Guidelines for Neonatal Parenteral Nutrition: 2019 Update by the Portuguese Neonatal Society. Part I. General Aspects, Energy, and Macronutrients

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Introduction

The first guidelines (previously called consensus) for neonatal parenteral nutrition (PN) prescription were published in 2004.[1] In 2008, these guidelines were updated[2] according to the most recent disclosed international guidelines issued by recognized scientific societies.[3,4] Eleven years later, relevant advances in clinical practice grounded in research were achieved to support the decision-making processes in neonatal PN, including the use of ready-to-use PN mixtures provided by pharmaceutical companies.

It should be highlighted that the 2008 update[2] of neonatal PN guidelines resulted in a remarkable adherence by neonatologists and the consequent improvement of clinical practice[5] by Portuguese neonatologists. A survey of prescribing practices, answered by 72% of coordinators of Portuguese neonatal units, revealed that 83% of the units followed the national recommendations,[2] 87% initiated amino acids on the first postnatal day and 95% started lipids in the first three postnatal days.[5] This performance was superior to what was reported in a contemporary systematic review that included four European and two American surveys, in which only 24%-54% of the units started amino acids on the first postnatal day and 46%-94% initiated lipids in the first three postnatal days.[6] Probably due to the absence of a recommendation for the preparation of neonatal PN performed by pharmacists, some limitations (*e.g.*, quality control) were detected in another national survey of professionals responsible for neonatal PN preparation in Portugal.[7]

Very recently, updated guidelines for neonatal, pediatric, and adolescent PN, resulting from a joint authorship of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the European Society for Parenteral and Enteral Nutrition (ESPEN), the European Society of Pediatric Research (ESPR), and the Chinese Society of Parenteral and Enteral Nutrition (CSPEN), were published.[8]

This update of guidelines for neonatal PN prescription is divided into two parts:

- Part I, herein included, in which the general aspects, such as indications and contraindications, formulation of admixtures, estimation of osmolality, routes of administration, heparinization of central venous catheters, storage conditions of solutions and emulsions, complications, and clinical and laboratory monitoring are reviewed. Recommendations for the prescription of fluids, energy, and macronutrients are also reviewed, particularly in very and extremely preterm infants.
- Part II, included in the same issue of the Portuguese Journal of Pediatrics, reviews recommendations for the prescription of micronutrients, using either an individualized prescription with hospital pharmacy compounding or commercial ready-to-use solutions, and PN recommendations in particular clinical conditions.

Levels of evidence (LoE) and recommendation grades (RG) used in the updated guidelines of ESPGHAN/ESPEN/ESPR/CSPEM are adopted in this document and shown in Appendix 1.[8]

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

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APPENDIX 1 - Levels of evidence and recommendation grades[8]

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

RCT - randomized control trial.

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 overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population; or A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
0	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2++ or 2+
GPP	Good practice points: Recommended best practice based on the clinical experience of the guideline development group

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.*

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

1. Indications

Parenteral nutrition is indicated when it is not possible to establish sufficient enteral nutrition for a prolonged period, in particular in the following conditions[9,10]:
- Prematurity, particularly < 33 weeks gestation;
- Major anomalies of the gastrointestinal tract or those affecting its functioning, *e.g.*, esophageal atresia, intestinal atresia, gastroschisis, and diaphragmatic hernia;
- Conditions severely affecting the digestive tract, *e.g.* necrotizing enterocolitis and short bowel syndrome;
- Newborn infants of < 33 weeks gestation with intrauterine growth restriction and abnormalities in the umbilical flow by Doppler imaging;
- Severe perinatal asphyxia;
- Congenital cardiac malformations with compromised visceral perfusion and during the early period after cardiac surgery.

2. Contraindications and limitations

Parenteral nutrition should be used with caution or not at all in the following conditions[11]:
- Dehydration;
- Sustained metabolic acidosis;
- Persistent hydro-electrolytic and metabolic imbalances, *e.g.* metabolic acidosis and marked imbalances in serum glucose, sodium, potassium, and calcium;
- Acute renal failure;
- Acute liver failure.

The trace elements provided by PN should be reduced or suspended in renal failure, hepatic failure, and cholestasis (Part II, section 3.2).

In most situations associated with stress (*e.g.* surgery, sepsis), PN should not be suspended. Instead, individual adjustments should be made.[12,13]

3. Formulation of admixtures

Generally, binary PN mixtures are used, consisting of two separate admixtures, that is, a hydro-electrolytic solution, containing glucose, amino acids, electrolytes, and trace elements, and a lipid emulsion with added vitamins.[14,15]

For economic and convenience reasons, an all-in-one admixture in a single bag prepared in the hospital pharmacy (also called a ternary or three-in-one mixture) may be used. This strategy may be conditioned by potential changes in physical and chemical compatibility and in the stability of several components, leading to non-detectable precipitation that may cause microemboli, and increasing the size of lipid particles.[14,15]

4. Compounding and ready-to-use solutions

A survey conducted in Portugal in 2009,[5] before the availability of commercial ready-to-use neonatal PN solutions, revealed that PN compounding (individualized preparation in hospital pharmacy) was used in all neonatal units. In the vast majority of these units, computer assisted prescription was used, a procedure that is known to improve prescription efficiency and reduce prescribing errors, saving neonatologists and pharmacists time with calculations and validations.[16]

The PN compounding should be centralized in hospital pharmacy, following a safe method to ensure aseptic conditions, reduce preparation errors, validate compatibility and stability, and adjust the prescribed intakes.[17]

Several Portuguese units use the PN mixtures of fixed composition prepared in hospital pharmacy, containing glucose, calcium, and amino acids in order to provide amino acids during weekends when PN compounding is unavailable.[5]

Recently, ready-to-use neonatal PN solutions with fixed composition and guaranteed stability of nutrients were commercialized.[16] These will be addressed in detail (Part II, section 2).

Individualized PN prescription with hospital pharmacy compounding should be preferred in very and extremely preterm infants at risk of metabolic imbalances, including hypo- and hyperglycemia, hypo- and hypernatremia, and hypo- and hyperkalemia.[16]

Recently, the Instituto Nacional da Farmácia e do Medicamento (INFARMED) authorized (not yet in practice) the distribution in the national market of commercial neonatal PN solution bags (B Braun®) manufactured in Spain, according to individualized prescription.

The addition of a drug to the PN solution or its infusion by Y-connection system with PN infusion should be strictly evaluated and supported by studies, since such procedure may interfere with the stability and physicochemical compatibility of PN components, affecting the effectiveness of both the PN and the drug.[17]

5. Estimation of osmolality

When nutrients are prescribed by PN at the recommended doses,[18] the osmolality of neonatal PN solutions rapidly exceeds 900 mOsm/kg of water.[19]
Osmolality is expressed in mOsm/kg of water (solvent) and osmolarity in mOsm/L of solution (solute plus solvent). As osmolality is obtained by measurement and osmolarity by calculation,[20,21] a simple equation for estimating the osmolality of neonatal PN solutions was validated by osmometry relying on concentrations of the four most influential components: glucose, amino acids, phosphorus, and sodium. The concentrations of glucose and amino acids are expressed as g/L, phosphorus in mg/L, and sodium in mEq/L.[19] Osmolarity (mOsm/ L) = (amino acids x 8) + (glucose x 7) + (sodium x 2) + (phosphorus x 0.2) - 50; it may be expressed in molar concentrations of nitrogen and other components. This equation was shown to have a good correlation with equations proposed by the American Society for Parenteral and Enteral Nutrition (ASPEN)[22] and has been suggested by several authors.[21,23-25] It can be incorporated into spreadsheets and computer programs. Since osmolarity is reported to underestimate osmolality at high concentrations,[26] equations and algorithms have been subsequently proposed for more accurate estimates of osmolality of neonatal PN solutions,[20,26] including a commercialized program.[26]

6. Routes of administration

In binary PN mixtures, the aqueous solution with glucose and amino acids is generally infused through a single line, to which the lipid emulsion is infused by a Y-connection system as close as possible to the venipuncture site or the catheter insertion.[3]
The option of infusing PN peripherally or centrally depends on several factors, including the expected duration of PN, the osmolality of the solution, and the ease of access of a central route.[3,14]

6.1. Peripheral

- Indications: The expected duration of PN is less than two weeks, available veins are favorable for peripheral access, and nutritional status is good.
- Limitations: Frequent venipuncture and insufficient intakes of energy and nutrients, since solutions with recommended nutrients content are hyperosmolar.[19,27,28]

6.2. Central

- Indications: The duration of PN is expected to be prolonged, osmolarity of the PN solution exceeds 900 mOsm/L, and/or glucose concentration exceeds 12.5 g/dL in the final solution.[14,18,21]
- Limitations: The difficulties in catheter insertion or its contraindication in the acute phase of infection. Even using the central route, the osmolarity of the final solution should not exceed 1,700 mOsm/L[14] or 15 g/dL of glucose.[29]
- Type of central catheter according to the expected duration of PN[30-33]:
1) Peripherally inserted central catheter (epicutaneous cava catheter), or centrally inserted venous catheter (*e.g.* in the subclavian vein, Arrow® type) - if PN < 2-3 weeks;
2) Tunneled central venous catheter (*e.g.* Broviac® type) - if PN > 2-3 weeks;
- Umbilical vessels: Vein (catheter tip ideally at entrance of the right atrium), especially in neonates < 1,000 g, for short-term use (< five days) and peripheral access not available. Artery, only when there is no alternative and its use is very temporary (< 48 hours).
In multi-lumen catheters, one lumen should be exclusively used for PN infusion.[33]

7. Heparinization for central venous catheters patency

There is controversy about the advantage of the prophylactic addition of heparin to PN solutions to avoid the occlusion of central venous catheters. Currently, ESPGHAN/ESPEN/ESPR/CSPEM do not recommend its routine prophylactic use (LoE 3, RG 0)[33] and the ASPEN has a similar position, but while recognizing that the recommendation grade is weak.[14] Nevertheless, a recent systematic review concluded that the prophylactic heparinization by continuous infusion in indwelling long catheters is advantageous to prolong the longevity of long lines in preterm infants.[34] As this systematic review was not included in the reference list of the updated guidelines of ESPGHAN/ESPEN/ESPR/CSPEM,[33] it is left on the physician discretion to use 10-15 IU/kg/day of heparin added to a PN aqueous solution.[34] An approximate daily dose that has been commonly used and easier to prescribe is 0.5 IU/mL,[23] although this may exceed 15 IU/kg/day.
As an alternative to the aforementioned routine prophylactic heparinization, flushing with small volumes of heparinized saline (5-10 IU/mL), 1-2 times per week may be used to maintain the patency of intermittently accessed central venous catheters (LoE 2, RG 0).[33]
Heparin should not be added to lipid emulsions because it can alter its stability (LoE 3, RG GPP).[13]

8. Storage and intravenous infusion conditions

The two main factors that determine the stability of PN solutions during storage are temperature and light exposure.[14,35]

A comprehensive study addressing the physicochemical stability of binary mixtures of neonatal PN concluded that they remain stable for four months at 4ºC-8ºC.[36]

All PN solutions should be protected from natural and artificial light (including phototherapy) during storage and infusion in order to reduce the degradation of some vitamins and the formation of hydrogen and lipid peroxides.[35,37] For this purpose, using multilayer bags (less oxygen-permeable), reinforced photoprotective bags, and opaque infusion systems or shielding the bag, syringe and all the infusion tubing from ambient light, are recommended.[17]

In order to retain microparticles or precipitates, the use of 1.2 µ filters for the infusion of ternary mixtures and 0.22 µ for binary mixtures is recommended.[17]

9. Complications

Complications most frequently associated to neonatal PN include[28,38]:

Central venous catheter-related sepsis: This should be suspected if the body temperature is > 38.5ºC, or rises > 1ºC, or there is a new-onset tachycardia, hyperglycemia, hemodynamic instability, and/or changes in the laboratory parameters. Central and peripheral blood cultures are recommended prior to the initiation of empirical antibiotic therapy. If a good response occurs in 48-72 hours, antibiotic therapy should be maintained for 10-14 days. In case of clinical deterioration or persistence of bacteremia, the catheter should be removed.

Thrombotic occlusion of central venous catheter: Immediate onset of thrombolytics is recommended; the recombinant tissue plasminogen activator (rtPA) is most often indicated, but urokinase can be used instead. Antithrombotic drugs should also be used for the subsequent maintenance of the catheter.

Extravasation, migration, and fracture of central venous catheter: The removal of the catheter or removal of the fractured fragment is recommended as soon as possible.

Parenteral mineral intake to prevent bone metabolic disease (Part II, section 1.4) and parenteral intake of nutrients in PN associated cholestasis will be detailed (Part II, section 3).

10. Clinical and laboratory monitoring

10.1. Anthropometry[35,39]

- Daily: body weight;
- Weekly: body length and head circumference.

The appropriate curves and reference values should be used to monitor growth particularly in preterm infants[40]. At birth, the Fenton curves[41] are appropriate. For the first postnatal days, a body weight calculator (www.growthcalculator.org) based on the Landau-Crangle curves[42] became recently freely accessible online.[43] For the long term, the Intergrowth 21st curves are more appropriate.[44]

After the initial physiological weight loss, the weight gain velocity in very and extremely preterm infants should ideally be of 17-20 g/kg/day.[45]

10.2. Laboratory[39,46,47]

If the infant is receiving predominantly or exclusively PN:

- In the first postnatal week: Three times daily to daily: blood gases, glycemia (for the infant's comfort, measurements from blood gases analyzers should be preferred), serum ionogram, serum calcium, urine specific gravity if possible, and glycosuria (*e.g.* Multistix®).

Every three days, if under exclusive PN: complete blood count, blood urea or blood urea nitrogen (BUN), and serum creatinine. Baseline serum levels of phosphorus, alkaline phosphatase, and magnesium may be measured.

- After the first postnatal week: Weekly assessment of: the aforementioned parameters *plus* serum levels of transaminases, alkaline phosphatase, total and conjugated bilirubin, γ-glutamyl transpeptidase (γ-GT), albumin, and triglycerides. Using the micromethods currently available, a 1-2 mL blood sample is usually enough to perform these measurements.

To avoid excessive blood spoliation in very and extremely preterm infants, the periodicity of analytical monitoring may be extended and adapted to the clinical condition.

11. Individualized prescription

11.1. Fluids (Table 1)

Comments:

- Within the first postnatal days, the major determinants of water balance in the very preterm infants are the relative oliguria and transepidermal water loss.[48,49] In order to not exceed the recommended fluid intake, it is necessary to counteract the transepidermal water loss by providing 80%-90% of environment humidity and neutral temperature, preferably using a double wall incubator.[48,50-53] As the epidermis keratinizes rapidly,

the supplemental humidity should be progressively decreased to the environment values after the fifth postnatal day to reduce the risk of infection.[48] A complementary strategy to reduce the transepidermal water loss is to cover these preterm infants with plastic bags and wraps.[48] Following the relative oliguric phase, diuresis and natriuresis are established, and it is expected that very and extremely preterm infants will lose 7%-10% of birth weight (LoE 2++, RG B).[48] Infants with intrauterine growth restriction lose less weight than appropriate for gestational age infants.[48,54]

- It may be necessary to increase fluid intake (around 10% of the baseline needs) if an open incubator or phototherapy are used,[48,49,55] although the routine fluid intake increase to compensate for phototherapy is controversial.[50]
- In very and extremely preterm infants, excessive fluid intake predisposes them to persistent ductus arteriosus, chronic lung disease, and necrotizing enterocolitis.[52]

Parameters guiding the prescription:

- Urine specific gravity: Ideally it should be between 1,005-1,010, roughly corresponding to osmolalities between 100-300 mOsm/kg water.[56]
- Serum sodium: In the first postnatal week it may reflect the hydration status (hyponatremia indicates hyperhydration and hypernatremia dehydration).[57]
- Diuresis: Ideally it should be 1-3 mL/kg/h; oliguria is defined as < 0.5-1 mL/kg/h and polyuria as > 6-7 mL/kg/h.[48,49]
- Body weight changes: In the first postnatal days, weight changes reflect the hydration status. Reference values that consider the physiological postnatal weight loss should be used,[40,58] such as what was recently published.[42]

11.2. Energy (Table 2)

Comments:

- An excessive energy intake predisposes to an exaggerated accumulation of fat mass, and an insufficient energy intake may negatively affect growth, neurodevelopment, and immunity.[45,47]
- Ideally, glucose should contribute with 45%-55% of total energy, lipids with 30%-40% and amino acids with 10%-15%.[18,59] Lipids should not exceed 40%-60% of non-protein energy intake.[60]
- Each gram of glucose and amino acids provides 4 kcal, and each gram of lipids provides 9 kcal.[61]

11.3. Glucose (Table 2)

Comments:

- Although the maximum recommended dose of glucose is 12 mg/kg/min,[47] its maximum oxidation capacity is 8.3 mg/kg/min in preterm infants (12 g/kg/day).[63]
- Excessive glucose intake should be avoided because it predisposes to lipogenesis and excessive fat storage, and increased susceptibility to infections and retinopathy of prematurity (LoE 2+, RG B).[46,47,63]
- Conditions like stress, infection, and methylxanthines therapy predispose to hyperglycemia.[64] In the acute phase of disease (*e.g.* sepsis), glucose intake should not exceed 5-7 mg/kg/min (LoE 4, RG GPP).[47]
- In case of hyperglycemia (> 145 mg/dL), the dose of glucose should be decreased. It may also be necessary to decrease the dose of lipids due to their hyperglycemic effect mediated by gluconeogenesis.[64]
- The use of insulin should only be considered if hyperglycemia persists despite reduction of glucose intake to 4 mg/kg/min,[18], and/or if glycemia is repeatedly higher than 180 mg/dL (LoE 2+, RG 0).[47]

Parameters guiding the prescription:

- Venous or capillary blood glucose levels: > 145 mg/dL constitute hyperglycemia, and those < 40 mg/dL hypoglycemia.[47,64] For the infants comfort, measurements from blood gas analyzers should be preferred (LoE 2+, RG B).[47]
- Search for glycosuria (reagent strips).[64]

11.4. Amino acids (Table 4)

Comments:

- Parenteral administration of amino acids is less physiological than enteral administration, since they are directly infused into the systemic circulation bypassing the hepatic and splanchnic metabolism.[53,65]
- To promote nitrogen retention, the intake of non-protein energy should be at least 65 kcal/kg/day (LoE 1+, RG A).[65] Nevertheless, if the non-protein energy intake is lower, the dose of amino acids should not be limited, since the amount that is not used for nitrogen retention is oxidized for energy production.[45]
- Two recent systematic reviews have concluded that high parenteral doses (> 3 g/kg/day) of amino acids administered early (< 24 postnatal hours) are safe and well tolerated, resulting in a positive nitrogen balance,

Table 1. Daily intakes (mL/kg) of fluids during the first postnatal week (LoE 4)[4,48]

Postnatal day	D1	D2	D3	D4	D5	≥ D6
Term infants	40-60	50-70	60-80	60-100	100-140	140-170
Preterm >1,500 g	60-80	80-100	100-120	120-140	140-160	140-160
Preterm < 1,500 g	80-100	100-120	120 -140	140-160	160-180	140-160

D - day, LoE - level of evidence.

although limited evidence exists on their advantages on growth, neurodevelopment, and retinopathy of prematurity.[66,67] In very and extremely preterm infants, high doses of amino acids and lipids during the first postnatal week (as currently recommended) may be independently associated with non-lactic metabolic acidosis.[68]

- In preterm infants, the early onset of intravenous amino acids stimulates endogenous insulin secretion and may prevent hyperglycemia without increasing the risk of hypoglycemia.[24,25,60]

- The profile of parenteral amino acid solutions is generally based on the umbilical cord blood aminoacidogram (*e.g.* Primene®, Baxter) or on the plasma aminoacidogram of healthy breastfed newborns (*e.g.* Vaminolact®, Fresenius Kabi).[53,59,69]

- In very and extremely preterm infants, more concentrated solutions (*e.g.* 10 g/dL) should be preferred since they provide the appropriate dose at a lower volume.[18,46]

- Specific amino acids[65,70]:

  - Cysteine is a semi essential amino acid, with a recommended dose of 50-75 mg/kg/day. Cysteine may have to be added to the PN solution before its administration due to its low solubility (LoE 1+, RG B); for instance, cysteine may be required if Vaminolact® (Fresenius Kabi), which contains 100 mg cysteine/dL, is used, but not in case of Primene® (Baxter) that contains the sufficient amount of 189 mg cysteine/dL.

  - Tyrosine is another semi-essential amino acid; a minimum daily dose of 18 mg/kg is required in preterm infants (LoE 2++, RG B) and 94 mg/kg in term infants (LoE 1+, RG B).

Table 2. Daily intakes (kcal/kg) of energy recommended by parenteral nutrition[45,59]

Postnatal day	D1	D2-6	≥ D7
Term infants	40	60-80	90-100
Preterm infants	45-55*	60-80	90-120†

D - day; LoE - level of evidence; RG - recommendation grade.
* LoE 2+, RG 0.
† LoE 2++, RG B.

Table 3. Intakes (mg/kg/min or g/g/day) of glucose recommended by parenteral nutrition (LoE 2+, RG B)[18,47,62]

- Onset: term infants 2.5-5 mg/kg/min; preterm infants 4-8 mg/kg/min
- Subsequently, increase gradually by 1-2 mg/kg/min, adjusting to maintain glycemia between 45-120 mg/dL
- Minimum: term infants 2.5 mg/kg/min (3.6 g/kg/day); preterm infants 4 mg/kg/min (5.8 g/kg/day)
- Maximum: 12 mg/kg/min (17.3 g/kg/day) in term and preterm infants

LoE - level of evidence; RG - recommendation grade.

- Glutamine instability makes its inclusion in commercial solutions impossible; its addition to PN solutions is not recommended (LoE 1++, RG A).

- Arginine may be used in preterm infants to prevent necrotizing enterocolitis (LoE 1, RG B).

Parameters guiding the prescription:

- Blood urea and blood urea nitrogen (BUN): Reference values for BUN: 5.5-22 mg/dL. Blood urea is 2.14 times the BUN value (*e.g.* 20 mg/dL of urea equals 9.3 mg/dL of BUN). BUN level is a good indicator of protein intake, except in the early postnatal days when it is influenced by the hydration status and renal function.[71] A low BUN value indicates insufficient nitrogen intake, but a value at the upper threshold may simply reflect efficient oxidation of amino acids and not their intolerance.[29]

- Blood gases: Metabolic acidosis (defined as base excess) should be checked in the first postnatal week when it may appear associated to currently recommended doses of amino acids and lipids.[68]

11.5. Lipids (Table 5)

Comments:

- Intravenous lipid emulsions are good sources of energy, essential fatty acids, and substrate for physiological fat accretion especially in very and extremely preterm infants who are born without fat stores.[53,60]

- To avoid a deficit in essential fatty acids, which occurs after 72 hours without exogenous supply, the minimum dose of 1 g/kg/day is needed using the current lipid emulsions containing soybean oil, medium chain triglycerides and/or fish oil.[13] The minimum recommended dose of linoleic acid is 0.25 g/kg/day in preterm infants (LoE 2, RG 0) and 0.1 g/kg/d in the term infants (LoE 3-4, RG 0), its content varying according to the type of lipid emulsion used.[13]

Table 4. Daily intakes (g/kg) of amino acids recommended by parenteral nutrition[65]

Postnatal day	D1	≥ D2	Maximum
Term infants*	> 1.5	2.5-3.0	3.0
Preterm infants†	> 1.5	2.5-3.5	3.5

D - day; LoE - level of evidence; RG - recommendation grade.
* LoE 1+, RG B.
† LoE 1++, RG A.

Table 5. Daily intakes (g/kg) of lipids recommended by parenteral nutrition[13]

- Onset: 1-2 g/kg from the first postnatal day (LoE 1, RG A)
- Daily increase of 0.5-1 g/kg up to the maximum of 4 g/kg (LoE 4)
- Minimum: term infants 2.5 mg/kg/min (3.6 g/kg/day); preterm infants 4 mg/kg/min (5.8 g/kg/day)
- 24 hours continuous infusion (LoE 2++, RG B)

LoE - level of evidence; RG - recommendation grade.

- Ideally, the lipid emulsion should contain n-6 and n-3 fatty acids (fish oil), components with good antioxidant capacity (*e.g.* α-tocopherol and monounsaturated fatty acids) and, possibly, medium chain fatty acids (less carnitine-dependent) (LoE 1, RG A).[28,60] A systematic review concluded that lipid emulsions containing fish oil are effective in reversing PN associated cholestasis, but not in preventing it.[72]
- Serum triglyceride clearance: 20% (instead of 10%) lipid emulsions should be used because their phospholipid content is lower, resulting in more efficient triglyceride clearance (LoE 1, RG B).[13,60] Serum triglycerides clearance depends on the activity of endothelial lipoprotein lipase, which is stimulated by heparin. However, there is no clinical evidence that the use of heparin improves the use of intravenous lipids.[4] In one trial, an emulsion containing soybean oil, fish oil, medium chain triglycerides, and olive oil resulted in better serum triglycerides clearance than an emulsion containing only soybean oil and medium chain triglycerides.[73]
- Corticosteroids and liposomal amphotericin B may transiently increase triglyceridemia.[46]
- Although preterm infants are deficient in carnitine (which facilitates the transport of fatty acids into the mitochondria for oxidation), its supplementation did not show any advantage (LoE 3-4).[74]
- Since intravenous lipid emulsions are isosmolar[75] they can be infused peripherally.[18,76]
- Especially in preterm infants, the entire infusion system (syringe, tubes) for lipid emulsions must be light protected, particularly from phototherapy, to reduce lipid and hydrogen peroxide formation and cellular damage (LoE 1, RG B).[13,37]
- Unproven concerns with intravenous lipids that should not limit their use[46,60]: 1) It had not been proven that intravenous lipids predispose to chronic lung disease or retinopathy of prematurity; 2) In thrombocytopenia, other cofactors are probably responsible for the adverse effects attributed to lipids, such as vitamin E deficiency (interfering with platelet count) and the administration of heparin (interfering with platelet function); 3) *In vitro* and *in vivo* studies have not clearly demonstrated a negative interference of intravenous lipids with the immune system, in particular with monocyte activity; and 4) The use of intravenous lipids may predispose to infection by coagulase negative *Staphylococcus* and *Candida*, but the nutritional advantages of their use clearly outweigh these risks.
- In unconjugated hyperbilirubinemia (Part II, section 3.3), acute phase of sepsis (Part II, section 3.1), pulmonary hypertension (Part II, section 3.4), and severe and unexplained thrombocytopenia, it may be necessary to reduce lipids to a minimum dose capable of preventing essential fatty acids deficit.[13,53]

Parameters guiding the prescription:
- Triglyceridemia should not exceed 265 mg/dL (LoE 4).[13]
- Blood gases: Metabolic acidosis (defined as base excess) should be checked in the first postnatal week when it may appear associated with currently recommended doses of amino acids and lipids.[68]

12. Conclusions

Newborn infants totally or partially unable to use the enteral route should be parenterally fed. Parenteral nutrition is especially important in very and extremely preterm infants because they were born deprived of the third trimester of gestation, a period characterized by a high transfer of nutrients to the fetus.

In the early postnatal hours, it is essential to provide an adequate amount of energy and amino acids. Lipids are an important source of energy and essential fatty acids. This update of guidelines for neonatal PN prescription represents a general orientation to support the clinical practice that should be adapted to each case.

Conflicts of Interest

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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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