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# Physicochemical Stability and Sterility of Standard Parenteral Nutrition Solutions and Simulated Y-Site Admixtures for Neonates

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## Abstract

*Background:* Parenteral nutrition (PN) is frequently needed in neonatal intensive care. The use of standard PN has emerged as an easy-to-prescribe approach that allows one to have on-site, ready-to-use PN. The aim of this study was to test the physicochemical stability and sterility of 2 specific PN solutions as well as simulate Y-site compatibility with lipid injectable emulsions (ILE). *Methods:* Our study considered 2 standard ILE–free PN solutions according to neonatal weight. These solutions were prepared in duplicate and stored at 4°C. The following physicochemical parameters were tested: visual alterations, turbidity, pH, osmolarity, and calcium concentration. Sterility was assessed by means of agar blood culture and glucose concentration determination. In addition, we assessed the stability of simulated Y-site admixtures. For each standard ILE-free PN solution, 2 3-in-1 PN admixtures were designed, considering extreme values of fluid requirements (50 and 150 ml/kg/d) and a fat supply of 2 g/kg/24 h. The physicochemical parameters tested were phase separation and fat mean droplet size distribution. *Results:* No alterations were detected by visual inspection. Calcium concentrations, turbidity, pH, and osmolarity values remained stable in all the determinations. All agar blood cultures were negative and glucose concentration was constant over time. Physical stability of simulated Y-site admixtures was considered acceptable as mean droplet size distribution remained below 500 nm in all the emulsions. *Conclusion:* The 2 tested standard ILE-free PN solutions for neonates are physicochemically stable and sterile for 31 days under refrigeration (4°C). These solutions are also stable in case of Y-site administration with ILE at the conditions tested. (*Nutr Clin Pract.* 2018;00:1–7)

## Keywords

neonates; parenteral nutrition; sterility; stability lipid injectable emulsions; newborn infant; intravenous fat emulsions; parenteral nutrition solutions; safety; drug stability

## Introduction

Parenteral nutrition (PN) is frequently needed in neonatal intensive care, especially for premature neonates with very low birth weight (<1.5 kg) and for those with gastrointestinal disorders, such as necrotising enterocolitis or gastrointestinal immaturity. Generally, PN solutions include glucose, amino acids, and micronutrients and tend to be administered separately from lipid injectable emulsions (ILE) to decrease the risk of precipitation, incompatibility, or infectious complications.[1,2]

Small volumes required for the preparation of individualized neonatal PN solutions may result in manipulation-related errors. Standard PN solutions may be safer and easier to prescribe and prepare, but not as precise and flexible as the individualized solutions. In addition, standard preparations allow early initiation of parenteral feeding regardless of technicians availability, which is especially important for preterm neonates. Although standard PN solutions appear to be advantageous, this issue still remains under discussion.[3,4] The use of standard PN solutions implies the design of an accurate nutrition composition that covers neonatal requirements with clear prescription

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instructions for neonatologists. Also, the design and preparation procedures must ensure physicochemical stability and sterility.

Stability and sterility are major concerns for the safety of PN administration. Several parameters have been described in the assessment of PN solutions stability, such as the incompatibility of calcium and phosphate salts. These salts can precipitate and cause occlusion of small blood vessels, thus enhancing the likelihood of an embolism.[5] To evaluate the risk of precipitation, the determination of calcium concentration, pH, and visual inspection are appropriate. Lower pH has been correlated with a lower risk of precipitation.[6] Degradation of certain vitamins is of concern as well. In this sense, previous studies have shown that the use of multilayered bags and refrigeration minimize this problem substantially.[7,8] Also, for the specific case of 3-in-1 admixtures or Y-site administration of PN solutions and ILE, destabilization can lead to the formation of large fat globules, which can occlude pulmonary capillaries, especially if they exceed 5 $\mu$m. In this way, the target is to achieve a particle diameter between 0.25 and 0.5 $\mu$m, similar to the size of chylomicrons.[9,10] Finally, because of its composition, PN solutions can function as a perfect growth media for microorganisms.[11,12] Therefore it is necessary to assess the sterility of these admixtures to prevent potential infections.

To date, few studies have assessed the stability and sterility of standard PN solutions and emulsions for neonates.[13,14] Moreover, it is essential to ensure the adequacy of every specific standard solution as changes in composition may compromise stability. Thus, the aim of this study was to assess the physicochemical stability and sterility of specific standard ILE-free PN solutions designed to cover neonatal requirements during all the nutrition treatment as well as simulate Y-site compatibility with ILE.

## Materials and Methods

### *General Procedures*

A total of 2 standard ILE-free PN solutions were designed to cover nutrition requirements of neonates with PN, according to their weight. These solutions included glucose, amino acids, and micronutrients. For each PN solution, admixture bags were prepared in duplicate. A total of 5 samples were taken from each bag at different times to test specific physicochemical stability and sterility parameters.

Also, because PN solutions and ILE are generally administered separately, we designed 4 3-in-1 PN admixtures to simulate Y-site administration. These 4 emulsions represented the range of neonates' fluid and fat requirements of 50–150 mL/kg/day and 2 g/kg/day, respectively. We then evaluated specific stability parameters for each 3-in-1 PN admixture, taking again 5 samples from each bag at different times for testing.

**Table 1.** Recommendations in Parenteral Fluid and Macronutrient Intake for Neonates, from the European Society for Clinical Nutrition and Metabolism blue book 2011[15].

| Nutritional requirements | Preterm neonates | Term neonates |
|---|---|---|
| Fluid, mL/kg/24 h | 60–180 | 60–180 |
| Amino acids, g/kg/24 h | 1.5–4<br>VLBW: 3–4 | 1.5–3 |
| Carbohydrates | | |
| • g/kg/24 h | 6–18 | 8–18 |
| • mg/kg/min | 4.1–12.5 | 5.5–12.5 |
| Fats, g/kg/24 h | 3–4 | 2–3 |

Preterm neonates include newborns with < 37 weeks of gestational age. VLBW, very low birth weight: <1.5 kg.

### *Standard ILE-Free PN Solution Composition*

A total of 2 standard ILE-free PN solutions were designed according to neonatal weight, below or above 1.5 kg, following the European Society for Clinical Nutrition and Metabolism blue book recommendations 2011[15] (Table 1). Standard ILE-free PN solution for neonates below 1.5 kg (solution A) aimed to cover an amino acid requirement of 3–4 g/kg/24 h, whereas the solution for neonates above 1.5 kg (solution B) intended to cover a requirement of 1.5–3 g/kg/24 h, according to the European Society for Clinical Nutrition and Metabolism and American Society for Parenteral and Enteral Nutrition guidelines.[15,16] The final composition of the ILE-free PN solutions also took into consideration standard, recommended fluid requirements. In the neonatal intensive care unit (ICU), fluid requirements vary according to variables such as gestational and postnatal ages, ranging from 60–180 ml/kg/d.[15] A commercial amino acid solution for intravenous infusion indicated in neonates was used as the protein source. This solution provides a mixture of essential, semi-essential, and nonessential amino acids, including taurine, tyrosine, and cysteine. Nutrition composition of the designed ILE-free PN solutions is shown in Table 2.

### *Simulated Y-Site Admixture Composition*

To study the stability of Y-site administration of PN solutions and ILE, 2 3-in-1 PN admixtures were designed for each of the available standard ILE-free PN solutions. These admixtures considered extreme values of fluid requirements used in daily routines: 50 and 150 ml/kg/day. According to regular clinical practice, fat supply for the simulated Y-site administration was 2 g/kg/24 h[17] (Table 3). SMOFlipid 20% (Fresenius Kabi España, Barcelona, Spain) was used as the fat source.[18] This product consists of a mixture of soybean oil, medium chain triglycerides, olive oil, and fish oil, which

**Table 2.** Composition of Standard Intravenous Lipid Emulsion–Free Parenteral Nutrition Solutions for Neonates.

| Components | Neonates < 1.5 kg, Volume 3200 mL[a] (Solution A) | Neonates > 1.5 kg, Volume 2700 mL[a] (Solution B) |
|---|---|---|
| Amino acids | 88 g | 59 g |
| Glucose | 300 g | 300 g |
| Sodium | 47.5 mmol | 45 mmol |
| Potassium | 90 mmol | 90 mmol |
| Calcium | 21 mmol | 21 mmol |
| Magnesium | 5 mmol | 5 mmol |
| Chloride | 64.5 mmol | 63 mmol |
| Acetate | 132.5 mmol | 105 mmol |
| Phosphate | 30 mmol | 30 mmol |
| Vitamins (Infuvite Pediatric) | 25 mL[b] | 25 mL[b] |
| Trace elements (Peditrace) | 20 mL[c] | 20 mL[c] |
| Carnitine | 1 g | 1 g |

[a]Volumes shown in the table result from mixing complete commercial units of each component (see Tables S1-S2 for more detailed information). Neonate-specific parenteral nutrition is prepared taking a prescribed volume from solutions A or B.
[b]Infuvite Pediatric (25 mL): vitamin C 400 mg, vitamin A 11500 IU, vitamin $D_3$ 2000 IU, vitamin $B_1$ 6 mg, vitamin $B_2$ 7 mg, vitamin $B_6$ 5 mg, niacinamide 85 mg, dexpanthenol 25 mg, vitamin E 35 IU, vitamin K1 1 mg, folic acid 700 $\mu$g, biotin 100 $\mu$g, vitamin $B_{12}$ 5 $\mu$g.
[c]Peditrace (20 mL): zinc 76.4 $\mu$mol, copper 6.3 $\mu$mol, manganese 364 nmol, selenium 506 nmol, fluorine 60 $\mu$mol, iodine 157.6 nmol.

**Table 3.** Supplies of Standard Standard Intravenous Lipid Emulsion–Free Parenteral Nutrition Solutions and Fats Considered for Simulated Y-Site Administration.

| Standard ILE-free PN type | Standard ILE-Free PN Solution Supply (ml/kg/24 h) | Fat Supply (g/kg/24 h) | 3-in-1 PN Emulsion |
|---|---|---|---|
| Neonates < 1.5 kg (solution A) | 50 | 2 | Emulsion C |
| | 150 | 2 | Emulsion D |
| Neonates > 1.5 kg (solution B) | 50 | 2 | Emulsion E |
| | 150 | 2 | Emulsion F |

ILE, lipid injectable emulsion; PN, parenteral nutrition.

is rich in $\omega$-3 fatty acids. The theoretical volume calculations of ILE-free PN solution and SMOFlipid 20% required to prepare the 3-in-1 admixtures are shown in Table 4.

## *Sample Preparation and Collection*

Standard ILE-free PN solutions and simulated Y-site admixtures were compounded in a horizontal laminar flow hood International Organization for Standardization (ISO 5 standard in an ISO 7 standard environment) by an expert technician, following standard operating procedures.[19] The solutions and emulsions were prepared in Ethylvinyl-acetate (EVA) multilayered bags, which were stored inside photoprotective covers at 4°C.

The 2 standard ILE-free PN solutions were prepared in duplicate (A1, A2, B1, B2). From each solution, 5 20-ml samples were taken and immediately analysed at times 0 hour, 24 hours, 48 hours, 7 days, 10 days, 15 days, 22 days, and 31 days. A shelf life of 31 days was considered to be appropriate for batching production and storing of PN solutions in the neonatal ICU.

With respect to the 4 simulated Y-site admixtures (C, D, E, F), 5 20-ml samples were taken from each one and immediately analysed at 0 and 48 hours. Although the American Society for Parenteral and Enteral Nutrition recommends 24 hours infusions, we decided to increase the assessment to 48 hours to ensure the validity of our results in case longer infusions were performed.

## *Stability Assessment*

There is lack of consensus on the parameters to be determined when evaluating stability of PN solutions. Our selection was based on previous neonatal PN stability studies[13,20] and relevant causes of PN instability and incompatibility stated in the Spanish Consensus on Compounding of PN admixtures.[19]

The physicochemical parameters, and their corresponding methods, used to assess stability of standard ILE-free PN solutions were the following:

- Presence of particles and changes in color according to the European Pharmacopoeia[21]: visual inspection against a black-and-white contrast background by 2 observers.
- Osmolarity: cryoscopic osmometry (Fiske Model 210 Micro Osmometer, Advanced Instruments, Inc., Norwood, Massachusetts, US)
- pH: potenciometry (pH-Meter BASIC 20+, Crison, Barcelona, Spain).
- Turbidity: spectrophotometry at 690 nm (UV-2450, Shimadzu, Tokyo, Japan).
- Calcium concentration: colorimetry (Architect Plus ci16200, Abbott, Palatine, Illinois, US).

The physicochemical parameters and methods used to assess the stability of simulated Y-site admixtures were the following:

- Phase separation: visual inspection against light by 2 observers.
- Mean lipid droplet size (MDS) distribution: dynamic light scattering (Zetasizer NanoZS90, Malvern Instruments Ltd, Malvern, UK).

**Table 4.** Volume Calculation of Simulated Y-Site Admixtures.

| 3-in-1 PN Emulsion | Calculation of the Volume Ratio: $\frac{\text{ILE} - \text{Free PN Solution Supply}}{\text{FatSupply}}$ | Volume of Standard ILE-Free PN Solution (mL) | Volume of ILE (mL) | Volume of 3-in-1 PN Emulsion (mL) |
|---|---|---|---|---|
| C | $\frac{50\ \text{mL/kg/24h}}{2\ \text{g/kg/24 h}} \times \frac{20\ \text{g}}{100\ \text{ml}} = 5$ | 1600 | 320 | 1920 |
| D | $\frac{150\ \text{mL/kg/24h}}{2\ \text{g/kg/24 h}} \times \frac{20\ \text{g}}{100\ \text{ml}} = 15$ | 1600 | 106,7 | 1706,7 |
| E | $\frac{50\ \text{mL/kg/24h}}{2\ \text{g/kg/24 h}} \times \frac{20\ \text{g}}{100\ \text{ml}} = 5$ | 1350 | 270 | 1620 |
| F | $\frac{150\ \text{mL/kg/24h}}{2\ \text{g/kg/24 h}} \times \frac{20\ \text{g}}{100\ \text{ml}} = 15$ | 1350 | 90 | 1440 |

ILE, intravenous lipid emulsion; PN, parenteral nutrition.

### *Sterility Assessment*

Sterility of ILE-free PN solutions was assessed by means of a validated 0.45-$\mu$m membrane filtration method.[22] A sample of 50 mL was taken from each bag at the times stated previously. Every sample was mixed with 50 mL of a 4% wt/vol sterile solution of polysorbate 80 (Tween 80; Roig Farma, Barcelona, Spain) in water for injection. The admixture was shaken and then filtered under vacuum through a 0.45-$\mu$m cellulose nitrate membrane filter, 47 mm in diameter (Millipore Corporation, Billerica, Massachusetts, US). After filtration, the membrane was transferred to a blood agar medium and the plate was incubated at 35°C in an atmosphere enriched with 5%–7% of $CO_2$ for 48 hours, and at 20°C in an aerobic atmosphere for the next 5 days. Readings were taken every 24 hours; isolation and identification of the bacteria were performed by conventional methods.[23]

Glucose concentration was selected as an additional sterility parameter of standard ILE-free PN solutions since microbial growth may result in decreased glucose concentration. This measure was determined by an enzymatic method (Architect Plus ci16200, Abbott, Palatine, Illinois, US).

## Results

### *Standard PN Solutions*

*Physicochemical stability*

a) Visual inspection. No alterations were detected by visual inspection throughout the study period. No precipitates or color changes were observed.

b) Osmolarity. Osmolarity results of the 2 PN solutions tested showed differing patterns according to their different compositions (Figure 1a). For each one, osmolarity values remained practically constant during the assessment period.

c) pH. The 4 samples presented a pH of about 5.6, with a minimal oscillation over time (Figure 1b). A small decrease was observed in days 21 and 31, not relevant in terms of stability.

d) Turbidity. Turbidity remained stable throughout the study period, around 0.04 (Figure 1c). Data on day 14 are not shown (spectrophotometer under reparation).

e) Calcium concentration. Calcium concentration differed substantially between both PN solutions according to their different compositions (Figure 1d). For each PN solution, calcium concentration remained stable over time.

*Sterility*

a) Agar blood cultures. All agar blood cultures of membrane filters through which PN solutions had been previously filtered were negative.

b) Glucose concentration. Glucose concentration differed substantially between both PN solutions according to their different compositions (Figure 1e). For each PN solution, glucose concentration remained stable over time.

### *Simulated Y-Site Admixtures*

No alterations were detected by visual inspection. Physical stability was considered acceptable as MDS remained below 500 nm in all of the emulsions at the 2 times tested (Table 5).

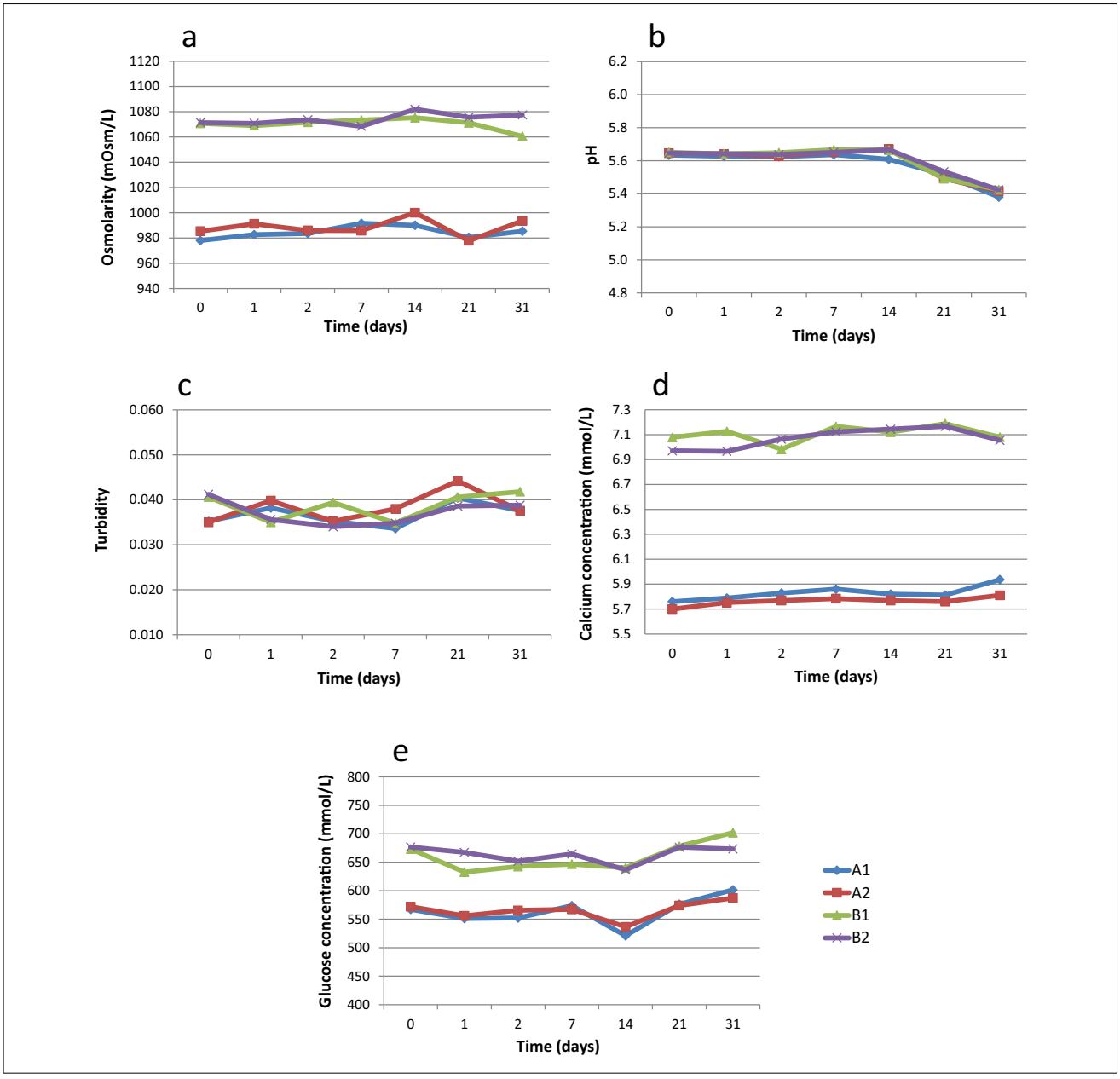


**Figure 1.** Results of the physicochemical parameters used in the assessment of stability and sterility: (a) osmolarity, (b) pH, (c) turbidity, (d) calcium concentration, (e) glucose concentration. A1 and A2: intravenous lipid emulsion–free parenteral nutrition solutions for neonates <1.5 kg. B1 and B2: intravenous lipid emulsion–free parenteral nutrition solutions for neonates >1.5 kg.

## Discussion

The use of standard ILE-free PN solutions in neonatal care aims to simplify their prescription and preparation by providing safe, ready-to-use admixtures. To the best of our knowledge, few studies have evaluated the stability and sterility of these solutions.[13,14] Our study has shown the physicochemical stability and sterility of both standard ILE-free PN solutions and simulated Y-site administration admixtures.

All physicochemical parameters were stable over time regarding the assessment of standard ILE-free PN solutions. First, as solutions remained visually unaltered for 31 days, we assume no macroscopic precipitates or chemical reactions such as the Maillard reaction had occurred. Second, osmolarity, pH, and turbidity were considered stable as variations among determinations were negligible and clinically not relevant. Because osmolarity results of the 2 PN solutions were above 900 mOsm/L, they must be

**Table 5.** Results of Mean Droplet Size in Simulated Y-Site Admixtures.

| | Mean Droplet Size (nm) ± SD | |
|---|---|---|
| 3-in-1 PN Emulsion | t = 0 hours | t = 48 hours |
| Emulsion C | 328 ± 7 | 302 ± 3 |
| Emulsion D | 330 ± 11 | 293 ± 2 |
| Emulsion E | 330 ± 9 | 299 ± 6 |
| Emulsion F | 329 ± 9 | 299 ± 4 |

PN, parenteral nutrition; SD, standard deviation.

administered through a central venous catheter to prevent thrombophlebitis.[10] Higher amino acid concentration relates to greater osmolarity, which mostly explains the difference observed between the 2 solutions. As expected, pH values were slightly acidic and comparable with those reported in other studies.[6,13,14] These pH values are compatible with central route administration. Also, turbidity, an additional parameter to assess precipitation, was found to be nearly constant. Finally, calcium concentration remained stable throughout the study period. One of the main physicochemical problems of PN solutions is the precipitation of calcium phosphate salts. Our results demonstrate the stability of the tested solutions regarding this concerning issue.

As for the sterility of PN solutions, all agar blood cultures were negative, and glucose concentrations remained stable during the study period. As 3-in-1 PN has been associated with central venous catheter–related bloodstream infections, it becomes critical to ensure sterility in these preparations.[24] Our results show no bacterial or fungal contamination.

In relation to 3-in-1 PN admixtures, in our case applicable to simulated Y-site admixtures, there is no consensus regarding the standards for ILE. Although the European Pharmacopoeia does not propose specific standards for ILE the U.S. Pharmacopeia sets 2 tests, the MDS and the volume–weight percentage of fat > 5 $\mu$m.[25] Although not mandatory by the European Pharmacopoeia, we considered it relevant to evaluate the specific stability parameters of ILE in the simulated Y-site admixtures. We found no visual, macroscopical evidence of coalescence. Also, the presence of large fat globules was discarded by dynamic light scattering, as MDS remained below 500 nm in all emulsions after compounding and 48 hours later. Unfortunately, single-particle optical sensing, the recommended technique to measure the volume–weight percentage of fat > 5 $\mu$m, was not available in our region when the study was performed. Moreover, it should be highlighted that MDS was only tested in 4 simulated Y-site admixtures, taking into account extreme values of fluid requirements and usual fat supply. The stability results of these emulsions are assumed to be generalizable to any supply of ILE-free PN solution within the aforementioned range (50–150 mL/kg/24 h).

Our study has some limitations. First, ILE-free PN solutions are stored refrigerated until administration. The evaluated samples were taken from cooled solutions, not considering that PN are perfused at room temperature. Second, vitamin degradation was not assessed as preparations were compounded in EVA multilayered bags and stored at 4°C inside photoprotective covers, which minimize oxidation.[7,8] Although vitamin concentration may progressively decrease in PN solutions under the conditions similar to that of our study, neonates are not usually fed by parenteral route exclusively. Because most neonates under nutrition treatment receive gradually enteral nutrition containing vitamins, an adequate vitamin supply may be assured. Also, the addition of vitamins to the PN solution prior to administration is a frequently used approach to avoid degradation. Third, peroxides may appear under certain circumstances known to promote fat oxidation, such as oxygen, ultraviolet light, or high temperature.[13] In our case, peroxide formation was considered negligible as simulated Y-site administration along with photoprotective covers minimizes this process. Fourth, the standard PN solutions tested may not be suitable for neonates with disorders such as hyperkalemia or hyperglycemia. Fifth, to prevent calcium and phosphate precipitation, we decided to be conservative and keep the supply slightly lower than the recommendations for neonates below 1.5 kg (solution A). A future approach replacing inorganic phosphate with glycerophosphate should aim to increase this supplementation. As for solution B, supplies of calcium and phosphate are within the recommended range. Finally, turbidity could not be measured on the 14th day as a result of technical problems. Because all turbidity results were consistent over time, precipitation would be discarded.

To conclude, our study shows that the 2 tested standard ILE-free PN solutions for neonates are physicochemically stable and sterile for 31 days under refrigeration (4°C). In addition, it confirms the stability of these solutions Y-site administered with ILE. In light of our results, these standard PNs are appropriate to use in the neonatal ICU.

## Statement of Authorship

P. Riera, G. Garrido-Alejos, J. Cardenete, E. Moliner, E. Zapico-Muñiz, D. Cardona, and N. Garin contributed to the conception and design of the research; P. Riera, G. Garrido-Alejos, and N. Garin contributed to the acquisition, analysis, and interpretation of the data, and drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript. P. Riera and G. Garrido-Alejos contributed equally to this study.

## Supplementary Information

Additional supporting information may be found online in the supporting information tab for this article.

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