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REVIEW ARTICLE

Parenteral nutrition in neonatology and pediatrics: physicochemical stability, risks and precautions. Narrative review

Nutrición parenteral en neonatología y pediatría: estabilidad fisicoquímica, riesgos y precauciones. Revisión narrativa

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What do we know about the subject matter of this study?

The physicochemical stability of parenteral nutrition represents a challenge in the pediatric/neonatal population, due to its high nutritional requirements and lower volumes. There is still scarce literature regarding stability and safety to minimize the risks of incompatibility/interactions.

What does this study contribute to what is already known?

There is variability in the use of physicochemical stability ranges, the role of nutrients, supplies, and environmental factors. In this article, a review was carried out according to SANRA criteria, to create physicochemical stability recommendations according to clinical relevance and describe how nutrients, supplies, and environmental conditions of the clinical units can affect the stability of the admixture.

Abstract

Parenteral nutrition is a high-risk therapy due to some of its components and the exceptional inclusion of drugs. It can contain more than 50 nutrients, with different characteristics of osmolarity, ionic charge, and pH, which can affect its physicochemical stability. In addition, environmental conditions such as light, temperature, and oxygen must be considered. Their prescription and administration represent a challenge for the healthcare team, especially in the pediatric and neonatal setting, due to factors such as the state of metabolic immaturity and greater susceptibility to oxidative damage. This group also requires smaller volumes with higher concentrations of nutrients, which complicates its preparation and risks of incompatibility/interactions. The objective of this article is to review current concepts of parenteral nutrition according to the criteria of the *Scale for the Assessment of Narrative Review Articles (SANRA)*, to make recommendations on physicochemical stability according to clinical relevance. It describes how environmental conditions and inputs can affect the stability of the

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mixture and provides recommendations and values to reduce the risks of instability, including amino acids, lipids, cations, anions, and different calcium and phosphate salts. Given the variability in the reproduction of the same mixture due to clinical conditions and inputs, this subject constitutes an open area for research due to the methodological diversity used in the reports. Finally, the recommendations from the pediatric/neonatal sphere are the strictest in the literature, so they are valid for adults.

Introduction

The prescription and administration of intravenous nutrients in parenteral nutrition (PN) represents a challenge for the healthcare team, despite access to information, especially in the pediatric and neonatal setting. Challenges include obtaining a PN with adequate nutrients in quantity and proportion in a given volume, minimizing the risks of degradation, and preventing interactions and incompatibilities between nutrients. In addition, environmental conditions in clinical units that may favor degradation through temperature, light, and oxygen, such as the use of phototherapy and radiant cribs in neonatal units, must be considered.

Cases of physicochemical instability related to PN have been reported in the literature, ranging from no clinical impact to harm and even death. Among the most described phenomena is the formation of calcium-phosphate precipitates. In 1994, a report by the *Food and Drugs Administration* in the USA alerted about patients who developed respiratory distress and death[1], and the autopsy described calcium-phosphate precipitates in the alveoli. Other instabilities include phase separation of the emulsion into aqueous and lipid layers (coalescence), degradation of lipids and vitamins, and formation of lipid peroxides[2]. Additional events without clinical impact have also been observed, related to component degradation such as amino-acid oxidation (Maillard reaction), nutrient absorption and desorption, drugs in the container, and formation of CO_2. It is important to distinguish between interactions that increase risk and those without clinical relevance[3].

PN is a high-risk medication due to certain components, and the exceptional drugs inclusion. It can contain more than 50 nutrients, with different characteristics of osmolarity, ionic charge, and pH, which can affect its physicochemical stability (PCS). Regarding the physicochemical aspects, it is a dynamic emulsion, stable only for short periods, composed of lipids and water-soluble components, prepared in sterile compounding prescriptions. When administered for 24 hours at room temperature, it is exposed to nutrient degradation and microbiological risk[4].

In pediatrics, especially in neonatology, it is even more complex given factors such as metabolic immaturity, greater susceptibility to oxidative damage from lipid peroxidation, lower antioxidant capacity due to immature enzyme systems, and a diminished ability to interconvert amino acids. In addition, requirements are calculated per kilogram per day, unlike adults whose dosing is per day, which increases the risk of exceeding stability ranges. Pediatric patients also require smaller volumes with a higher concentration of nutrients, administered at low infusion rates. Even more complex is the case of extremely preterm infants; these requirements exceed those allowed by the PCS and cannot be extrapolated to the intake they would receive intrauterine. This risk increases in the use of prolonged PN associated with the use restriction of the enteral route. On the contrary, the increasing prevalence of excess malnutrition in the pediatric population requires a calculation of requirements per kilogram per day, without exceeding the maximum daily limits recommended for adults.

When preparing PN, one should consider the nutrients' characteristics, calculate recommended doses, identify interactions and incompatibilities, set cut-off limits for components that add risk, and consider environmental conditions and supplies that promote stability. This article presents a review, performed according to *SANRA* criteria, to create recommendations based on their clinical relevance, and describes how nutrients, supplies, and environmental conditions can affect PCS. Components without nutritional characteristics, such as drugs, were excluded from this review.

Components Of Parenteral Nutrition

Macronutrients

Amino acids. The formulations contain about 20 types of essential, non-essential, and conditionally essential amino acids. They have an energetic value of 4 kcal/gr and their main function is tissue synthesis[5]. The composition of pediatric formulations is characterized by higher amounts of cysteine, tyrosine, and taurine, which are limiting or conditionally essential amino

acids in neonates due to renal and hepatic immaturity[6]. The age range for the use of pediatric amino acids versus adult formulations has not yet been established, however, some available recommendations suggest using them at least up to one year of age[5] which could be insufficient in the pediatric age. Others recommend up to 30 kg which would cover 80-90% of pediatric patients[7] and later will depend on the resources of each center due to its higher cost.

In terms of PCS, amino acids are considered a protective factor of the admixture due to their buffering capacity, since they stabilize and decrease pH fluctuations, even with the addition of nutrients with extreme pH such as 50% glucose (pH 2). In addition, amino acids form complexes with calcium and/or phosphate, thus decreasing the interaction between them and their precipitation[8]. To provide stability, the admixture should have concentrations ≥ 2% weight/volume (w/v)[9] and 5% maximum[10]. Other studies in adults mention values > 2.5%[11] and 4%[12], so it is suggested that at least > 2%. However, there are unpublished experiences that these ranges could vary depending on the supplies used.

Lipids. The formulations can be composed of one or several oils in different proportions, coming from soybean (LCT), medium-chain fatty acids (MCT), olive (W-9), and fish (W-3). Their main function is to provide essential fatty acids and energy, which can vary between 9-10 kcal/gr[5].

The *first-generation* lipid formulations are derived from soybean oil (W-6), which contains unsaturated long-chain fatty acids essential for humans, however, they have inflammatory characteristics; the *second-generation* formulations are derived from coconut, which contains medium-chain fatty acids, and from long-chain monounsaturated olive (W-9), both are neutral regarding inflammatory aspects; finally the *third generation* are derived from fish (W-3) and have anti-inflammatory characteristics[5,13-15]. Phytosterols from soybean oil-based lipid formulations are cholesterol derivatives that inhibit enzymes involved in the synthesis of cholesterol and bile acids. These compounds are excreted by bile, which is why they have been associated with liver damage by PN, and are found in smaller proportions in other lipid sources and are not contained in those derived from fish[5].

Intravenous lipids adopt a negative charge on their surface, due to substances added in their manufacture as emulsifiers/detergents. This characteristic provides transitory stability, keeping them in suspension and avoiding the phenomenon of aggregation and coalescence characterized by phase separation and lipid droplets > 5 µm in size[16]. Currently, the most recommended presentations are those of higher concentration (20% vs 10%), since their formulation requires lower phospholipid content, which is related to hypertriglyceridemia, and generation of slow-clearing particles[5].

It is recommended that the lipid concentration in the final admixture be between 1-2% and a maximum of 5%[10], in order to favor stability and avoid phase separation[10,12]. Extreme concentration ranges can destabilize, since it is an emulsion that has transient stability over time. They have a basic pH ~6-8, but this does not carry over to the final pH of the solution, which is slightly acidic. The factors that decrease stability are variations in pH and the temperature rise that favors its oxidation and increases the kinetics and interaction between its particles, generating larger droplets[16,17].

At the same time, the addition of +2 and +3 valence cations (zinc, magnesium, and iron) can decrease stability by neutralizing the lipid surface (negative charge) and favoring its aggregation. In contrast, cations and ions with valence +1 (sodium, potassium, and acetate) and -1, have less risk of neutralizing the lipids and do not affect the stability of the micelle. Finally, for lipid emulsion stability, the percentage of > 5 µm-lipid droplets should be < 0.05% w/v[18,19], and for the final admixture, the percentage of particles > 5 µm should be < 0.4%[20].

Carbohydrates. Only D-glucose solutions are used, which have a caloric value of 3.4 kcal/gr. There are solutions of concentrations between 5-50%, but those of higher value (30-50%) are the most used. To provide stability, the concentration of the final admixture must have values between 5-35%[10]. The higher the concentration, the more acidic the pH (~2), however, this does not carry over to the extreme final pH of the admixture due to the buffering capacity of the amino acids[21]. It is a nutrient with low interaction potential and its elaboration outside these ranges (peripheral PN), is associated with a lower viscosity in the admixture[21]. It also has a high osmolarity value; 20, 30, and 50% glucose have osmolarities of 1110, 1666, and 2777 mOsmol/L, respectively.

Micronutrients

Electrolytes. There are different electrolyte solutions (Table 1), in general they are stable in the admixture, and they are primarily prescribed according to the recommendations by age group and clinical condition, except for calcium-phosphate salts, one of the most described instabilities due to their risk of precipitation.

Calcium. There are two types of salts: organic calcium gluconate 10% and inorganic calcium chloride 10%. The use of calcium gluconate is recommended over calcium chloride since the latter has a higher dissociation potential. If only calcium chloride is available, it is recommended to combine it with an organic source of phosphorus[22].

Phosphorus. There are two types of salts: the organic sodium glycerophosphate 21.6%, and the inorganic monobasic and dibasic potassium phosphate 15%. The organic salt can be combined with both types of calcium sources (calcium gluconate and calcium chloride). However, monobasic and dibasic potassium phosphate should only be used with the organic calcium salt[23,24].

Magnesium. It can be supplied as magnesium sulfate. This salt acts as a protective factor regarding the formation of calcium-phosphate precipitates since it forms complexes with phosphorus[25]. Its maximum concentration described is 15-20 mEq/L[10], which should be associated with the maximum daily requirements in adults that range between 8-24 mEq/day[26].

Sodium. It can be supplied as chloride, acetate, and glycerophosphate, and all sources must be counted when assessing stability. Its maximum concentration described is 154-180 mEq/L[20]. Daily requirements in the pediatric/neonatal population vary between 1 and 7 mEq/kg/day, so the final concentration must be adjusted accordingly[25].

Potassium. It can be provided as chloride, acetate, and mono/dibasic potassium phosphate, and all sources must be included in the final admixture. Its maximum concentration reported is 80-100 mEq/L[10]. Daily requirements in the pediatric/neonatal population range from 1 to 3 mEq/kg/day[25], so the final concentration should be adjusted to meet those needs.

Chlorine. It can be supplied as sodium and potassium chloride. To reduce the contribution of this ion in hyperchloremic metabolic acidosis, sodium acetate is used instead of sodium chloride[17]. Its maximum concentration described is 180 mEq/L[10], as provided by sodium and potassium salts according to their daily requirements.

Acetate. Sodium acetate, the most commonly used in our context, is equimolar with sodium bicarbonate (1 mEq of bicarbonate is equivalent to 1 mEq of acetate) and is used to replace sodium bicarbonate, which cannot be added to PN because it forms an insoluble calcium carbonate salt. Its maximum concentration described is 85 mEq/L[10], and there are no maximum daily requirement recommendations available. Potassium acetate can also be used in case of unavailability of sodium acetate, considering the contribution of potassium instead of sodium. Both are salts with specific use, as in metabolic acidosis for which the value of excess base, bicarbonate, and hydration status must be considered. It should not be corrected considering the net value of base excess.

Trace elements. These metals are required only in minute amounts and circulate in the blood at extremely low (ppm) levels, which vary according to age, clinical indication, and underlying disease[28]. Deficiencies due to gastrointestinal or cutaneous losses, or on the contrary accumulation due to hepatic or renal dysfunction, must be considered for their dosage[28]. PN delivery bypasses the homeostatic barrier of the gas-

Table 1. Commercial presentations of electrolytes available in Chile

Nutrient	Abbreviation	Presentation	Grams	Electrolyte	mEq/mL	mmol/mL	mg/mL
Sodium Chloride 10%	NaCl	10 mL	1	Na^+	1.7	1.7	39.34
				Cl^-	1.7	1.7	60.66
Potassium Chloride 10%	KCl	10 mL	1	K^+	1.3	1.3	52.44
				Cl^-	1.3	1.3	47.56
Mono or Dibasic potassium phosphate 15%	KPO_4	10 mL	1.5	K^+	1.1	1.1	43.1
				P	1.1	1.1	34
Zinc Sulfate Heptahydrate 0.88%	Zn	10 mL	0.088	Zn^{+2}	0.06	0.12	2
				SO_4	0.06	0.12	2.94
Magnesium Sulfate 25%	Mg	5 mL	2,5	Mg^{+2}	2.03	4.06	24.6
				SO_4	2.03	4.06	97.48
Calcium Gluconate 10%	Ca	10 mL	1	Ca^{+2}	0.46	0.92	9
				Gluconate	0.46	0.92	43.52
Sodium Acetate 30%	$C_2H_3Na0_2$	10 mL	3	Na^+	2.2	2.2	50.7
				$Acetate^-$	2.2	2.2	130.21
Sodium Glycerophosphate 21.6%	$C_3H_7N_20_65H_20$	20 mL		Na^+	2	2	46
				P	2	1	31

trointestinal tract, so there is a risk of overload with excessive amounts if the patient's baseline status is not considered, especially in prolonged PN. In addition, the solutions may unintentionally contain chromium, manganese, and aluminum in unquantified amounts.

Trace elements can be divided into three risk groups: i) risk of deficiency, such as selenium and zinc, especially in premature infants due to limited reserves and rapid postnatal growth; ii) risk of excess, such as chromium and manganese[29]; and iii) risk of deficiency/excess, such as copper[28].

There are different formulations of trace elements available in Chile, such as Tracelyte®, Peditrace®, Tracutil®, and Addaven® (Table 2). They contain 4 elements (zinc, copper, manganese, and chromium) or 6-9 elements (plus iodine, selenium, molybdenum, and fluorine). The recommendations suggested by manufacturers vary and should be adjusted in neonates, with adequate selenium and zinc content, but without exceeding manganese and chromium, and in liver disease, considering the accumulation of copper, chromium, and manganese[30]. No stability problems have been reported since the +2 and +3 cations in its formulation are added in low doses.

Zinc. Newborns have the highest zinc requirement (400-600 ug/kg/day) and it is necessary to add extra zinc sulfate since trace element preparations do not contain enough zinc. Due to the +2 valence, there is a potential risk of interaction with lipids, however, this is reduced by the small amount given and the fact that it is a soluble salt[2].

Iron. Iron salts are not routinely added to the mixture since their +3 valence binds to lipids and may favor their aggregation and/or flocculation. Only some trace element formulations (Tracutil® and Addaven® in Chile) contain it in small amounts and as ferric chloride, so it is stable in the PN. Salts such as dextran/sucrose or others used for the treatment of anemia are not recommended, since changes in coloration and increase in the particle size of lipids have been observed[2,31].

Multivitamins. They are one of the most labile nutrients, which are affected by environmental conditions and achieve stability during 24 hours of administration, through supplies and strategies to minimize their degradation. In case of suspicion of a specific vitamin deficiency, it is suggested to analyze it individually. Riboflavin is particularly sensitive to light and acts as a catalyst in oxidation-reduction (redox) reactions at a wavelength of 420 nm. This is mainly influenced by orange/maroon colors, which help reduce their degradation[32].

Physicochemical stability of parenteral nutrition

pH

In the admixture, the pH of greatest stability is ~5 (slightly acidic), which favors the solubility of the calcium-phosphate salt, and also reduces the coalescence of lipid droplets[33,34]. At the usual pH < 6.4, the monobasic phosphate ion predominates, producing monobasic calcium phosphate, the most soluble form (solubility of 18 g/L) as opposed to higher pH where dibasic calcium phosphate predominates, which is almost insoluble (0.3 g/L).

Calcium-phosphate

It depends on several factors such as the type of salt used (organic or inorganic), the concentration of macronutrients, which influences the final pH, magnesium addition[25], increased temperature, which promotes particle interaction and precipitation, and finally, the

Table 2. Adult and pediatric trace elements available in Chile

	Tracelyte ®	Tracutil®	Addaven®	Peditrace®
Presentation	2 mL	10 mL	10 mL	10 mL
Iron (mg)	-	2	1.1	-
Zinc (µg)	2000	3270	5000	2500
Manganese (µg)	400	550	55	10
Copper (µg)	1000	760	380	200
Chromium (µg)	10	10	10	-
Molybdenum (µg)	-	10	19	
Selenium (µg)	-	24	79	20
Fluorine (µg)	-	570	950	570
Iodine (µg)	-	127	130	10

order of addition[23,24]. The maximum concentrations of each component are determined using the following equations, which must be associated with the maximum daily requirements in adults: calcium (10-15 mEq/day) and phosphorus (20-40 mmol/day)[20].

Calcium-phosphate stability equations

For preparation, different equations are available depending on the combination of salts used. The most commonly described formulas involve summing the calcium and phosphate ions in relation to the amino acid concentration.

Calcium gluconate 10% - Mono- and dibasic potassium phosphate 15%

This equation depends on the sum of calcium (mEq/L) and phosphorus (mmol/L) according to the amino acid concentration per total volume (grams per 100 mL) (Table 3) for organic calcium/inorganic phosphate concentrations[11,27]. There are other more flexible values such as the sum of 10 mEq/L calcium + 30 mEq/L phosphate with ranges from 35-45 up to 60 mEq/L[18]. However, it is suggested to use stricter options or those with higher solubility[11,22-24,27,31,35,36].

Calcium gluconate 10% - Sodium glycerophosphate 21.6%

It is a combination of both components in organic salt form, used in clinical conditions of high calcium and phosphorus requirements, with small volume limits.

Depending on the amino acid concentration, the maximum levels of calcium (mEq/L) and phosphorus (mmol/L) vary according to organic calcium/organic phosphorus (Table 3)[35,36].

Calcium chloride 10% - Sodium glycerophosphate 21.6%

Calcium chloride is an inorganic salt and therefore it is not recommended for use with inorganic phosphorus due to its solubility and high interaction capacity. Calcium chloride is currently used exceptionally[24], however, there are incipient studies given its low aluminum content, in relation to gluconate[12].

Table 3. Summary of physicochemical stability ranges in parenteral nutrition for macronutrients and calcium-phosphorus compatibility

Components	Range	Observations
Total % Aa/vol.	≥ 2% pediatrics	Protective NP stability factor, stabilizes pH to slightly acidic
	≥ 2,5% adults	
Total % Lipids/vol.	≥ 1-2%	Lower values promote emulsion instability
Organic calcium / inorganic phosphate	Several ranges	Aa not less than 2%
	≤ 30-45 up to 60 mEq/L	
Total % Aa/vol. (associated with organic calcium / inorganic phosphate)	> 1.5% Aa: Ca mEq/L + P mmol/L ≤ 30	Recommended equation
	1-1.5% Aa: Ca mEq/L + P mmol/L ≤ 20	
	< 1% Aa: only Ca or only P	
Organic calcium / organic phosphorus sum	≤ 160	
Total % Aa/vol. (in organic calcium / organic phosphate ratio)	< 0.5% Aa: Same as inorganic phosphates	Recommended equation
	0.5-1.25% Aa: 20 mmol/L (40mEq/L) of Ca and 25 mmol/L of P	
	1.25-2.5% Aa: 35 mmol/L (70mEq/L) of Ca and 30 mmol/L of P	
	≥ 2.5% Aa: 56 mmol/L (112 mEq/L) of Ca and 48 mmol/L of P	
pH	~ 5	Promotes calcium-phosphate insoluble solubility *per se*
		Promotes lipid stability with droplet repulsion
Mg^{+2}	< 15-20 mEq/L	

Abbreviations: Aa, amino acids; vol, volume.

Table 4. Summary of physicochemical stability ranges for parenteral nutrition for electrolytes

Components	Ranges	Observations
Na^+	< 154-180 mEq/L	Sodium can be provided as chloride, acetate, and glycerophosphate
K^+	< 80-100 mEq/L	It can be supplied as chloride, acetate, or mono/dibasic potassium phosphate
Cl^-	< 180 mEq/L	It can be supplied as sodium and potassium chloride
Acetate	< 85 mEq/L	It can be supplied as sodium and potassium acetate
Electrolytes	Anions -1	No deleterious effect has been described
	Cations +1 y +2	Stable in the micelle at recommended doses
	Cations +3	No additions are recommended except for low contents of trace elements

Order of addition

There are several recommendations on the order of addition, with a particular emphasis on the protective role of amino acids. These act as buffers, helping to stabilize pH fluctuations and forming complexes with calcium and/or phosphate, which reduces their interaction and risk of precipitation[8]. It is recommended to start with the macronutrients, specifically amino acids along with either calcium or phosphate. Calcium and phosphate should never be added using the same syringe or consecutively; therefore, one of them should be reserved for the end. Next, add the cations in order of increasing valence (+1, +2). Magnesium, for example, serves as a protective factor by forming complexes with phosphate, thus reducing its interaction with calcium[21,25]. Then, add the trace elements, medications, and colored or opalescent products[10,27]. It is also important to avoid the consecutive mixing of components with extremely acidic pH (such as glucose and trace elements) and those with basic pH (such as lipids)[21].

Osmolarity

It is the sum of the osmolarity of all the components in relation to the final volume and is expressed in mOsm/L[8]. The components with the highest osmolarity are amino acids which contribute 10 mOsm/gr, glucose 5 mOsm/gr, and electrolytes 1 mOsm/mEq, unlike lipids with 1.3-1.5 mOsm/gr, and water which does not contribute osmolarity but volume. This will determine its route of administration whether it is central or peripheral[8].

General Recommendations

Prescription

It is recommended that an electronic prescription form be designed to calculate the percentage of amino acids and lipids in the final volume of the admixture, calcium-phosphate sum with their respective cut-off points according to the salt used, maximum electrolyte concentrations, and calculation of osmolarity. Tables 3 and 4 show ranges and values[27,37].

Administration

Maintain the solution at room temperature for 30-60 minutes before administration. Confirm patient identity and match with the preparation. Assess the homogeneity of the admixture at the beginning and at least every 12 hours, and make sure there is no phase separation or presence of particulate matter. Verify the proper functioning of the venous access, the route of administration, and the infusion rate. Register the start and end times, and reconcile the medical order with the nursing record and the actual infusion rate. If the line is disconnected, it must not be reconnected to the IV access; the solution should be discarded, and the administration must wait until the new PN arrives. In case of a procedure, the infusion should be cycled (reduce the drip rate to half before stopping), in order to gradually decrease the glucose load and prevent hypoglycemia.

Supplies

External factors such as temperature, light, and oxygen act as catalysts for redox reactions, generating oxidizing compounds such as lipo- and hydroperoxides, among others. Therefore, to prevent and minimize nutrient degradation, supplies must have specific characteristics (Table 5).

Temperature

The PN should not be exposed to extreme temperatures, or heat sources, or be frozen. From the time of preparation until 30-60 minutes before administration, it must be stored under cold chain conditions at 2-8°C[38]. Administration at room temperature should not exceed 24 hours due to microbiological risk and nutrient degradation, mainly lipids and

Table 5. General recommendations

Components	Ranges	Observations
Administration time	Do not administer > 24 hours at room temperature	Due to potential microbiological risk and degradation of more labile nutrients
Temperature	≤ 28 °C in PN bag	At higher temperatures, particle kinetics and potential calcium-phosphate and lipid precipitates increase
		If the room temperature is higher than indicated, this is not necessarily equivalent in the bag
Conservation	Refrigeration 2-8 °C	Minimizes degradation of the most labile nutrients and reduces microbiological growth potential
Expiration	9 days refrigerated + 24 hours of room temperature[2]	With multilayer bags, photoprotection, and refrigeration
	4 days refrigerated + 24 hours at room temperature[10]	
Supplies	EVA Bag	PN prepared and administered the same day (maximum 24 hrs. administration at room temperature)
		It is not recommended in prolonged PN due to longer exposure time and accumulation of lipid peroxides
	Multilayer Bag	Recommended for daily use in neonatology
		If not administered on the same day of preparation (see expiration date), keep refrigerated. Once installed in the patient, do not administer > 24 hours at room temperature

vitamins[12,39-42]. Therefore, more than 24 hours can elapse from preparation to administration, as long as it is kept in cold chain and with the appropriate supplies. It has been reported that with temperatures above 28ºC, more lipid peroxides and free fatty acids are generated, although the temperature of the PN does not increase directly.

Light

The PN should not be administered under direct sunlight or phototherapy in order to reduce exposure to both[42]. There are photoprotective bags of different colors such as maroon, orange, blue, and green, and the most recommended due to their effectiveness are the orange and maroon ones[32]. There are also different types of infusion sets: some are transparent and allow light to pass through, while others have orange-colored photoprotection that reduces it. Ultraviolet (UV) light penetration is also minimized, along with the oxidation of other components such as lipids, vitamins, and amino acids, the latter having less clinical impact[42].

Oxygen

EVA bags are made of ethylene and vinyl acetate. They should be used for processing and administration on the same day (not to exceed 24 hrs.), as they are permeable to the passage of oxygen, which causes nutrient degradation[43]. Multilayer bags are composed of different material layers, including an ethylene-vinyl acetate (EVA) copolymer and an ethylene-vinyl alcohol (EVOH) layer that serves as a UV filter. Compared to bags made solely of EVA, these significantly reduce oxygen permeability, by up to 100 times[44].

Lipid peroxidation

The most susceptible population is neonates[32,45-49]. Increased levels of different types of peroxides in PN, blood, and urine have been observed in patients using EVA bags versus multilayer ones and exposed to different environmental conditions such as phototherapy, ambient light, and photoprotection[45-49].

In-line filters

They reduce the passage of particulate material larger than 2 μm (glass, rubber stoppers, gauze, plastics, etc.), which pose the greatest risk and are not useful for infection control. They are available in different pore sizes, such as 0.2 μm (for administration with no lipids or 2:1 ratio) and 1.2 μm (for administration with lipids or 3:1 ratio)[50]. Currently, their use is especially recommended in prolonged PN, which may destabilize and generate particles. According to international recommendations, PN in the neonatal population should be administered with complete photoprotection (bag and infusion set), in-line filters, and daily multilayer bag[44,46,48,51,52].

Conclusion

In this article, a review was performed to create PCS recommendations in PN, to reduce the risks of incompatibilities and interactions, so the most critical parameters must always be considered. These recommendations include ranges for components and describe how supplies and environmental conditions can influence them. Given the variability in the reproduction of the same admixture due to clinical conditions and supplies, this field constitutes an open area for research due to the methodological diversity used in the reports.

Use of artificial intelligence

ChatGPT 3.5 was used for proofreading the abstract, introduction, and conclusion; DeepL translate for the abstract.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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