Parenteral Nutrition in Premature Infants

7

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Introduction

Major improvements have been made in neonatal care during the past decade leading to a dramatic decrease in neonatal mortality [1]. The impact of perinatal undernutrition on growth and brain development has been well known for years from both human and animal studies [2–5]. In premature infants, reports also suggest that postnatal protein and energy malnutrition increase the severity of postnatal diseases and induce postnatal growth restriction, inadequate brain development, and poor neurodevelopmental outcomes [3, 6–12].

During the early days or weeks of life, parenteral nutrition (PN) is frequently required in premature infants, especially in very low birth weight (VLBW, <1500 g) infants, due to the immaturity of their gastrointestinal tract. Despite recent recommendations from scientific experts, PN practices are currently nonoptimal [13–15]. A recent survey in the UK observed a high variability in PN composition, supply, and administration in the health-care organization and in the quality assurance [15]. A "good standard of care" was only observed in 24% of cases with frequent delay in recognizing the need for PN (28%), delay in the administration of PN (17%), inadequate intakes for needs (37%), inadequate monitoring (19%), and few multidisciplinary nutritional team [15]. In addition, Lapillonne et al. [14] recently demonstrated that neonatal unit PN protocols were rarely compliant with international guidelines, particularly during the first days of life. Such practices lead to severe cumulative nutritional deficits and postnatal growth restriction that may be considered as iatrogenic malnutrition [13].

Several recent reports have evaluated how to optimize PN support in premature infants [16–24]. This chapter discusses the most important features regarding PN in premature infants, outlining most recent practical aspects and guidelines.

The Standard for Premature Infants Growth

Optimal growth for premature infants is generally defined as similar to that of the fetus of similar gestational age (GA) up to the due date and similar to that of the breast-fed term infant afterwards [25–27]. Fetal growth rate is extremely high during the third trimester of gestation and much greater than during any other periods of life (Fig. 7.1). If the mean fetal weight gain during the last trimester of gestation is around 15 g/kg/day, it must be emphasized that fetal weight gain usually decreases from ~20 g/kg/day at 24–28 weeks of gestation to ~10 g/kg/day at 39–40 weeks [27]. The body weight composition also changes during the last trimester of pregnancy explaining why nutritional requirements also vary in relation to postmenstrual age. Even if these concepts are well accepted, they are not easy to apply in clinical practice due to the major differences observed between the intrauterine and the extrauterine physiology. Postnatal growth is physiologically associated with an increase in fat-mass deposition. Therefore, it has been suggested that lean body mass (LBM) gain should be regarded as the gold standard reference for growth in premature infants [28, 29].

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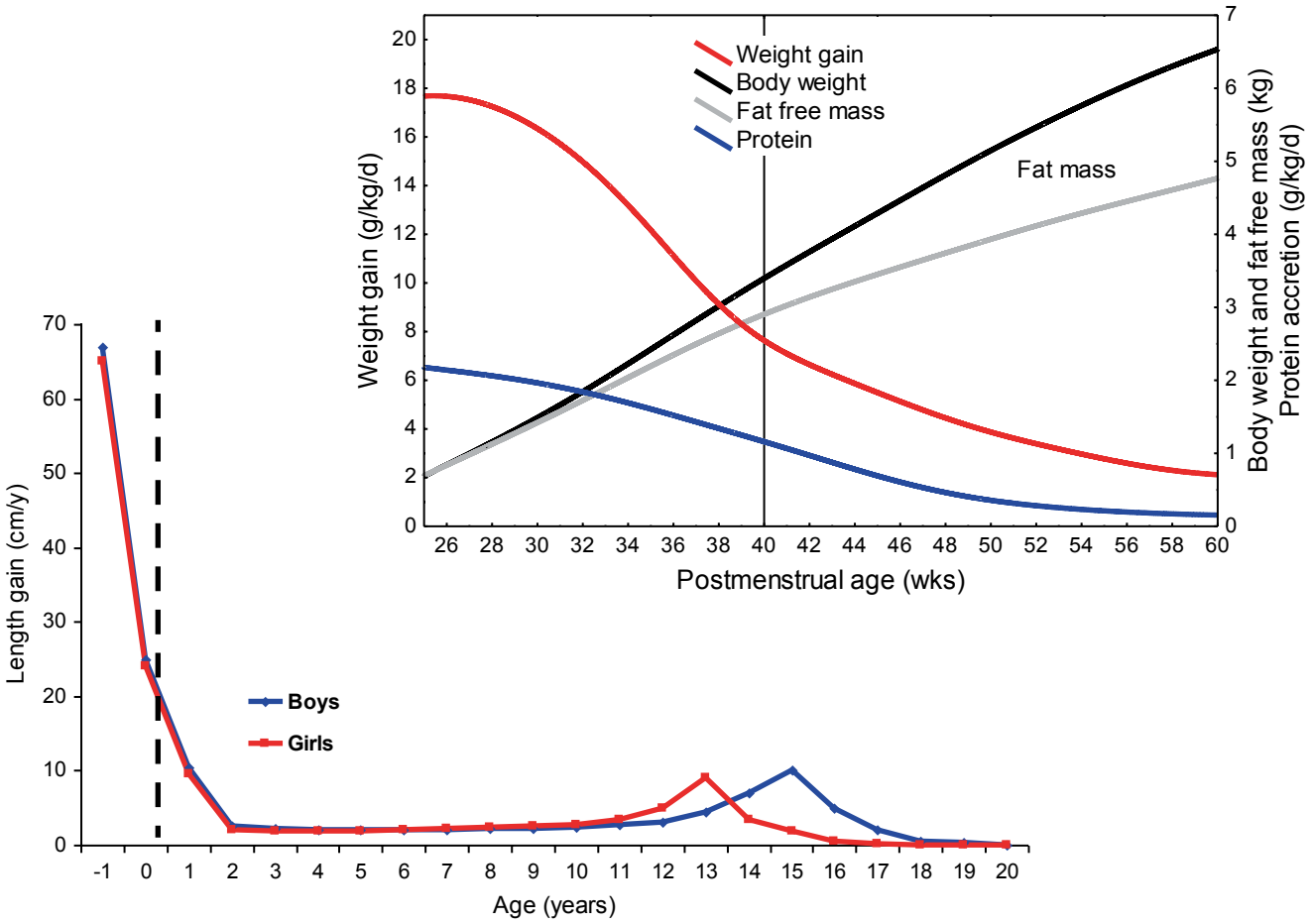

Fig. 7.1 Perinatal growth and changes in weight gain, body composition, and protein accretion

Nutritional Support in Premature Infants

Nutrition of VLBW infants may be divided into two distinct periods: the immediate adaptive or "transitional" period during the first 3–7 days of life and a stable "growing" period up to discharge from the neonatal intensive care unit (NICU). Depending on birth weight (BW) and GA, the transitional period including the immediate postnatal adaptation of the premature newborn to the extrauterine environment may be prolonged, particularly in the more vulnerable infants with major clinical disorders. The more premature a neonate is the more challenging is the influence of the immaturity and the accompanying morbidity on the nutritional supply [13, 14, 30, 31]. During this period, most of these infants require PN as their major source of nutrients despite frequent initiation of enteral nutrition. Recently, several studies have highlighted the importance of reducing the transitional period by rapidly providing sufficient intakes to promote anabolism and to reach stable-growing requirements [16–18, 20, 21].

Energy

Postnatal Energy Metabolism

The Atwater's factors are usually used to calculate the metabolizable energy contents and intakes both in PN and enteral nutrition. However, the energy available from macronutrients is not exactly similar. The gross energy content of 1 g of amino acid (AA, ~4.75 kcal/g) is about 10% lower than that of 1 g of protein (~5.25 kcal/g). By contrast, the energy provided after oxidation of AA in urea is ~3.75 kcal/g, whereas the energy of AA stored in protein is ~4.75 kcal/g, a value identical to gross energy. Gross and metabolizable energy content of glucose (~3.75 kcal/g) is less than that of more complex carbohydrate (~4 kcal/g). For intravenous lipid emulsions (IVLE), metabolizable energy content is also similar to gross energy (~10 kcal/g including glycerol energy content) but could be lower in IVLE containing medium-chain triglycerides (MCT) [32, 33]. These differ-

Table 7.1 Advisable nutritional intakes for premature infants requiring parenteral nutrition

	Initial dose after birth	Target dose
Amino acids (g/kg/day)	2–3	3–4
		3.5–4.5 (VLBW)
Glucose (g/kg/day)	6–7	12–17
Lipids (g/kg/day)	1–2	3–4
Energy (kcal/kg/day)	40–60	95–125
Water (mL/kg/day)	60–90	120–180
	80–100 (ELBW)	
Sodium (mmol/kg/day)	0–1	3–5
		3–7 (VLBW)
Potassium (mmol/kg/day)	0–1	2–3
Chloride (mmol/kg/day)	0–1	3–5
Calcium (mmol/kg/day)	0.6–1	1.6–2.5
Phosphorus (mmol/kg/day)	0.6–1	1.6–2.5
Magnesium (mmol/kgday)	0.1–0.2	0.2–0.4

ELBW extremely low birth weight infants (< 1000 g), *VLBW* very low birth weight infants (< 1500 g)

ences are not easy to incorporate into practice. This explains why energy requirements in PN are close to that in enteral nutrition when the Atwater's factors are used.

The energy requirements for premature infants correspond to the sum of total energy expenditure plus the energy stored in the new tissue with growth. Energy expenditure measured by indirect calorimetry increases slightly with postnatal age and varies from 45 to 55 kcal/kg/day. The energy cost of growth implies making allowance for fetal LBM accretion, postnatal fat deposition, and the cost of tissue deposition. The energy cost for a postnatal weight gain of 17–20 g/kg/day with adequate LBM accretion vary from 50 to 70 kcal/kg/day in premature infants. Therefore, metabolizable energy requirements for premature infants on PN are estimated to be between 95 and 125 kcal/kg/day [32, 34, 35]. Taking into account the potential need for a prior energy deficit and for catch-up growth, 120 kcal/kg/day is required for most premature infants.

Recommendations for Energy Supply During Total P N

Current recommendations suggest providing a minimum of 40–60 kcal/kg/day on the first day of life followed by a rapid increase of energy intakes up to 95–125 kcal/kg/day within the first week of life. This needs to be adjusted according to growth and metabolism during the stable growing period (Table 7.1).

Recommendations for Energy Supply During Partial PN

Nutritional recommendations include early introduction of enteral feeding in premature infants [36]. However, minimal feeding below 25 mL/kg/day mainly serves as trophic gut feeding. It may not be well absorbed, and therefore, it should not be considered in the total energy intakes. Thereafter, when feeding increases above 40 mL/kg/day, total energy intakes would be calculated as the sum of the parenteral and the enteral intakes taking into account an energy absorption rate of 80 % with human milk and 90 % with preterm formula [16, 33].

Amino Acids

Intravenous AA Solutions

Considerable improvements in intravenous AA solutions have been achieved since the 1960s. Specific pediatric AA solutions were designed in the early 1990s with high essential and conditionally essential AA content for use in premature infants [28]. Three different standards of AA profile have been suggested for premature infants: umbilical fetal cord blood AA during last trimester of gestation, healthy breast-fed term infant's plasma AA, and human milk AA composition. Due to the poor solubility of tyrosine and cystine, current AA solutions have some relative AA imbalance compared to enteral nutrition. The ideal intravenous AA mixture for PN in premature infants is still a matter of debate. Nevertheless, biochemical tolerance and nitrogen utilization in infants do not change significantly despite the different compositions of current pediatric intravenous AA solutions [28, 37, 38].

Postnatal AA Requirements

Fetal protein accretion is estimated around 2–2.5 g/kg/day during the last trimester of gestation [39]. Isotope studies in animals and in human fetuses have demonstrated that fetal AA not only are used for protein synthesis but also serve as an energy source by oxidation [40]. The fetal AA uptake during the last trimester of gestation has been estimated to be between 3.5 and 4.5 g/kg/day up to term [41, 42]. Similarly, Postnatal nitrogen balances in premature infants on PN have shown that an AA intake above 1.5–2.0 g/kg/day from the first day of life allows the infants to avoid a negative nitrogen balance. Thereafter, during the stable growing period, AA intake between 3.5 and 4.5 g/kg/day enables infants to obtain a nitrogen retention between 360 and 400 mg/kg/day, similar to fetal accretion [16, 32, 39, 43, 44]. In addition,

an AA intake as high as 2.5–3.5 g/kg/day from the first day of life with current available intravenous AA solutions improves nitrogen retention, protein synthesis, insulin secretion, glucose tolerance, and early postnatal growth without inducing metabolic disturbances and adverse effects [20, 45–50]. In a recent cohort study, Senterre and Rigo demonstrated that providing such AA intakes with a well-balanced PN solution from the first day of life was not only feasible but also improved electrolyte and minerals homeostasis during the first 2 weeks of life, thereby reducing postnatal cumulative nutritional deficits, and may abolish postnatal growth restriction at discharge [17, 21, 47, 51].

Despite any evidence, several concerns persist about potential toxicities of such high AA intakes. The association that has been described between PN and metabolic acidosis is not related to early high AA intakes but is mainly due to imbalance in the electrolyte content in PN solutions [49, 52–54]. Uremia, or blood urea nitrogen (BUN), is frequently used to evaluate the adequacy of protein intakes in infants considering that BUN reflects protein degradation and AA oxidation. However, in VLBW infants during the first 2 weeks of life, BUN is poorly related with AA intakes and mainly reflects renal immaturity and hydration status [48, 55]. Indeed, BUN is highly correlated with plasma creatinine concentration and postnatal increase of BUN is inversely related to GA and BW and normalizes progressively during the first month of life [48, 56]. Therefore, high BUN cannot be used as a marker of protein or AA overload during the first week of life in premature infants.

Recommendations for AA Supply

Practical recommendations for premature infants on PN are to provide 2–3 g/kg/day of AA on the first day of life and to rapidly increase AA intake up to 3–4 g/kg/day within 2–3 days in moderately premature infants and to 3.5–4.5 g/kg/day in VLBW infants (Table 7.1).

Carbohydrates

Intravenous Carbohydrates Solutions

Glucose is the only intravenous carbohydrate used for nutritional support with the exception of the glycerol content in IVLE. Early provision of carbohydrate supply is required to prevent hypoglycemia in premature infants. Glucose is readily available for brain metabolism and represents its main source of energy during PN.

Postnatal Glucose Metabolism

Early postnatal glucose infusion is essential in VLBW infants and an intake of 6–7 g/kg/day (4.2–4.9 mg/kg/min) is necessary to prevent early postnatal hypoglycemia resulting from the interruption of the materno-foetal glucose transfer and the low glycogen reserves of premature infants [34, 57, 58].

After birth, glucose metabolism is frequently impaired and VLBW infants are not only at risk of early hypoglycemia but are also prone to hyperglycemia, in particular during PN. The incidence of hyperglycemia increases with prematurity and has been associated with insulin resistance, persistence of glucose production, and clinical disorders like sepsis or pain. In VLBW infants, the mechanisms for glucose homeostasis are still immature. The endogenous glucose production is not completely suppressed by glucose intakes and the maximal glucose oxidation rate is generally limited to 17 g/kg/day (11.8 mg/kg/min) or less in critically ill VLBW infants [34, 42, 58, 59].

Hypo- and Hyperglycemia in Premature Infants

The definition of hypo- and hyperglycemia, as well as long-term consequences of glucose metabolism disorders, remains controversial in neonates. Reference plasma glucose concentrations are generally defined between 2.6 mmol/L (0.47 g/L) and 6.6 mmol/L (1.2 g/L). In premature infants, hypoglycemia is always a metabolic emergency that needs to be rapidly corrected with 200 mg/kg glucose slow bolus infusion (2 mL/kg of 10% glucose solution) and by increasing the nutritional intakes.

In contrast, while on PN and due to the continuous glucose infusion rate, the highest reference plasma glucose concentrations needs to be adjusted. A plasma glucose concentration up to 10 mmol/L (1.8 g/L) is usually well tolerated without significant adverse effects. When faced with high plasma glucose concentrations, the first step is to evaluate the various contributing factors and to try to correct them (high glucose and energy intakes, hypophosphatemia, stress, sepsis, pain, dehydration, and steroid treatment). Glycosuria also needs to be ruled out to avoid osmotic diuresis, dehydration, and plasma hyperosmolarity [57, 59].

In the case of persistent hyperglycemia during the early transitional and the stable-growing periods, glucose intakes might be initially reduced by 10–15% for a transient period of time. Nevertheless, high AA intakes and high protein to energy ratio are important contributing factor to improve glucose tolerance and decrease the incidence of hyperglycemia. Additionally, considering that adequate protein and energy intakes need to be maintained to avoid nutritional deficits and postnatal growth restriction, insulin treatment could be required when hyperglycemia persists above 10 mmol/L

(1.8 g/l) or if it occurs with glucose intakes below 12–14 g/kg/day (8.3–9.7 mg/kg/min) during the stable-growing period. The initial dosage should be between 0.02 and 0.05 IU/kg/h and needs to be adjusted to avoid hypoglycemia. To adapt insulin infusion rate, the time necessary to adjust the plasma insulin concentration needs to be factored in during the correction of glycemic perturbations, in particular, to avoid any iatrogenic hypoglycemia [59, 60].

Recommendations for Glucose Supply

In premature newborns and especially in VLBW infants, 6–7 g/kg/day (4.2–4.9 mg/kg/min) glucose infusion should be started as soon as possible to avoid hypoglycemia. Afterwards, intakes may be gradually increased during the transitional period up to 12–17 g/kg/day (8.5–11.8 mg/kg/min) according to tolerance in order to provide adequate energy intakes (Table 7.1). The maximum glucose intake should not exceed the maximum glucose oxidation rate and more than 60–75 % of the nonprotein energy intakes.

Lipids

Intravenous Lipid Emulsions

IVLE are important constituents of PN because they are the only source of essential fatty acids: linoleic acid (LA, C18:2n-6) and alpha-linolenic acid (ALA, C18:3n-3). IVLE also represent a high-density energy substrate that can be readily utilized. They are isotonic and can be easily infused in peripheral veins [34].

Initially, IVLE were only based on soybean oil which contained about 45–55 % LA, 6–9 % ALA, and very little saturated or monounsaturated fatty acids. Although apparently safe, experimental reports and clinical studies indicate that these purely soybean-based IVLE could exert an oxidative stress, a negative influence on immunological functions, and a role in PN-associated liver disease. These findings were related to its absolute high polyunsaturated fatty acids (PUFA) content favoring lipid peroxidation and the relative excess of n-6 PUFA favoring pro-inflammatory effects [10].

Newer IVLE have been developed and differ by their fatty acids content and sources: soy, safflower, coconut, olive, and/or fish oil [10, 61, 62]. Composition of IVLE available for clinical use is shown in Table 7.2. These new IVLE have a smaller proportion of soybean oil. MCT are frequently added as they may be preferentially metabolized even if they provide less energy than long-chain triglycerides (LCT). Indeed, structured MCT/LCT emulsions formulated from a random combination of triglycerides synthesized on the same glycerol carbon chain have a less tendency to accumulate in the reticuloendothelial system and are cleared faster from blood in moderately catabolic patients. The addition of olive oil provides derived n-9 monounsaturated fatty acids that are less immunosuppressive and inhibits pro-inflammatory cytokine's release. Olive oil is also less susceptible to peroxidation and well tolerated in critically ill neonates. Fish oil provides predominantly n-3 PUFA and improves PN-associated liver disease. However, it lacks some essential fatty acids and needs to be used as a supplement or manufactured as physical oils mixture (10 % fish, 40 % soy, and 50 % MCT or 30 % soy, 30 % MCT, 25 % olive oil, and 15 % fish) [10, 61–63].

Table 7.2 Commercially manufactured intravenous lipid emulsions

Product	Soybean	Coconut	Olive	Fish
Intralipid®	100	0	0	0
Lipofundin MCT/LCT®	50	50	0	0
Structolipid®	64	36	0	0
ClinOleic®	20	0	80	0
LipoPlus®	40	50	0	10
SMOFlipid®	30	30	25	15
Omegaven®	0	0	0	100

MCT medium-chain triglycerides, *LCT* long-chain triglycerides

Direct comparisons between purely soybean-based IVLE to some of the more recent IVLE have shown several disadvantages for purely soybean-based IVLE [10, 62–64]. A recent systematic review suggests that these IVLE are deleterious to VLBW infants by increasing the incidence of sepsis [62]. Therefore, it seems logical that the routine use of purely soy-based IVLE for VLBW infants should be abandoned [62–64]. Recent studies comparing IVLE containing fish oils to exclusive soybean IVLE have demonstrated several benefits from increasing n-3 PUFA intakes, which include a reduction of oxidative stress, liver diseases, and severity of retinopathy of prematurity [63, 65–68]. Although promising, more research is required to determine the advantages of these newer IVLE with fish oil compared to other mixed IVLE and the safety of providing as much eicosapentaenoic acid as docosahexaenoic acid and no arachidonic acid in premature infants [63].

Postnatal Lipid Metabolism

Lipid oxidation depends on lipid intakes, energy intakes, and energy needs for metabolism. During PN, lipid oxidation is inversely related to glucose intakes that promote lipid storage. Carbon dioxide production is lowered when a part of energy intakes is provided by IVLE instead of a high proportion of glucose. Maximum lipid oxidation in neonates usually occurs when IVLE intakes provide 40 % of nonprotein energy intakes, corresponding to 1 g of lipid for 3.6 g of glucose. Additionally, it has been suggested that nitrogen retention could also be improved by adding IVLE to PN [34].

In the past, many pediatricians have expressed concerns about IVLE in neonates due to perceived potential adverse effects. However, recent studies do not support these concerns, especially with the most recent IVLE, which can be used from the first days of life [18, 34, 62, 69]. Continuous lipid infusion is generally preferred in neonates, and plasma triglyceride levels need to be monitored to avoid hyperlipidemia, particularly in VLBW infants, in small for gestational age (SGA) infants, and in neonates with high lipid intakes, hyperglycemia, sepsis, hypoxemia, or severe hyperbilirubinemia. Even if there are some controversies about the level of maximal plasma triglycerides tolerance in premature infants because high concentration may be deleterious, there is general consensus that lipid intakes should be reduced when plasma triglycerides concentrations exceed 2.85 mmol/L (250 mg/dL) during continuous IVLE infusion [34].

The use of carnitine supplementation during PN in premature infants is still controversial. Carnitine is necessary for the transportation of long-chain fatty acids through the mitochondrial membranes and the lipids metabolism. Its synthesis and storage are insufficiently developed at birth particularly in premature infants and carnitine is not available through commercial intravenous solutions. In parenterally fed infants, plasma and tissue carnitine levels decline with postnatal age suggesting that carnitine supplementation could be necessary [70]. However, a meta-analysis based on 14 randomized controlled studies showed no effect of carnitine supplementation on lipid metabolism, lipogenesis, or weight gain suggesting that up to now, there is no evidence to support the systematic addition of carnitine supplementation during short-term (< 3 weeks) PN in preterm infants. In newborns who require prolonged PN of more than 2 weeks, carnitine supplementation at a dose of 10–20 mg/kg/day could be suggested [63, 71].

Recommendations for Lipid Supply

Lipid intakes during PN should represent 25–40 % of non-protein energy intakes in order to promote lipid oxidation and to reduce lipid deposition in fat mass. Current recommendations encourage the provision of IVLE as soon as possible after birth in all premature infants at dosage of 1–2 g/kg/day. Thereafter, IVLE need to increase by 0.5–1 g/kg/day up to 3–4 g/kg/day during the transitional postnatal period according to metabolic tolerance (Table 7.1).

Fluids and Electrolytes

Postnatal Fluid and Electrolytes Metabolism

Birth is associated with major changes in fluid and electrolytes homeostasis. Water as part of the body composition significantly decreases. This is due to physiological contraction of the extracellular compartment. It leads to the so-called postnatal physiological weight loss of the newborn [72].

Compared to term infants, premature infants are characterized by higher transcutaneous and insensible water losses. Due to their renal immaturity, urine output and fractional sodium excretion might also be deregulated. Therefore, fluid and electrolytes disturbances are frequently observed and are associated with increased morbidity, mortality, and adverse developmental outcomes, especially in VLBW infants [54, 73–75]. In particular, dehydration (weight loss above 10 %) combined with or without inadvertent increase sodium intake frequently induces severe hypernatremia above 150 mmol/L and brain injuries [54, 74, 76–78]. On the other hand, excessive water intake and relative hyponatriemia below 130 mmol/L might also compromise cardio-respiratory functions and induce brain injuries in premature infants. Fluid overload is associated with patent ductus arterisosus, bronchopulmonary dysplasia, necrotizing enterocolitis, and long-term adverse outcomes [34, 79].

Catabolic state induced by insufficient protein and energy intakes during the first week of life can also induce non-oliguric hyperkalemia. Hyperkalemia can also be potentiated by dehydration, renal failure, and postnatal use of nonsteroidal anti-inflammatory drugs (indomethacin, ibuprofen) to treat patent ductus arteriosus [80, 81].

In order to reduce the occurrence of fluid and electrolytes disorders, previous recommendations were to provide 90–120 mL/kg/day of water on the first day of life and to progressively increase intakes up to 140–180 mL during the stable-growing period [34, 58, 74]. In addition, it was also advised to postpone sodium and potassium supplementation until after 48 h of life or after the increase of urinary output over 1.5 mL/kg/h [34, 58, 74].

Recent studies, however, suggest that optimizing early PN intakes from the first hour of life positively influences postnatal fluid and electrolytes homeostasis [47, 82, 83]. By optimizing early AA and energy intakes combined with early electrolytes supplies from the first day of life with a reduction of insensible water losses, it is possible to limit postnatal weight loss to 6–7 % and to regain BW after 7 days on average in both VLBW and extremely low birth-weight (ELBW, < 1000 g) infants, [21, 51]. Such strategy also improves the electrolyte homeostasis during the first 2 weeks of life decreasing dramatically the incidence of hypernatremia and non-oliguric hyperkalemia in VLBW infants [47, 82, 83]. As a result of early induction of an anabolic status, the new strategy could induce a “new” metabolic disorder during the first days of life, especially in SGA and VLBW infants, in the form of hypophosphatemia and hypokalemia and sometimes hyponatremia and hypercalcemia [19, 47, 84–88]. These studies suggest that actual optimized PN strategy needs to be accompanied by an increase in early electrolyte and mineral intakes during the first days of life to ensure a complete bal-

anced PN solution from the first day of life in VLBW infants [16, 21, 47, 89].

Chloride homeostasis is also important in premature infants because imbalance between sodium, potassium, and chloride intakes may promote metabolic acidosis or alkalosis [49, 47, 72]. Chloride requirements are generally considered similar to sodium requirements and pediatricians frequently do not control chloride intakes transferring chloride content in PN to the authority of the pharmacist. Hidden chloride intakes are frequent and combined with many other intakes like sodium, potassium, calcium, AA, and also in some drugs like dopamine and dobutamine. Therefore, as a result of the poor ability of the premature kidney to eliminate acid load, an excessive chloride intake frequently induces metabolic acidosis. Thus, limiting chloride intakes and providing sodium and potassium intakes as organic phosphate or as sodium or potassium acetate/citrate in PN preparation might prevent hyperchloridemic metabolic acidosis [49, 47, 54, 72, 90–94].

Postnatal Fluid and Electrolytes Monitoring

Rigorous monitoring of fluid and electrolyte homeostasis is required during the first week of life for all premature infants, especially VLBW and ELBW infants with high insensible water losses. The idea is the close assessment of fluid and electrolyte balance every 6–12 h during the first days of life to monitor intakes, urinary output, and body weight. Prevention of excessive insensible water losses is essential to maintaining fluid and electrolyte homeostasis. Insensible water losses can be easily estimated by subtracting from the total fluid intakes the weight change and the urinary output in order to adapt fluid intakes. Additionally, excessive urine output above 5 mL/kg/h needs to be rapidly compensated volume for volume with 0.45% sodium chloride infusion to balance water and sodium losses. Excessive sodium intakes from medications should be controlled to avoid any sodium overload and hypernatremia [54, 76–78]. In VLBW infants, urine sodium fractional excretion is high due to immature kidney functions. Regular determination of plasma and urine electrolyte concentrations may also be helpful to adjust intakes.

Recommendations for Fluid and Electrolytes Supply

Current recommendations advocating for revisions are based on the most recent publications. Our suggestion is to provide an initial fluid supply on the first day of life at 60–80 mL/kg/day in VLBW infants and 80–100 mL/kg/day in ELBW infants combined with double wall incubator and high-humidity environment. Then, fluid supply should be increased progressively with careful monitoring of hydration, allowing for a weight loss of 5–10% during the first 3 days of life. A target fluid intake of between 120 and 160 mL/kg/day is estimated to maintain adequate fluid and electrolyte homeostasis and an appropriate weight gain (Table 7.1).

For sodium and potassium, an initial intake of around 1 mmol/kg/day is currently recommended on the first day of life to match an optimized high protein and energy intake from birth. Thereafter, intakes should be increased up to 3–5 mmol/kg/day for sodium (up to 7 mmol/kg/day in VLBW infants) and 2–3 mmol/kg/day for potassium in order to meet requirements for growth (Table 7.1).

For chloride, an intake of around 1 mmol/kg/day is recommended on the first day of life, then 3–5 mmol/kg/day afterwards assuming the maintenance of a positive difference of 1–2 mmol/kg/day between the sum of sodium and potassium intakes and chloride intakes ($Na + K - Cl = 1–2$ mmol/kg/day). The use of acetate or lactate (1–2 mmol/kg/day) instead of chloride in PN could be helpful to prevent hyperchloridemia and metabolic acidosis (Table 7.1).

Minerals: Calcium, Phosphorus, and Magnesium

Minerals Sources

In contrast to enteral nutrition, calcium and phosphorus in PN are directly available for metabolism. Calcium may be provided in the form of calcium gluconate, calcium chloride, or calcium glycerophosphate. Due to aluminum contamination, calcium gluconate is now being progressively faced out by the industry to meet the rule of < 5 µg/kg/day of aluminum exposure in infants but it still remains frequently used in homemade hospital pharmacy preparations [95, 96]. Calcium chloride is easy to use but its high chloride content needs to be considered in the electrolytes balance of the PN solution. Calcium glycerophosphate with one to one calcium to phosphorus ratio (mmol/mmol) is an adequate source but is not registered for use in PN and need to be prescribed from powdered anhydrous calcium glycerophosphate.

Phosphorus may be provided in the form of inorganic (sodium and potassium phosphate) or organic salts (glucose 1 phosphate, fructose 1–6 diphosphate, sodium glycerophosphate). Thus, phosphorus intake is also associated with sodium or potassium intake. Inorganic potassium phosphate induces a risk of precipitation that limits its use in PN. Organic phosphorus salts and especially disodium glucose-1-phosphate are widely used in PN solutions. However, their sodium content limits their utilization for premature infants, especially during the first days of life. Frequently, potassium salts could be preferred to sodium salts and used as the unique source of potassium in the PN solution.

Magnesium is generally provided as magnesium sulfate because magnesium chloride could induce anionic–cationic imbalance with the risk of metabolic acidosis.

Postnatal Mineral Metabolism

Calcium and phosphorus fetal retention is high during the last trimester of gestation: 2.3–3.2 mmol/kg/day (90–130 mg/kg/day) and 2.4–2.7 mmol/kg/day (65–75 mg/kg/day), respectively. Magnesium fetal accretion is lower at 0.12–0.20 mmol/kg/day (2.9–4.8 mg/kg/day). Due to the interruption of placental transfer at birth and the high metabolic demand, a decrease in blood minerals concentrations may be rapidly observed. In particular, it is well known that early hypocalcemia may rapidly occur during the first days of life due to the relative immaturity of hormonal control [97]. Therefore, minerals need to be provided from the first day of life [97, 98].

In addition to its implication in bone metabolism, phosphorus also plays a critical role in energy metabolism and severe deficiency may induce several clinical disorders including muscle weakness, delay in weaning from respiratory support, glucose intolerance, and nosocomial infections [88, 97, 98]. VLBW infants and SGA premature infants are particularly at risk for early hypophosphatemia due to their limited store and their high needs for growth. Recently, it has been shown that severe hypophosphatemia is frequently observed in VLBW infants and is potentiated by optimized AA intakes. These observations linking hypophosphatemia and hypokalemia have been interpreted as resulting from a potential refeeding-like syndrome [19, 47].

Reference values for hypophosphatemia differ in adults (1.0 mmol/L, 3 mg/dL) and in preterm infants (1.6 mmol/L, 5 mg/dL) [97]. Unfortunately, most pediatricians are unaware that most laboratories use adult reference of plasma phosphate concentration in VLBW infants. Therefore, the diagnosis of hypophosphatemia may be easily missed with the risk of hypercalcemia, hypercalciuria, osteopenia, and nephrocalcinosis [97, 98].

Optimal calcium to phosphorus ratio differs in parenteral and enteral nutrition due to the bypass of the gastrointestinal tract with PN. Phosphorus retention is related to not only bone mineralization with a 1.7 calcium to phosphorus ratio (mmol/mmol) but also LBM accretion with the deposition of nearly 0.3 mmol (10 mg) of phosphorus for 1 g of protein accretion [97, 98]. Therefore, considering the high phosphorus requirements for LBM accretion when optimizing growth with high protein and energy intakes, early provision of calcium and phosphorus are necessary from the first day of life and the optimal calcium to phosphorus ratio on PN is probably between 0.8 and 1.0 (1–1.3 w/w) [16, 17, 47, 85].

Optimal magnesium requirements are not well defined for preterm infants on PN, and little attention is generally focused on postnatal magnesium homeostasis in neonates unless hypomagnesemia below 0.66 mmol/L (1.6 mg/dL) occurs in association with persistent and refractory hypocalcemia. Until recently, plasma magnesium determination was rarely included in the routine biochemical evaluation of premature infants on PN. Like for phosphorus, reference values of serum magnesium provided by laboratories are frequently the adult reference values (0.6–1.0 mmol/L). Recent studies in premature infants during the first 2 weeks of life showed that their reference values are significantly higher than adult reference values and are estimated to be between 0.75 and 1.5 mmol/L. These studies also suggest that plasma magnesium concentrations are related to magnesium intakes, BW, and GA. Magnesium concentrations are also increased in cases of relative renal failure and in infants of mothers that have received magnesium sulfate before delivery. Some other studies have shown that antenatal magnesium sulfate administration prior to delivery might be neuroprotective for premature infants [99, 100]. In those infants, the postnatal magnesium concentrations are higher than that of controls and are frequently between 1.4 and 1.8 mmol/L without demonstrating any adverse effects. This finding tends to suggest that such a level could not be considered as deleterious when renal function is normal. In fact, clinical symptoms with central nervous system depression and hypotonia are generally not observed with a magnesium concentration below 2.0–2.5 mmol/L [97].

Current recommendations for magnesium intakes are based on fetal accretion and on enteral metabolic balance studies suggesting that magnesium retention accounted for 60–70% of the absorbed magnesium. With such data, magnesium requirement for premature infants on PN is estimated between 0.2 and 0.3 mmol/kg/day in several international recommendations [34, 58]. Besides, some other authors have suggested that higher intake of between 0.3 and 0.4 mmol/kg/day may be needed [101–103]. Additional studies are required to better define magnesium requirements in VLBW infants.

Recommendation for Mineral Supply

With the most recent data on VLBW infants receiving optimized PN, on the first day of life, we recommend providing 0.6–1 mmol/kg/day of calcium (25–40 mg/kg/day) and phosphorus (18–31 mg/kg/day) and 0.1–0.2 mmol/kg/day of magnesium (2.4 mg/kg/day). Afterwards, intakes should increase progressively with macronutrients up to 1.6–2.5 mmol/kg/day for calcium (65–100 mg/kg/day) and phosphorus (50–78 mg/kg/day) and 0.2–0.4 mmol/kg/day for magnesium (5–7.5 mg/kg/day). Such mineral intakes are lower than fetal accretion but are usually higher than the retention observed with enteral nutrition (Table 7.1).

Table 7.3 Reasonable trace elements intakes for premature infants on parenteral nutrition

Iron	100–250 µg/kg/day
Zinc[a]	400–500 µg/kg/day
Copper[b]	20–40 µg/kg/day
Selenium	5–7 µg/kg/day
Chromium	0.05–0.2 µg/kg/day
Molybdenum	0.01–0.25 µg/kg/day
Manganese[b]	0.5–1.0 µg/kg/day
Iodine	1–10 µg/kg/day

[a] Zinc to copper ratio should not exceed 20
[b] Copper and manganese intakes should be decreased in cholestatic liver disease

Trace Elements

Trace elements are essential micronutrients involved in many metabolic processes. Their needs in premature infants during PN are not well defined and Table 7.3 summarizes recent recommendations [34, 58, 104]. There are few trace element solutions available and designed for neonates. Commercial mixtures usually do not provide iron, but supplements can usually be postponed during short-term PN (<3 weeks). Chromium frequently contaminates PN solution during preparation and additional supplementation is rarely necessary. Micronutrient deficits are rare with current preparations of trace elements, except for zinc, which usually requires supplements, even during short-term PN. In the case of long-term PN (>4 weeks), plasma levels of trace elements should be monitored. Excessive intakes are rare with current neonatal preparations, but in the case of cholestasic liver disease, copper, and manganese toxicity may occur.

Vitamins

Vitamins are essential organic substances that humans cannot synthesize. Neonates have small vitamin stores and deficiencies may occur rapidly if not provided, especially in premature infants with high nutritional requirements and high metabolic rates. The optimal intake of vitamins for premature infants on PN is not well defined, and most studies were undertaken with commercial mixtures. Table 7.4 summarizes most recent recommendations [34, 58, 105].

There are few vitamin preparations designed for neonates on PN available on the market. They distinguish water-soluble and fat-soluble vitamins. Most pediatric vitamin formulations that are currently used in neonatal units are not designed for VLBW infants. Recent data suggest that additional intakes of fat-soluble vitamins A and E may provide some value for VLBW infants [106–109]. For premature infants, vitamin deficiencies are usually defined as below 200 µg/L for vitamin A and below 1 mg/dL for vitamin E, but for vitamin E a ratio below 0.8 mg/g of total lipid is usually preferred. However, biological assessment of premature infant's vitamins status is only required in the case of long-term PN [34, 58, 105].

Table 7.4 Reasonable vitamins supply for premature infants on parenteral nutrition

Hydrosoluble vitamins	
Thiamin (vitamin B1)	350–500 µg/kg/day
Riboflavin (vitamin B2)	150–200 µg/kg/day
Niacin	4–6.8 mg/kg/day
Pyridoxine (vitamin B6)	150–200 µg/kg/day
Folic acid	56 µg/kg/day
Cobalamin (vitamin B12)	0.3 µg/kg/day
Panthotenic acid	1–2 mg/kg/day
Biotin	5–8 µg/kg/day
Ascorbic acid (vitamin C)	15–25 mg/kg/day
Liposoluble vitamins	
Vitamin A	700–1500 IU/kg/day
Vitamin D	40–160 IU/kg/day
Vitamin E[a]	2.8–3.5 IU/kg/day
Vitamin K[b]	10 µg/kg/day

1 mg niacin = 1 niacin equivalent (NE) = 60 mg tryptophan; 1 µg retinol equivalent = 3.33 IU vitamin A; 1 µg vitamin D (cholecalciferol) = 40 IU vitamin D (cholecalciferol); 1 mg tocopherol = 1 IU vitamin E
[a] Vitamin E need may be increased when using DHA and ARA parenterally
[b] 0.5–1.0 mg vitamin K need to be given at birth

Fat-soluble vitamins are generally prepared in a 10% IVLE, and water-soluble vitamins are usually presented as powder that needs to be dissolved by addition to IVLE, sterile water, or glucose solution. Several vitamins are light sensitive and need to be protected from light even if significant clinical consequences are not obvious in premature infants [110]. Therefore, dilution of water- and lipo-soluble vitamins in IVLE should be done to increase vitamin stability and to reduce peroxide load.

Individualized and Standardized PN Solutions

PN solutions can be prescribed using either of two formats: individualized or standardized [111–113]. Individualized solutions are formulated specifically to meet the daily nutritional requirements of each patient, whereas standardized solutions are designed to provide a formulation that may meet most of the nutritional needs while maintaining these infants in stable biochemical and metabolic parameters. Both of these methods have advantages and disadvantages associated with their use.

Individualized solutions are based on the principle that no single standardized solutions can be ideal for all patients, for a wide variety of pathological processes, for all age groups, or for the same patient during a single disease course. The main advantage of individualized solutions is

their flexibility. Each solution is formulated for one individual patient and they can be modified when the patient's nutritional needs and metabolic, electrolytes or clinical status change. The disadvantage of these solutions is linked to the expertise and the time required for prescription and the time involved in daily preparation, which may be reduced with the use of specific computer programs. These solutions should be prepared every day with strict aseptic techniques, in the pharmacy, not in the ward, and stored in a refrigerator at 4 °C. They are stable for 96 h and should be rewarmed slowly up to room temperature before infusion [114].

Standardized solutions contain fixed amounts of each component per unit volume. In some hospitals, there are few types of fixed standardized solutions to cover the nutritional requirements of premature infants. The advantage of these solutions is that they include all the essential nutrients in fixed amounts, which eliminates the chances of inadvertent omission or overload. The disadvantage of standardized solutions is their lack of patient specificity and the persistent need for some minimal adjustments, particularly during the first days of life [114]. Some recent surveys suggest that the availability of a unique well-balanced standardized PN solution helps improve nutritional support, postnatal growth, and biological homeostasis in VLBW infants [21, 22, 24, 47, 51, 83].

The development of ready-to-use industrially manufactured multi-chamber bags containing the three macro-nutrient solutions (amino acids, glucose, and lipids) in separate chambers of a single closed plastic system represents a major technological advances for PN in adults [115, 116]. It assures sterility, longer shelf life, and it also minimizes the risks of inadvertent contamination during compounding and storage [116]. It may also contribute to reduced nosocomial infection, especially by reducing lipid manipulations. Recently, an all-in-one standardized PN solution has been evaluated in premature infants [113]. It demonstrated the ease of use of such a system with intakes in the range of recommended doses. Most importantly, it facilitates the prevention of early malnutrition and the promotion of postnatal growth in premature infants [113].

Conclusion

Prematurity occurs during a critical period of development, and optimal nutritional support represents a major challenge for pediatricians. PN plays a major role for all premature infants who cannot be enterally fed from the first day of life and sometimes for a prolonged period. Recent studies demonstrate that optimizing early nutritional support from birth allows reducing or abolishing postnatal cumulative nutritional deficit and postnatal growth restriction in VLBW infants. However, they also highlight the need to upgrade the current recommendations for PN to improve the electrolyte and mineral homeostasis, especially during the first 2 weeks of life.

In summary, the following guidelines could be useful in the management of premature infants requiring PN, especially VLBW infants.

- Well-balanced PN solutions should be available at all the times for any premature infant who cannot be totally fed enterally within a few days. In VLBW infants, PN should be initiated in the first hour of life.
- Nutritional supply during the first days of life requires consideration of the clinical conditions and biochemical homeostasis. After a short transitional period, all premature infants should receive appropriate nutritional intakes in order to maintain biological homeostasis and promote optimal growth and development.
- Amino acid intakes should be initiated at a starting dose of 2–3 g/kg/day to induce positive nitrogen balance and anabolism. Thereafter, amino acids intakes should be progressively increased to 3.5–4.5 g/kg/day by the end of the first week of life.
- Energy intakes should cover the energy expenditure and be above 40 kcal/kg/day from the first day of life and progressively increased to 95–125 kcal/kg/day by the end of the first week of life.
- Glucose intakes should be initiated with 6–7 g/kg/day (4.2–4.7 mg/kg/min) and increased progressively to a maximum of 17 g/kg/day (12 mg/kg/min) as tolerated. All plasma glucose concentrations above 10 mmol/L (180 mg/dL) require the evaluation of the contributing factors and their correction (infection, pain, stress, dehydration, high intakes, hypophosphatemia, and steroid treatment). The initial treatment of hyperglycemia is a 10–15 % reduction of the glucose infusion rate. Continuous insulin infusion with a strict blood glucose monitoring is mandatory in persistent hyperglycemia while maintaining protein and energy intakes within recommendations.
- Most recent lipid emulsions need to be use in premature infants. A initial lipid intake of 1–2 g/kg/day is recommended from the first day of life. Thereafter, intakes should be progressively increased to 3–4 g/kg/day and adjusted to maintain a plasma triglyceride concentration below 250–300 mg/dL during continuous lipid infusion.
- After birth, initial fluid intake should be 60–80 mL/kg/day and need to be adjusted to postnatal weight evolution to allow for an initial weight loss of 5–10 % of BW during the first 3–4 days of life. Fluid intake should be increased when daily weight loss is above 5 %, total weight loss above 10 %, or plasma sodium concentration above 145 mmol/L but also in premature infants on a radiant warmer or during phototherapy. In contrast, fluid intake should be reduced if initial daily weight loss is below 2 % or if plasma sodium concentration is below 135 mmol/L.

- The use of a relatively concentrated PN solution to provide all the nutritional intakes with 120–140 mL/kg/day could facilitate the fluid control without impairment of the nutritional requirement.
- Electrolyte intake should be initiated on the first day of life with about 1 mmol/kg/day of sodium, potassium, and chloride; this will allow early provision of phosphorus and the development of LBM gain. Thereafter, electrolyte intake may then be progressively increased to 3–7 mmol/kg/day for sodium, 2–3 mmol/kg/day for potassium, 2–5 mmol/kg/day for chloride. Careful monitoring of hydration, plasma electrolytes concentrations, and urinary excretions is necessary to adjust the intakes and to improve electrolyte homeostasis. The anion gap (Na + K–Cl) in the PN solution should be maintained between 1 and 2 mmol/kg/day to maintain adequate acid–base homeostasis.
- Mineral intake should be initiated on the first day of life with 0.6–1 mmol/kg/day of calcium and phosphorus and a balanced calcium to phosphorus ratio of 0.8–1.0 to avoid hypocalcemia and hypophosphatemia. Initial magnesium intake should be 0.1–0.2 mmol/kg/day. Thereafter, mineral intake should be progressively increased up to 2.0–2.5 mmol/kg/day for calcium and phosphorus and 0.2–0.4 mmol for magnesium. Careful monitoring of the plasma concentrations and of urinary excretion of minerals is necessary to ensure appropriate intake and to avoid the development of nephrocalcinosis.

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