.2-0.3
	mEq/kg	0.2-0.4	0.2-0.4	0.4-0.6

LoE - level of evidence; RG - recommendation grade.

in preterm infants, Table 8 indicates the recommended doses.[36,37]

- It is suggested that zinc should be administered from the beginning of exclusive PN.[19]
- The commonly used trace elements solutions include manganese and molybdenum, which are only recommended in prolonged PN (> 2 weeks).[37]
- There are no recommendations on parenteral fluoride supplementation in newborns.[38]
- Parenteral nutrition solutions are generally contaminated with aluminum and chromium in doses that meet the requirements and, therefore, parenteral supplementation is not necessary.[37]
- Iron contributes to oxidative stress, and parenteral iron should not be given routinely if duration of PN is less than three weeks (LoE 4, RG 0). Iron supplementation should preferentially be given enterally; if this is not possible and exclusive PN is prolonged for more than three weeks, consider parenteral iron supplements (LoE 4, RG 0).[37]
- In cholestasis and hepatic insufficiency, doses of copper and manganese should be reduced to avoid toxicity (LoE 3, RG 0).[37] In acute renal failure, the dose of selenium should be reduced (NE 4, GR 0).[37] The same would be indicated for chromium, but this is not included in the composition of most trace element solutions for newborn infants.[39] If the volume of the trace elements solution is reduced or suspended, the dose of zinc should be adjusted.[39]

Table 6. Daily intakes of water soluble vitamins recommended by parenteral nutrition in term and preterm infants[35]

Vitamin	Dose/kg
Vitamin C (ascorbic acid) (mg)*	15-25
Thiamine (vitamin B1) (mg)	0.35-0.5
Riboflavin (vitamin B2) (mg)	0.15-0.2
Pyridoxine (vitamin B6) (mg)	0.15-0.2
Niacin (nicotinamide or vitamin B3) (mg)	4.0-6.8
Vitamin B12 (cobalamin) (mg)	0.3
Pantothenic acid (vitamin B_5) (mg)	2.5
Biotin (vitamin B7) (µg)	5.0-8.0
Folic acid (µg)*	56

LoE - level of evidence; RG - recommendation grade.
* LoE 3, GR 0.

Table 8. Daily intakes of trace elements recommended by parenteral nutrition (LoE 4, RG 0)[37]

Trace element	Term infants	Preterm infants
Zinc (µg/kg)	250	400-500
Copper (µg/kg)	20	40
Selenium (µg/kg)	2.3	7
Chromium (µg/kg)	0	0
Manganese (µg/kg)	1	1
Molybdenum (µg/kg)	0.25	1
Iodine (µg/kg)	1-10	1
Iron (µg/kg)	50-100	200-250

LoE - level of evidence; RG - recommendation grade.

- Suggestion: PN solution should be supplemented with zinc gluconate 0.1% (1 mL = 1000 µg zinc) from its beginning. After two weeks of exclusive PN, a complete solution of trace elements should be given; *e.g.* Peditrace® (Fresenius Kabi) at daily dose of 1 mL/kg, 1 mL containing: zinc 250 µg, copper 20 µg, manganese 1 µg, selenium 2 µg, iodine 1 µg and fluoride 57 µg. While in term infants this solution provides sufficient zinc, in preterm infants it is necessary to add zinc gluconate 0.1% to make up the recommended dose of zinc (Table 8).[37] If iron supplementation is needed by PN, the daily dose is 50-100 µg/kg in term infants and 200-259 µg/kg in preterm infants (LoE 4, RG 0).[37]

2. Commercial ready-to-use parenteral nutrition solutions

As an alternative to individualized PN prescription with hospital pharmacy compounding, commercial ready-

Table 7. Daily intakes of lipid soluble vitamins recommended for parenteral nutrition in term and preterm infants[35]

Vitamin		Term infants	Preterm infants
Vitamin A (retinol)*	IU	150-300/kg or 697/day	227-455/day or 700-1,500/kg
	µg	2,300/day	227-455/kg
Vitamin D (calciferol)*	IU	40-150/kg or 400/day	80-400/kg or 200-1,000/day
Vitamin E (α-tocopherol)†	IU	2.8-3.5/kg	2.8-3.5/kg
	mg	2.8-3.5/kg‡	2.8-3.5/kg‡
Vitamin K (phytomenadione)*	µg	10/kg§	10/kg§

LoE - level of evidence; RG - recommendation grade.
* LoE 3, RG 0.
† LoE 2+, RG B.
‡ Maximum 11 mg/day.
§ Current multivitamin solutions provide higher doses.

to-use neonatal PN solutions with fixed composition are currently available.[40] Potential advantages of these ready-to-use solutions include improved physical-chemical stability of solutions and macro and micronutrient intakes, cost-effectiveness, reduction of prescription errors and bacterial contamination, and 24-hour availability in any day of the week without dependence on pharmaceutical services.[9,36] For these reasons, these ready-to-use neonatal PN solutions are recommended over individualized PN prescription with hospital pharmacy compounding, including for preterm infants, provided that they are stable and the ready-to-use solutions are used for less than 2-3 weeks, under adequate laboratory monitoring.[40] The ready-to-use PN solutions should not be used in very and extremely preterm infants at risk of metabolic imbalances, such as hypo- and hyperglycemia, hypo- and hypernatremia, and hypo- and hyperkalemia, conditions that may require frequent adjustments of macro and micronutrients (LoE 2, RG B).[40]

In Portugal, the ready-to-use Numeta® (Baxter) neonatal PN solutions are currently commercialized, and the Instituto Nacional da Farmácia e do Medicamento (INFARMED) has recently issued the marketing authorization for ready-to-use Pediaven NN® (Fresenius Kabi) neonatal PN solutions (Appendix 3).

Numeta® (Baxter) solutions

A study has compared effects, on nutrient intakes and costs, of the ready-to-use Numeta® (Baxter) PN solutions *versus* individualized PN prescription with hospital pharmacy compounding, in preterm infants.[41] It was concluded that Numeta® (Baxter) is an alternative to individualized PN for infants > 1,000 g in the period of stable growth; it is more expensive than individualized PN but it saves human resources.[41].

According to the manufacturer specifications, Numeta G13% E® (Baxter) (Appendix 3, Supplementary Table 1) is indicated for preterm infants and Numeta G16% E® (Baxter) (Appendix 3, Supplementary Table 2) for term infants. They are composed of three-compartment bags, containing a solution of glucose, one of amino acids (Primene®, Baxter) with electrolytes, and a lipid emulsion, respectively. At the time of administration, the removal of the seal between the glucose and amino acid/electrolyte compartments is activated and, when lipids are to be administered, the seal is removed from the respective compartment.

Numeta® (Baxter) solutions do not contain vitamins or trace elements, which must be added when they are administered.

Comments:

- Numeta G13% E® (Baxter): Is designed to provide aggressive nutrition in low volume (about 140 mL/kg/day) to very preterm infants. When such volume is exceeded, the recommended intake of nutrients is exceeded. If 140 mL/kg/day is administered even when activating the lipid compartment, the maximum recommended intake of amino acids is exceeded, and the maximum recommended dose of glucose (Part I, sections 11.3 and 11.4) is reached or exceeded; *e.g.* in an infant weighing 1,000 g, the amino acids and glucose intakes will be 4.34 g/kg/day (Part I, section 11.4) and 12.9 mg/kg/min (Part I, section 11.3), respectively.
- For both Numeta G13% E® and G16% E® (Baxter) solutions, the manufacturer accepts the addition of water for injections or other solutions to reduce potential exaggerated concentration of certain nutrients (*e.g.* glucose); however, this procedure has the inherent disadvantage of diluting and decreasing the desirable intake of other nutrients, in addition to the drawbacks related to the manipulation itself.
- Numeta G13% E® and G16% E® (Baxter) solutions contain an appreciable amount of sodium, chloride, and potassium; therefore, it is advisable to use these solutions carefully on the first postnatal day or days, especially in preterm infants (Part II, sections 1.1, 1.2, and 1.3).

Pediaven® (Fresenius Kabi) solutions

- Pediaven NN1® (Fresenius Kabi) (Appendix 3, Supplementary Table 3) and Pediaven NN2® (Fresenius Kabi) (Appendix 3, Supplementary Table 4) have been designed for newborn infants. Both solutions contain no lipids, and the chosen lipid emulsion should be infused via a Y-connection system (Part I, section 6). These solutions contain trace elements but not vitamins, which must be added when they are administered. The amino acids have the profile of Vaminolact® (Fresenius Kabi). Both solutions have osmolarities which allow their peripheral infusion.
- According to the manufacturer, Pediaven NN1® (Fresenius Kabi) is indicated for term and preterm infants in the first 24 to 48 postnatal hours. It contains neither potassium nor phosphorus and has a residual amount of sodium. Pediaven NN2® (Fresenius Kabi) is indicated for term and preterm infants more than 2 postnatal days old.

Comments:

- Pediaven NN1® and Pediaven NN2® (Fresenius Kabi) solutions have been introduced very recently and a clinical study has shown that they are safe.[38] In addition, the solutions have osmolarities < 800 mOsm/L, so they can be infused peripherally.[42]
- Since Pediaven NN1® and Pediaven NN2® (Fresenius

Kabi) solutions were designed both for term and preterm infants, they provide lower than recommended doses of certain nutrients for very and extremely preterm infants[1]; *e.g.* in an infant weighing 1,000 g who is receiving 150 mL/kg/day of Pediaven NN2®, this provides 2.55 g/kg/day of amino acids (Part I, section 11.4) and 45.75 mg/kg/day of calcium (Part II, section 1.4).

3. Particular conditions

3.1. Sepsis

In the acute phase of sepsis, hyperglycemia may occur due to increased insulin resistance and hypertriglyceridemia due to elevated catecholamines and cortisol and decreased lipoprotein lipase activity.[43] When sepsis is complicated with thrombocytopenia, there is no evidence that intravenous lipids decrease the number or the function of platelets, which may be due to vitamin E deficiency and heparin infusion, respectively. In the acute phase of sepsis, increased need of amino acids has not been demonstrated, and the excess of nutrients during the catabolic phase can be counterproductive.[44] In necrotizing enterocolitis, in particular, energy and protein metabolism rates are similar to those of stable infants.[45]

Approach:

1) Glucose should be the preferred energy source; if hyperglycemia (> 145 mg/dL) occurs, glucose intake should be reduced, if necessary, to 2.5 mg/kg/min in term infants and 4 mg/kg/min in preterm infants[46,47];

2) If hypertriglyceridemia (> 265 mg/dL) occurs, the lipid intake should be reduced, if necessary, to 1 g/kg/day to avoid essential fatty acid deficit, with an apparent advantage of emulsions containing fish oil[48];

3) In the acute phase of sepsis, a daily intake of at least 60 kcal/kg and 2.5 g/kg of amino acids should be guaranteed.[49]

3.2. Cholestasis

In newborn infants, PN associated cholestasis is multifactorial. A multivariate analysis has identified as independent factors the duration of PN and a high dose of glucose, but not the doses of lipids or amino acids.[50] A systematic review in newborns and children corroborated that PN duration is a preponderant risk factor.[51] Concerning components of lipid emulsions, it seems that a high content of phytosterols and n-6 fatty acids and a low α-tocopherol content predispose to PN associated cholestasis, while high fish oil contents protects against it.[50,52]

The potential toxicity of copper and manganese in cholestasis, due to the difficulty of their excretion by bile, should be taken into account.[19,39]

Approach:

To prevent or mitigate PN associated cholestasis (conjugated bilirubin > 2 mg/dL), it is recommended that:

1) The dose of glucose be reduced, perhaps to levels that do not exceed its oxidative capacity (Part I, section 11.3);

2) Enteral nutrition be increased and PN reduced or suspended as possible;

3) Lipid emulsions containing fish oil and α-tocopherol should be preferred (Part I, section 11.5);

4) Depending on the severity of cholestasis, the dose of trace elements solution containing copper and manganese should be suspended or reduced (Part II, section 1.8).

3.3. Serum unconjugated bilirubin

In preterm infants, controversy exists about the possibility that free fatty acids resulting from the hydrolysis of serum triglycerides displace bilirubin from binding sites on albumin, thus potentially elevating the free fraction of bilirubin to neurotoxic levels. [53,54] This does not appear to occur if the molar ratio free fatty acid: albumin is < 6.[54] In other words, it is less likely to occur if serum albumin levels are within the reference range. Given this uncertainty, some authors propose to reduce the dose of lipids when serum unconjugated bilirubin exceeds 10 mg/dL.[34,55]

Approach:

In preterm infants, it is prudent to reduce the dose of lipids if serum unconjugated bilirubin levels exceed 10 mg/dL.

3.4. Pulmonary hypertension

In term and preterm infants, intravenous lipid infusion may aggravate pulmonary hypertension, with dose- and time-dependent effects.[54]

Approach:

In severe pulmonary hypertension it is prudent to temporarily suspend the lipids or decrease their dose to 1 g/kg/day.[48]

3.5. Major surgery

Newborn infants undergoing major surgery who were adequately anesthetized and receiving appropriate analgesics will at most need a slight increase in energy intake (about 15%) in the immediate postoperative period (about 4 h after surgery).[56] During this period, it has also been shown that the protein turnover does not increase significantly.[45]

In case of extensive bowel resection, ranitidine is effective in reducing gastric hypersecretion that may cause hydroelectrolytic imbalance.[2]

Approach:

In the first postoperative days there is no need to increase the energy and protein intakes if analgesia is adequate. In case of extensive bowel resection, ranitidine may be prescribed at a dose of 10-15 mg/kg/d.

4. Conclusions

Research has contributed to the better compatibility of higher mineral concentrations and adequate calcium to phosphorus ratios in PN solutions in order to optimize mineral deposition in the skeleton.

There are particular conditions, such as the acute phase of sepsis, pulmonary hypertension, and PN associated cholestasis, under which the dose of nutrients need to be adjusted.

As an alternative to the individualized PN prescription with hospital pharmacy compounding, commercial ready-to-use PN solutions with a guaranteed stability of nutrients are available, reducing preparation errors and microbial contamination. Due to their advantages, they have been recommended over individualized PN. However, they often require the addition of solutions or the simultaneous infusion of solutions to correct ionic and metabolic imbalances, with inherent inconvenience. This update of the guidelines for neonatal PN prescription represents a general orientation to support the clinical practice that should be adapted to each case.

APPENDIX 3 - Numeta® (Baxter) and Pediaven® (Fresenius Kabi) ready-to-use neonatal parenteral nutrition compositions

Supplementary Table 1. Numeta G13%E® (Baxter) composition

Per 100 mL	Without lipids	With lipids
Total energy (kcal)	82	91
Amino acids (g)	3.9	3.1
Glucose (g)	16.7	13.3
Lipids (g)	0	2.5
Sodium (mEq)	2.7	2.2
Chloride (mEq)	3.9	3.1
Potassium (mEq)	2.6	2.1
Magnesium (mmol)	0.2	0.16
(mEq)	0.4	0.32
Calcium (mmol)	1.6	1.3
(mg)	64	52
Phosphorus (mmol)	1.3	1.3
(mg)	40.3	40.3
Osmolarity (mOsm/L)	1,400	1,150

Supplementary Table 2. Numeta G16%E® (Baxter) composition

Per 100 mL	Without lipids	With lipids
Total energy (kcal)	96	103
Amino acids (g)	3.4	2.6
Glucose (g)	20.6	15.5
Lipids (g)	0	3.1
Sodium (mEq)	3.1	2.4
Chloride (mEq)	3.7	2.8
Potassium (mEq)	3	2.3
Magnesium (mmol)	0.4	0.3
(mEq)	0.8	0.6
Calcium (mmol)	0.82	0.62
(mg)	32.8	24.8
Phosphorus (mmol)	0.85	0.87
(mg)	26.4	27.0
Osmolarity (mOsm/L)	1,585	1,230

Supplementary Table 3. Pediaven® NN1 (Fresenius Kabi) composition per 100 mL

Total energy (kcal)	46
Amino acids (g)	1.5
Glucose (g)	10
Lipids (g)	0.45
Sodium (mEq)	0.5
Chloride (mEq)	0
Potassium (mEq)	0.21 0.42
Magnesium (mmol)	0.94
(mEq)	37.7
Calcium (mmol)	0
(mg)	0
Phosphorus (mmol) (mg)	715
Osmolarity (mOsm/L)	

Supplementary Table 4. Pediaven® NN2 (Fresenius Kabi) composition per 100 mL

Total energy (kcal)	47
Amino acids (g)	1.7
Glucose (g)	10
Lipids (g)	2
Sodium (mEq)	2.6
Chloride (mEq)	1.7
Potassium (mEq)	0.16 0.32
Magnesium (mmol)	0.76
(mEq)	30.5
Calcium (mmol)	0.91
(mg)	28.2
Phosphorus (mmol) (mg)	790

Conflicts of Interest

Luís Pereira-da-Silva and Pedro Vieira da Silva received honoraria for collaborating in scientific meetings organized by Baxter Médico-Farmacêutica Lda.

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Protection of human and animal subjects

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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