# Parenteral Nutrition in Very Low Birth Weight Preterm Infants

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**ABSTRACT:** Parenteral nutrition (PN) must be initiated as soon as possible after delivery in very low birth weight (VLBW) preterm infants in order to prevent postnatal growth failure and improve neurodevelopmental outcome. When administered early, high levels of parenteral amino acids (AA) are well tolerated and prevent negative nitrogen balance. Although proteins are the driving force for growth, protein synthesis is energy-demanding. Intravenous lipid emulsions (ILE) constitute a good energy source because of their high energy density and provide essential fatty acids (FA) along with their long-chain polyunsaturated fatty acid (LC-PUFA) derivatives necessary for central nervous system and retinal development. Early supply of ILE is not associated with increased morbidity. No significant differences were found between ILE based on soybean oil only and mixed ILE containing soybean oil in combination with other fat sources, except for a reduction in the incidence of sepsis with non-pure soybean ILE, and possibly less PN-associated liver disease with mixed ILE containing some fish oil. In preterm infants glucose homeostasis is still immature in the first days of life and abnormalities of glucose homeostasis are common. VLBW infants may not tolerate high levels of glucose infusion without hyperglycemia. Administering lower levels of glucose infusion as part of full early PN seems more successful than insulin at this stage. Postpartum there is a transition period when the water and electrolyte balance may be severely disturbed and should be closely monitored. Avoiding fluid overload is critical for preventing respiratory and other morbidities.

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**KEY WORDS:** very low birth weight (VLBW) preterm infants, parenteral nutrition (PN), protein and amino acids, intravenous lipid emulsions (ILEs), glucose, fluids and electrolytes, vitamins, trace elements (TE)

Parenteral nutrition (PN) in preterm infants should be initiated as soon as possible after delivery, preferably within the first 24 hours [1,2], in order to minimize weight loss, correct intrauterine growth restriction and poor fetal nutrient deposition, and prevent extrauterine growth restriction. Early PN also meets the increased metabolic demands due to postnatal morbidities [3], and was shown to improve short- as well as long-term outcomes [4], especially in growth and neurodevelopment [5]. The required dietary components for preterm infants are described below.

## PROTEIN

Early high protein intake [6] is the cornerstone of the "aggressive" nutrition approach [7]. Providing more than 2 g/kg/day amino acids (AA) from the first day of life prevents protein catabolism and negative nitrogen balance, induces positive nitrogen balance, and encourages protein accretion, weight gain and growth [6,8,9]. It also increases endogenous insulin secretion and gluconeogenesis, thereby improving glucose tolerance and preventing hyperglycemia [1,10]. Recent recommendations [11] suggest 2–3 g/kg/day of AA on the first day of life using PN, and increasing gradually during the first week of life. High early parenteral AA intake is usually well tolerated with no significant acidosis or hyperamonemia [6,12], although some increase in blood urea nitrogen (BUN) occurs when AA are oxidized. AA intake should be progressively increased up to 3.5–4.0 g/kg/day by the end of the first week [11]. This intake was shown to promote weight gain and growth [13] and improve neurodevelopmental outcome [14]. It has been suggested that in extremely low birth weight infants (ELBW) (< 1000 g) AA intake of > 4.0 g/kg/day, up to 4.5 g/kg/day, is well tolerated and is associated with weight gain and lower rates of bronchopulmonary dysplasia [12]. The composition of parenteral AA mixtures suitable for preterm infants was devised to mimic the optimal amino acid profile based on fetal and neonatal AA blood levels (Primene®, Baxter SA, Belgium). These mixtures contain both essential and conditionally essential AA that preterm infants have limited ability to synthesize (cysteine, glutamine, glycine, histidine, taurine and tyrosine). The proven benefits of providing early high AA intake outweigh the concerns related to the different AA concentrations although more long-term studies are needed to assure safety. Another possible issue of concern relates to the "early protein hypothesis," i.e., the association between high protein intake in excess of metabolic requirements and possible enhancement of insulin and insulin-like growth factor

1 (IGF1). This might predispose to adiposity and metabolic syndrome later in life [15]. This issue is related to the wider concept of "programming" that addresses early postnatal life as a critical or sensitive period of development during which a stimulus or insult can have long-term or lifetime effects on the organism. Providing too much or too little during this 'critical window' for nutrition can 'program' the individual for subsequent health. While slow growth might have some benefit for later metabolic and cardiovascular outcome, it carries the risks of under-nutrition and its adverse consequences on growth and has a profound adverse effect on later cognition. Nutritional insults at this vulnerable period of brain development can affect brain size, cell number, behavior, learning and memory. Thus, there is currently general agreement among neonatologists and nutritionists that in preterm infants, especially those appropriate for gestational age, early high protein and energy intake is crucial to prevent extrauterine growth restriction [16].

## ENERGY AND LIPIDS

In preterm low birth weight (LBW) infants, energy intake should cover both energy expenditure and energy needed for growth. In order to prevent postnatal growth failure in very low birth weight (VLBW) infants, full PN must be provided immediately. Although proteins are the driving force for growth, protein synthesis is an energy-demanding process [8,9,17]. Lipids are a very good energy source because of their high energy density. In addition, the supply of essential n-6 and n-3 fatty acids (FA) along with their long-chain polyunsaturated fatty acid (LC-PUFA) derivatives are necessary for central nervous system development and retinal growth. Intravenous lipid emulsions (ILE) prevent essential fatty acid (EFA) deficiency that is biochemically evident in premature infants within 72 hours and clinically by the end of the first week of life [18]. EFA deficiency in premature infants can be prevented by providing a minimum daily dose of 0.25 g/kg/day linoleic acid [11], which is equivalent to a minimum 0.5–1.0 g/kg/day of ILE [18].

**Early full balanced parenteral nutrition prevents growth failure and supports better long-term neurodevelopmental outcomes in very low birth weight preterm infants**

Estimates of energy requirements are dependent on protein intake [2], as energy intake is required for both protein metabolism (i.e., avoiding catabolism) and deposition [1]. In order to achieve optimal growth, the energy intake for a premature infant on PN should be set at about 90–100 kcal/kg/day. This is based on the minimum energy requirements that allow unlimited accretion of lean body mass. Above this intake, energy is presumably stored in adipose tissue [2]. Of this, 40–60 (average 50) kcal/kg/day account for resting energy expenditure (REE) [19]. This is the minimum energy required to minimize protein catabolism to 1.5 g/kg/day in VLBW infants. This energy and protein intake is the minimum required to induce a positive nitrogen balance from the first day of life [9]. If more amino acids are provided and energy intake is above this REE, weight gain is usually achieved. REE varies widely in premature infants, ranging from 30 to 70 kcal/kg/day (higher in lower birth weights with associated morbidities such as sepsis, and lower with advancing postnatal age and weight gain) [19]. In order to support further growth, an additional 20–25 kcal/kg/day should be provided [20]. VLBW preterm infants on PN have lower energy requirements compared to infants on enteral nutrition (90–100 vs. 120–130 kcal/kg/day, respectively). Later on, energy intake of 110–120 kcal/kg/day is required for optimal weight gain and growth, even in VLBW infants on PN. Due to glucose and lipid intolerance this amount of energy can usually be achieved only several days after birth [2]. The recent recommendations aim at providing 40 kcal/kg/day on the first day of life, 60–80 kcal/kg/day in the following days, reaching the goal of 90–100 kcal/kg/day from PN by the end of the first week of life [11]. Balanced distribution of calories from carbohydrates and lipids is necessary for protein accretion [21] and avoids protein oxidation that may occur if high glucose is given parenterally without sufficient lipids. The gold standard for caloric distribution is human milk, with 40–45% calories from carbohydrates and lipids. In preterm infants the energy distribution with PN usually comprises 45–55% from carbohydrates, 35–40% from lipids and 10–15% from protein (AA). In order to maximize protein accretion, improve lipid and protein tolerance and avoid acidosis, the average protein/energy ratio should be maintained at 3.3 g protein/100 kcal (range 2.7–3.9 for PN, higher ratios for infants with lower gestational ages and birth weights) [1,2]. Recent data including meta-analyses suggest that initiating ILE within the first 2 days of life in VLBW infants, preferably immediately on the first day, is safe and well tolerated. Early provision of ILE was not found to be associated with increased morbidity or mortality or significant short- or long-term sequelae [17,22]. Nevertheless, there is some evidence to suggest better long-term neurodevelopmental outcomes [23]. Currently, 1 g/kg/day of ILE is recommended for VLBW infants on the first day of life, increasing gradually (by 0.5–1.0 g/kg/day), if well tolerated without hypertriglyceridemia, to a maximum of 3.0–3.5 g/kg/day by the end of the first week of life [11]. A dose of 4 g/kg/day might be occasionally used in chronically ill infants with high energy needs. Limiting ILE intake to less than 3 g/kg/day in preterm infants with extreme neonatal hyperbilirubinemia may be justified due to the concern that FA might displace bilirubin from albumin-binding sites. There are concerns that ILE may increase the risk of infection in general, and coagulase-negative Staphylococcal bacteremia in particular. Although this issue has not been settled, the nutritional benefits of lipid administration outweigh these potential risks [11]. There

are also concerns about lipid clearance during infection. In septic preterm infants triglyceride levels tended to be higher and fatty acid oxidation lower. However, administering ILE in ill septic infants is important to avoid excessive carbohydrate intake and provide EFA. Close monitoring of plasma triglycerides and adjustment of lipid infusion rate if necessary is recommended in these infants [11].

Soybean oil-based ILE rich in ω-6 FAs continues to be one of the main lipid sources for PN (Intralipid®, Fresenius Kabi AB, Sweden). Soybean oil contains high concentrations of PUFA, around 60% of the total fatty acids. Second-generation ILE consisting of a physical mix of equal parts of soybean oil and medium-chain triglycerides (MCT) (from coconut oil) (Lipofundin®, B. Braun Melsungen AG, Germany) contains 50% less ω-6 PUFA, still adequate for meeting the needs of infants. Compared to long-chain triglycerides (LCT), MCT-based ILE has greater solubility, faster clearance, improved resistance to peroxidation, and faster oxidation. A third-generation ILE, containing olive oil and soybean oil in a ratio of 4:1 (Clinoleic®, Baxter SA), has a high content of the monounsaturated FA oleic acid and of biologically active vitamin E (α-tocopherol). In infants, olive oil-based emulsion showed comparable tolerance and safety to a soybean oil emulsion, but resulted in more favorable serum FA and vitamin E levels and reduced markers of lipid peroxidation.

**Protein is the driving force for growth and brain development, thus early high amino acid intake should be assured along with intravenous lipid emulsions, a rich energy source for protein utilization**

Fish oil containing emulsions represent the most recent development in ILE. Fish oil is currently found in either pure fish oil emulsion (Omegaven®, Fresenius Kabi, Deutschland GmbH, Germany) or as a mixture (SMOFlipid®, Fresenius Kabi AB) of 30% MCT, 30% soybean oil, 25% olive oil and 15% fish oil. Fish oil is rich in ω-3 PUFA, particularly EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). Compared to MCT and olive oil, ω-3 FA are highly bioactive compounds with anti-inflammatory properties and important pharmacological benefits. Addition of fish oil to PN has been associated with several immunomodulatory effects, including reduction of ω-6 FA tissue content and an increased incorporation of ω-3 FA in the phospholipids of plasma, platelets, red blood cells and leukocytes, as well as in lung tissue, liver cells and intestinal mucosa. ω-3 PUFA inhibit the production of the pro-inflammatory cytokines – tumor necrosis factor-alpha (TNFα) and interleukin (IL) 6 and 1β – and modulate the production of the anti-inflammatory cytokine IL-10. ω-3 PUFA also exert metabolic effects, including reduction in plasma triglyceride levels and increased lipid oxidation in liver and skeletal muscle. Use of fish oil-based ILE seems to be especially advantageous in infants with PN-associated cholestatic liver disease [24]. Among the concerns regarding fish oil monotherapy is the development of EFA deficiency or bleeding, although neither complication has been reported to date. A recent meta-analysis in VLBW infants found no difference between ILE based only on soybean oil and mixed ILE containing soybean oil in combination with other fat sources with regard to weight gain, pulmonary morbidity, hypertriglyceridemia, hyperglycemia or mortality before discharge. However, it found that the use of non-purely soybean-based ILE was significantly, although weakly, associated with reduced incidence of sepsis [17,25]. Given the high vulnerability of VLBW infants to PN-associated liver disease, the association between the use of mixed ILE with some fish oil and lesser occurrence of hyperbilirubinemia and cholestasis, although not yet fully established in VLBW preterm infants, has been advanced as an argument for future routine use of such ILE in neonates [25].

## CARBOHYDRATES

Glucose is the major energy source and the single parenteral carbohydrate. In newborns it has the advantage of being readily available to the brain [1]. The predominant energy supply in the fetus is represented by glucose which is transported across the placenta from the mother. Glucose delivery to the fetus increases as pregnancy progresses, allowing glycogen and fat stores to be accumulated during the third trimester. In the healthy term newborn baby, hormonal and metabolic adaptation in the immediate perinatal period ensures that adequate fuel is supplied to the brain and other vital organs. However, in preterm infants glucose homeostasis is still immature in the first days of life, and abnormalities of glucose homeostasis are common. These infants are therefore prone to hyperglycemia as well as hypoglycemia. After the initial hypoglycemia, due to limited glycogen and fat stores, VLBW preterm infants often become hyperglycemic because of persistent endogenous glucose production by the hepatocytes, and decreased insulin sensitivity, combined with relative insulin deficiency [1,26]. Hyperglycemia is associated with increased morbidity and mortality. It is generally accepted that glucose blood levels should be maintained within the following range: from > 40–45 mg/dl on the first day of life and > 50 mg/dl thereafter, to < 200 mg/dl, preferably < 150–180 mg/dl [1,26,27]. Approximately 4 mg/kg/min (7 g/kg/day) of glucose cross the placenta in the last trimester of pregnancy. Glucose production rate ranges from 5.5 mg/kg/min (8 g/kg/day) in full-term healthy newborn to 8 mg/kg/min (11.5 g/kg/day) in VLBW infants [28]. Accordingly, initial glucose infusion rates of 4–7 mg/kg/min are appropriate for most newborns, although ELBW infants may need higher rates of 8–10 mg/kg/min to match endogenous glucose production from the liver and preserve their limited carbohydrate stores. Unfortunately, many of these ELBW infants will not tolerate these high glucose

infusion rates in the first days of life without hyperglycemia. Thus, lower glucose infusion rates of 4–5 mg/kg/min (6 g/kg/day) are initially given, usually in solutions with 5% dextrose [1,27]. Initial glucose infusion rates as low as 3.5 mg/kg/min are used in VLBW, and more often in ELBW, preterm infants [10]. It is critical to provide fully balanced PN, including AA and lipids, immediately after birth. This allows maintenance of normoglycemia by glucose production primarily from gluconeogenesis, with glycerol as the main substrate, while reducing glucose infusion rates [10]. High amino acid intake of 2–3 g/kg/day from the first day of life was suggested as one of the contributing factors to improved glucose tolerance in ELBW infants [6]. Providing lower glucose infusion levels as part of full early PN might be a more successful approach than administering insulin [27], probably due to the relative insulin resistance in VLBW infants during the first week of life [1]. However, data on long-term outcomes in comparison to uncorrected hyperglycemia or insulin administration are lacking [27]. If low intake of intravenous glucose (4–5 mg/kg/min, i.e., 6 g/kg/day) is tolerated it may be increased gradually to 8, 10, and up to 12–16 g/kg/day over the first week of life [1]. This can usually be achieved with 10–12.5% dextrose-based PN solutions. An infusion rate of 18 g/kg/day glucose is probably maximal [1], because higher rates will exceed glucose oxidative capacity. If higher intakes of glucose are not tolerated, further increase of glucose intake should be stopped and glucose intake reduced. Insulin infusion can also be considered, based on the clinical and nutritional status of the infant, starting with an initial dose of 0.05 IU/kg/hr. Insulin administration may help control plasma glucose concentration, achieve increased energy intake and promote nitrogen retention and growth. However, early insulin administration to reduce hyperglycemia did not improve growth or reduce mortality, sepsis, intracranial hemorrhage, necrotizing enterocolitis, or chronic lung disease, and was associated with more episodes of hypoglycemia and increased weight gain, probably attributable to fat mass accumulation [27,29]. Thus, current evidence does not support the routine use of insulin in ELBW infants on PN even for short periods, unless they remain hyperglycemic despite very low glucose infusion rates in the first days of life.

**Glucose homeostasis may be immature in preterm infants with hyperglycemia which follows the initial hypoglycemia. Hyperglycemia is best treated by lowering glucose infusion rate while providing full balanced parenteral nutrition**

## FLUIDS, ELECTROLYTES AND MINERALS

The total body water (TBW) content is age-related and diminishes from about 90% in a 24 week gestation preterm infant to 75% in a term newborn infant [11]. Fluid volume intake per kg body weight is higher in newborns as compared to older children. This is related to increased urine output (UOP) (renal immaturity and reduced ability to concentrate urine) and increased insensible losses (greater body surface area and skin immaturity). Immediately after birth there is a transition period that can extend from < 12 hours up to 3–5 days. During this transition period water and electrolytes balance may be severely disturbed as a result of discontinuation of placental exchange, considerable increase in insensible water loss (radiant warmers and intensive phototherapy), and huge requirements for thermoregulation, especially in VLBW infants. The immediate postnatal phase is characterized by an initial relative oliguria followed by a diuretic phase that may be critical in unstable ELBW infants. In these first hours of life contraction of the extracellular fluid space should be allowed to occur, while maintaining normal intravascular fluid volume and cardiovascular function, as well as maintaining as normal as possible rates of serum electrolytes and UOP. Attention to avoiding fluid overload may be critical during this transition period, because fluid restriction was shown to decrease respiratory morbidity, patent ductus arteriosus and especially bronchophulmonary dysplasia later on [30]. This can be achieved by restricting fluid and sodium administration, even in face of very high UOP and high urinary sodium excretion and net negative sodium balance. Fluid intake in the initial transition period should be started at 60–100 ml/kg/day (VLBW infants born at younger gestational age will require the higher fluid intakes due to their increased losses) and increased gradually over the next days [11]. Weight loss during this transitional period is expected but should be closely monitored along with input and output balance, and serum electrolytes. Subsequent adaptation involves the onset of autonomic renal regulation of fluids and electrolytes. UOP will usually decrease and urine osmolarity increase above serum osmolarity. By the end of this period, which may extend for 5–15 days in VLBW infants, birth weight will be regained. During this adaptation period total fluid intake could already reach 150 ml/kg/day (range 140–160 ml/kg/day) [11], although some ELBW infants may need slightly more. The recommendation to avoid fluid overload is still applicable in this adaptation period. During the stable growing period that follows, intravenous fluids are regarded more as the carrying vehicle for PN and are dictated mainly by the nutrient requirements. Fluid intake of 150 ml/kg/day (range 140–160 ml/kg/day) for term and preterm infants should be appropriate, even for VLBW infants on PN [11].

Sodium and potassium supplementation is usually not required during early PN in premature infants, because their high initial extracellular fluid needs to decrease with sodium diuresis which occurs in the first 1–2 days. Most preterm infants (28 weeks or less) get sodium from other sources as well (transfusions, saline infusions for arterial line, flushes, drugs). At this stage the risk is that the ELBW infant will lose significantly more

water than sodium with ensuing hyperosmolar hypernatremia, or will develop non-oliguric hyperkalemia from immature distal tubular function [1]. Thus, close monitoring of serum electrolytes in the first days of life is mandatory even though Na and K are not given in PN during the first 1–3 days. Supplementation of Na and K is started gradually based on decreasing serum levels. This usually coincides with cessation of the initial weight loss, although it may be required earlier. The range of electrolyte requirements for preterm infants on PN is 2–3 to 5 mEq/kg/day sodium, 1–3 mEq/kg/day potassium, and 2–3 mEq/kg/day chloride. In preterm infants on PN, metabolic acidosis is quite common. This is due to the relatively acidic AA admixtures [31], and to renal immaturity and decreased renal reabsorption of bicarbonate. This can be corrected by adding acetate (1–2 mEq/kg/day) as sodium or potassium salt to the PN solution.

Since most of the calcium and phosphorus transfer and retention occur during the third trimester of pregnancy, and because hormonal control systems (parathyroid hormone and vitamin D) are also immature, preterm infants are at increased risk of hypocalcemia and hypophosphatemia. Inadequate intakes of calcium and phosphorus can lead to poor bone mineralization, with signs of oteopenia of prematurity that can even lead to frank rickets and fractures [32]. Since adequate intakes of calcium and phosphorous are harder to provide parenterally because of solubility issues, premature infants on PN are at increased risk for osteopenia of prematurity. By using organic preparations, higher amounts of calcium and phosphorus can be given parenterally [1]. Calcium must be given to preterm infants from the first day because of the risk of early hypocalcemia. Phosphate supplementation may sometimes be postponed for 1–2 days because of reduced glomerular filtration and low initial renal phosphorus excretion, resulting in normal or even slightly elevated serum phosphorus levels. However, phosphate should be added soon after, in order to avoid hypophosphatemia. Special attention should be paid to keeping an appropriate calcium phosphorus ratio. Proportional increase in calcium and phosphorus intakes to 80–100 mg/kg/day and 60–80 mg/kg/day, respectively, results in increased net retention of these minerals in premature infants and higher bone mineral content during and after PN administration [33]. Magnesium is rarely adjusted unless the infant has high levels due to magnesium treatment given to the mother before delivery, or persistent hypocalcemia secondary to hypomagnesemia. The currently recommended intakes of minerals for preterm infants on PN are: calcium 60–100 mg/kg/day (1.5–2.5 mmol/kg/day), phosphorus 50–80 mg/kg/day (1.5–2.5 mmol/kg/day), and magnesium 6.5–10.5 mg/kg/day (0.25–0.4 mmol/kg/day) [1,11]. The quantities of calcium that can be provided by the parenteral route are 60–80% of that deposited in the fetal tissue during the last trimester of pregnancy (100–120 mg/kg/day), but quite similar to those provided by most currently available enteral preterm formulas. The optimal calcium-to-phosphorous ratio depends on the route of administration (parenteral route bypasses the gastrointestinal tract), bone mineralization and nitrogen retention. The optimal calcium:phosphorous ratio for PN is 1.3–1.7:1 Ca:P (weight:weight/mg:mg) and nearly 1:1 molar ratio [1]. This Ca:P ratio appears to promote the highest retention of both minerals and simulate in utero bone mineral accretion rates. Lower ratios lead to elevated urinary and serum phosphorous, suggesting inadequate utilization of phosphorous due to insufficient calcium intake [33].

## VITAMINS AND TRACE ELEMENTS

Compared to term infants, premature infants need higher amounts of some vitamins because of their increased requirements for growth and possible greater losses [34].

Accretion of trace elements (TE) occurs mainly during the third trimester of pregnancy. Preterm infants are thus at increased risk of TE deficiencies because of their low body stores and high demand for rapid growth. Probably, the only TE that need to be provided from the first day of life, when PN is initiated in VLBW infants, are zinc and selenium [34,35]. Supplementation with other TE is probably not necessary in the first 2 weeks, although the TE preparation is usually supplied. Preterm infants with necrotizing enterocolitis [36], especially those left with an ileostomy after bowel resection, need extra supplementation of zinc. Selenium is specifically important in VLBW preterm infants because it is a component of glutathione peroxidase. Supplemental doses of selenium for VLBW preterm infants on PN should be provided early, probably from the first day and in higher doses than those currently used [37]. Selenium supplementation was associated with a significant reduction in sepsis episodes, but not with improved survival, reduction in neonatal chronic lung disease, or retinopathy of prematurity [35]. Since selenium is excreted in the kidneys, its intake should be reduced in patients with impaired renal function. Iron is probably not needed in preterm infants in the first few weeks, especially if they were transfused. However, concern regarding its possible contribution to oxidative stress [38] suggests that iron should not be added routinely to early PN in VLBW preterm infants. Later iron supplementation, at least a maintenance dose, is necessary and is associated with an increase in the levels of hematological indicators of iron status and reduction in the prevalence of iron deficiency. There is insufficient evidence to make a definitive statement regarding the effects of iron supplementation on growth and neurodevelopment. The enteral route is preferred for iron supplementation, and most preterm infants are already on enteral nutrition when iron supplementation is required.

## STANDARDIZED VS. INDIVIDUALIZED PN

This question was reviewed previously by us [39]. Regarding the value of early PN, batch-produced standardized PN bags are

readily available in ward stocks of neonatal intensive care units, enabling initiation of early PN immediately after the delivery of premature VLBW infants. A combination of standardized PN bags for most neonates, with a small number of specifically tailored individualized PN formulations for those requiring them, seem to be the optimal nutritional model. The combination of computerized prescriptions and the use of multi-chambers may enhance our ability to rely on standardized PN with minimal usage of individualized prescriptions [40].

In summary, fully balanced early PN prevents growth failure and enables better long-term neurodevelopment outcomes in VLBW infants. Protein is the driving force and lipids the high energy source for protein utilization.

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