Parenteral Nutrition

39

Jacques Rigo and Thibault Senterre

Contents

Abstract

Modern perinatal medicine has resulted in a dramatic decrease of mortality in premature infants, especially in very low birth weight (VLBW, <1500 g) infants. Nutrition has become one of the most debated issues in the care of low-birth-weight infants. Nutrition of VLBW infants may be divided into two subsequent periods: the immediate adaptive or "transitional" period after birth and a stable "growing" period up to discharge from the NICU. VLBW infants need parenteral nutrition from the first days of life to promote early positive nitrogen retention and growth. Parenteral nutrition may be required or prolonged during the stable "growing" period due to feeding intolerance, gastrointestinal disorders, or surgery. Parenteral nutrition can be prescribed using tailored or standard solution; the former is formulated specifically to meet the daily nutritional requirements of the individual patient, whereas the latter is designed to provide a formulation that meets most of the nutritional needs of the stable biochemical and metabolic parameters. Very recently, it was suggested that the use of unique standard parenteral solution may contribute to a significant improvement of nutritional support for both extremely and very preterm infants.

J. Rigo (✉) · T. Senterre
Department of Neonatology, University of Liège, CHR de la Citadelle, Liège, Belgium

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39.1 Salient Points

- Nutrition of VLBW infants may be divided into a "transitional" period (after birth) and a stable "growing" period (up to discharge from the NICU).
- The aim of nutritional support during the transitional period is: to reduce protein catabolism, to provide amino acid, water, and electrolytes; to promote nitrogen retention; and to limit postnatal metabolic stress.
- The aim of the nutritional support during the stable growing period is to induce the growth of body mass; to abolish the nutritional deficit during the first weeks of life; and to reach normal anthropometric parameters.

39.2 Introduction

Modern perinatal medicine has resulted in dramatic decrease of mortality in premature infants, especially very low birth weight (VLBW, <1500 g) infants. With the major advances in life-support measures, nutrition has become one the most debated issues in the care of low-birthweight infants. In this regard, several reports have shown the major effect of quantitative and qualitative nutrition during the first period of life on early and late outcome.

Incidence of intrauterine growth restriction (IUGR) is relatively high in VLBW infants and postnatal growth restriction (PNGR) is frequently observed during the early weeks of life resulting in a major growth deficit at the time of discharge. According to population, clinical disorders and nutritional support, growth restriction affected 60–100% of VLBW and extremely low birth weight (ELBW) infants (Ehrenkranz et al. 1999).

PNGR is mainly the result of the cumulative nutritional deficit occurring during the transitional period from birth to the time of full enteral feeding (Embleton et al. 2001; Rigo et al. 2002) but additional effects during the stable growing period have also been suggested (Curtis and Rigo 2004). Therefore, several studies evaluated the effect of more optimal (aggressive) nutrition during the early weeks of life (Wilson et al. 1997; Thureen et al. 2003; Ziegler et al. 2002; Simmer 2007) and various international scientific committees reconsidered current nutritional recommendations in preterm infants focusing on ELBW and VLBW infants (Table 1) (Tsang et al. 2005; Agostoni et al. 2010).

Due to gastrointestinal tract immaturity, cardio-respiratory adaptation, clinical status and high nutritional requirements, VLBW infants require parenteral nutrition from the first days of life to promote early positive nitrogen retention and growth. In addition, parenteral nutrition could

Table 1 Recent recommendations of daily parenteral intakes for ELBW and VLBW infants

		Tsang et al. (2005)			ESPEN-ESPGHAN (Koletzko et al. 2005)		
		Day 0	Transition	Growing	Day 0	Transition	Growing
FluIDs	mL/kg/day	90–120	90–140	120–180	80–90	100–150	140–180
Energy	kcal/kg/day	40–50	75–85	90–115	50–60	60–100	100–120
Protein	g/kg/day	2	3.5	3.5–4	1.5–2.5	2.0–3.5	3.5–4
Carbohydrate	g/kg/day	7	8–15	13–17	7–10	9–15	12–18
Fat	g/kg/day	1	1–3	3–4	0–1	1–3	2–4
Sodium	mmol/kg/day	0–1	2–5	3–7	0–3	2–3	2–7
Potassium	mmol/kg/day	0	0–2	2–3	0–2	1–2	2–5
Chloride	mmol/kg/day	0–1	2–5	3–7	0–3	2–3	2–5
Calcium	mmol/kg/day	0.5–1.5	1.5	1.3–4	NP	1–2	1.3–3.0
Phosphorus	mmol/kg/day	0–1	1.5–2	1.5–2	NP	1–2	1.0–2.5
Magnesium	mmol/kg/day	0	0–0.3	0.2–0.3	NP	NP	0.2–0.4
Zinc	µmol/kg/day	0–2	2,5	6	NP	3	4

NP not provIDed

be required or prolonged during the stable "growing" period due to feeding intolerance, gastrointestinal disorders or surgery. Provision of parenteral nutrition (PN), total or suppletive, can be ordered using individualized prescription, homemade standardized parenteral solution or ready to use industrialized prepared multichamber bags.

In this chapter we discuss the most important features regarding parenteral nutrition that have been recently reviewed (Rigo and Curtis 2004; Koletzko et al. 2005; Ben 2008; Fusch et al. 2009) (Table 1), outlining more recent practical aspects and guidelines particularly for ELBW and VLBW infants.

39.3 Nutritional Support in VLBW Infants

Nutrition of VLBW infants may be divided into two subsequent periods, firstly the immediate adaptive or "transitional" period after birth, and a stable "growing" period up to discharge from the NICU. Depending on birth weight (BW) and gestational age (GA) the transitional period may be prolonged, particularly in the more vulnerable infants with major clinical disorders. The more premature a neonate, the more challenging are the influences of immaturity and the accompanying morbidity on nutritional supply. Most of these infants receive parenterally delivered nutrients as their major source of nutrition for the first days, and sometimes weeks, of life.

Nutrition during the "stable-growing" period on PN is exceptional, used only when preterm infants are recovering from surgery and/or severe gastrointestinal problems, to prevent or limit the use of the gastrointestinal tract.

39.3.1 Parenteral Nutrition During the Transitional Period

The aim of the nutritional support in VLBW infants during the transitional period is:

1. To reduce protein catabolism providing an energy intake at least at the level of energy expenditure;
2. To provide amino acids (AA) at a level sufficient to induce a positive nitrogen retention;
3. To provide water and electrolytes to control hydration status and postnatal physiological fluid adaptation;
4. To progressively increase AA, energy and mineral intake to promote nitrogen retention and early growth and to limit a possible cumulative nutritional deficit;
5. To limit postnatal metabolic stress in this high-risk population.

Recent data suggest that provision of a more "aggressive" nutritional support from the first day of life reduces postnatal growth deficit and improves neurodevelopmental outcomes in VLBW infants (Senterre and Rigo 2011a; Martin et al. 2009).

39.3.1.1 Fluids and Electrolytes

A number of adaptive processes occurring at birth affect nutritional support. During the early weeks of life, water, electrolyte and mineral homeostasis, and glucose control are more challenging. Placental clearance and placental supply of fluids, electrolytes, minerals and nutrients are discontinued. Thermoregulation and insensible water losses influence water metabolism, especially in VLBW infants. Subsequent adaptation and compensatory regulative processes need time to stabilize.

Fluid and electrolyte administration during the transitional period should allow contraction of extracellular fluid space without compromising intravascular fluid volume and cardiovascular function, maintain normal plasma electrolyte concentrations, without impairing urinary output (<0.5–1.0 mL/kg/h) for more than 12 h.

Water balance may be very unstable, especially in ELBW infants, urinary output may be high (6–10 mL/kg/h) and insensible fluid losses can be huge, especially under a radiant warmer and/or with phototherapy.

A negative net balance for sodium is allowed and intakes should be less than 2 mmol/kg initially. Restricted sodium intake in VLBW infants has a positive influence on oxygen supply and risk of later bronchopulmonary dysplasia. However,

high sodium urinary excretion (10 mmol/kg) may occur, especially in case of high fluid perfusion over 170–200 mL/kg/d compromising sodium balance.

This transitional phase may last for a variable period of several hours or days and result in initial weight loss. The end of the transitional period is usually characterized by a urine volume <2.0 mL/kg/h, urine osmolarity>serum osmolarity, fractional Na excretion diminishing from >3% to <1% and specific gravity above 1012. In preterm infants, these changes complete after 3–5 days and water and electrolytes intake will be progressively increased to replete the body losses.

During the transitional period, VLBW infants should be weighted twice daily and in/out balance, plasma sodium concentration and urinary excretion should be monitored attentively during first days of life. Fluid intake on PN should be 50–100 mL/kg/d in VLBW infants according to clinical and environmental conditions and sodium and potassium intake limited to less than 2 mmol/kg/d (Koletzko et al. 2005; Fusch et al. 2009).

39.3.1.2 Amino Acids

To reduce the temporary interruption of the transfer of nutrients, to limit the high protein catabolism up to 1.5 g/kg/d and to induce a positive nitrogen balance from the first day of life a high-protein supply (>2 g amino acids/kg per day) has recently been suggested in the so-called "aggressive" nutrition (Thureen et al. 2003; Ziegler et al. 2002; Simmer 2007).

Although, long-term benefits were not clearly demonstrated, it has been suggested that high protein intake during the first week of life induces positive nitrogen balance, increases insulin secretion, improves glucose tolerance, promotes early weight gain and improves neurodevelopmental outcome at 18 months (Stephens et al. 2009). Thus, new recommendations (Koletzko et al. 2005; Fusch et al. 2009) suggest providing 2–3 g of AA on the first day of life using a parenteral solution with a high AA:energy ratio and to progressively increase the AA intake up to 4 g/kg/d at the end of the first week of life.

39.3.1.3 Energy

Energy intake is required for both protein metabolism and deposition. Theoretically, an energy intake approximating the resting energy expenditure (i.e., 40–60 kcal/kg/day) allows the minimization of protein catabolism to about 1.5 g of protein/kg/d in ELBW infants. If amino acid intake is adequate and energy intake is in excess of resting energy expenditure, weight gain is achieved. However, because of individual differences in energy expenditure, the resting energy requirement varies considerably in this population. New recommendations (Koletzko et al. 2005; Fusch et al. 2009) suggest providing 40 kcal/kg/d on the first day of life, to increase up to 75–85 kcal/kg/d during the transitional period and to reach close to 100 kcal/kg/d at the end of the first week of life.

39.3.1.4 Carbohydrates

Glucose homeostasis is still immature during the early days of life in VLBW infants who are subject to hyper or hypoglycemia. Glucose is the main carbohydrate in fetal life and approximately 7 g/kg/d (4 mg/kg/min) of glucose crosses the placenta in the last trimester of pregnancy. Glucose production around 8 mg/kg/min (11.5 g/kg/d) in preterm infants is maximal in the postnatal period and decreases gradually with age. Gluconeogenesis may be responsible for a part of glucose production. During high rates of glucose infusion, endogenous production is not completely suppressed in VLBW infants. By contrast, maximum glucose oxidation is relatively limited, 7–8.5 mg/kg/min (10–12 g/kg/d), but could be less in critically ill VLBW infants. The imbalance between glucose infusion rate and endogenous production on one hand and the maximum oxidation rate explain the increasing incidence of hyperglycemia in VLBW infants. In addition, due to their immaturity and their underlying diseases, VLBW infants are relatively resistant to insulin during the first week of life.

During the transitional phase, fluctuations in blood sugar levels are frequently observed resulting from an insufficient glucose and energy intake associated with low substrate reserves

(hypoglycemia) or from a relative excess of glucose and energy intake associated with some degree of insulin resistance (hyperglycemia). Although the definition and the long-term consequences of neonatal hypo- and hyperglycemia remain controversial, plasma glucose concentration should be monitored to remain in a normal range for VLBW infants on parenteral nutrition between 50 mg/dL (2.75 mmol/L) and 150 mg/dL (8.3 mmol/L). Hyperglycemia can be decreased by reducing insensible water loss, glucose infusion rate and by providing exogenous insulin supply. Insulin administration may help to control plasma glucose concentration, to achieve increased energy intake and to promote nitrogen retention and growth, although there is need for more data on its safety and long-term consequences as a growth-promoting agent. More recently, it has been proposed that high AA intake from the first day (2–3 g/kg/d) improves glucose tolerance in ELBW infants by stimulating growth, by enhancing insulin and insulin-like growth factors secretion (Thureen et al. 2003). This approach requires further randomized control trials.

In practice, 6 g glucose/kg per day are generally well tolerated (4–5 mg/kg/min) even on the first day of life in VLBW infants. If this intake is tolerated, it may be increased progressively to 12–16 g/kg per day at the end of the first week of life. If it is not tolerated, progression of glucose intake will be reduced and insulin perfusion will be considered according to clinical and nutritional status with an initial dose of 0.05 IU/kg/h.

39.3.1.5 Lipids

Intravenous lipid emulsions are important constituents of total PN as they provide in an isotonic solution, high energy density and essential fatty acids to VLBW infants. Intravenous lipids play two separate roles in the PN of VLBW infants. The first role is as a high-density energy substrate to be readily utilized by VLBW infants. The other role is as a source of essential fatty acids as well as long-chain PUFAs. Essential fatty acid deficiency is avoided by infusions of 0.5–1.0 g lipid per kg per day. The importance of long-chain PUFAs for the development of the brain and the retina has also been recognized. Intravenous lipid emulsions contain small amounts of these fatty acids as part of the egg phospholipid used as a stabilizer. However, clearance of lipid emulsion could be impaired in ELBW infants particularly those with IUGR requiring the monitoring of triglyceridemia.

Actually, new recommendations (Koletzko et al. 2005; Fusch et al. 2009) suggest providing 1 g/kg/d on the first day increasing stepwise fashion to 3.0 g/kg/d at the end of the first week of age.

39.3.1.6 Minerals: Ca, P and Mg

Calcium and phosphorus transfer and retention is high during the last trimester of gestation. Combined with a relative immaturity of hormonal control (Vit D, PTH), VLBW infants particularly are at risk of early neonatal hypocalcemia and hypophosphoremia (see ▶ Chap. 41, “Calcium and Phosphorus Homeostasis: Pathophysiology”).

Calcium supply needs to be provided from the first day of life in combination with an adequate calcium phosphorus ratio to limit the risk of hypocalcemia and/or hypophosphoremia. Phosphorus plays a critical role in energy metabolism, and deficiency of phosphorus results in clinical disease, including muscle weakness. Early phosphorus deficiency is also potentiated by IUGR. Reference values for plasma phosphorus concentration differ in adults (>1.0 mmol/L, 3 mg/dL) and in preterm infants (>1.6 mmol/L, 5 mg/dL). Unfortunately, most neonatologists are unaware that the laboratory reports plasma phosphorus concentration of VLBW infants with regard to adult references and tolerates hypophosphatemia with the risk of hypercalciuria and osteopenia. Optimal calcium to phosphorus ratio differs in parenteral and oral nutrition due to the bypass of the gastrointestinal tract; phosphorus retention is related to bone mineralization with a weight-to-weight calcium:phosphorus ratio of 2.15:1 but also to nitrogen retention with a weight-to-weight nitrogen:phosphorus ratio of 15:1. Therefore optimal Ca to P ratio in parenteral nutrition ranges between 1.5 and 1.3.

Magnesium is rarely adjusted even in the transitional period unless the infant has persistent hypocalcemia secondary to hypomagnesemia, or has abnormally high magnesium levels due to

maternal levels. Serum magnesium levels should be checked in any small infant whose mother was treated for hypertension or preeclampsia.

Actually, new recommendations (Koletzko et al. 2005; Fusch et al. 2009) suggest providing around 25–40 mg (0.6–1 mmol) of Ca/kg/d, 18–31 mg (0.6–1 mmol) of P/kg/d and 2.5–4.0 mg (0.1–0.2 mmol)/kg/d of magnesium on the first day and to progressively increase the intake according to energy and AA supplies up to 65–100 mg (1.6–2.5 mmol) of Ca/kg/d, 50–78 mg (1.6–2.5 mmol) of Phosphorus and 7–10 mg (0.3–0.4 mmol/kg/d) of magnesium.

39.3.2 Parenteral Nutrition During the Stable Growing Period

The aim of the nutritional support in VLBW infants during the stable growing period is:

1. To induce growth rate and protein accretion in the range of the fetal weight gain considering the lean body mass gain as reference;
2. To abolish the development of a cumulative nutritional deficit during the first weeks of life;
3. To reach, at the time of discharge and/or of theoretical term, an anthropometric parameter in the range of reference values for term infants.

39.3.2.1 Fluids and Electrolytes

Intravenous fluid is the carrying vehicle for parenteral nutrition. A fluid intake about 140–160 mL/kg/d in both VLBW and VLBW preterm infants allows for covering the water requirement for replacing water loss and providing enough extra water to build new tissues during the stable growing period. Fat mass is relatively free of water content. By contrast, lean body mass content is about 80%. Thus a weight gain of 20 g/kg/d containing 40% of fat results in a net storage of 13 g of water and 1–1.5 mmol of Na+/kg/d.

Sodium and potassium requirements are in the range of 3–7 mmol/kg/d for Na^+ and 2–5 mmol/kg/d for K^+ in VLBW infants respectively. A mean intake of 3 mmol/kg/day of sodium and 2 mmol/kg/day of potassium seem to be appropriate to maintain normal plasma concentration for most stable growing infants. In parenteral solution, sodium is frequently provided with phosphorus in the form of sodium glycerophosphate and limitation of sodium content also limits the phosphorus content. Chloride supply requires particular attention in parenteral nutrition. Chloride requirement is generally considered similar to sodium requirement. Chloride content in parenteral solution is related to several potential components, AA solution, sodium chloride, potassium chloride or calcium chloride and is difficult to control. However, chloride intake plays a role in the acid-base homeostasis and imbalance between $Na^+ + K^+$ and Cl^- promotes metabolic acidosis or alkalosis (Kalhoff et al. 1997). Therefore, monitoring of plasma and urinary electrolyte concentrations and appropriate correction remains recommended, during parenteral nutrition.

39.3.2.2 Amino Acids

Nitrogen requirement in parenteral nutrition is close to 95% of the enteral requirement, but corresponds in terms of g AA/kg/g to the figure in g protein/kg/d recommended in enteral nutrition, due to a relatively lower nitrogen content. Protein requirement has been recently reviewed according to fetal nitrogen accretion, lean body mass gain and the need to compensate early cumulative protein deficits during the transitional period. 3.5–4.5 g of AA /kg/d is recommended during the stable growing period in ELBW and VLBW infants (Tsang et al. 2005; Agostoni et al. 2010; Rigo 2005).

39.3.2.3 Energy

In contrast to what is generally suggested, the energy requirement in PN approximates to that of enteral nutrition. In fact, the gross energy content, measured by bomb calorimetry, of 1 g of amino acid is lower than that of 1 g of protein. Similarly, gross energy content of glucose is less than that of more complex carbohydrates. In contrast, while in parenteral nutrition the metabolizable energy of amino acid and fat solutions are identical to the gross energy, the metabolizable energy of dietary protein and fat in oral nutrition represents about 90% and 80% respectively (Curtis et al. 1986). Consequently, the recommendation for energy intake during the stable-growing

period in VLBW infants on parenteral nutrition is relatively similar to that in oral nutrition and corresponds to 110–130 kcal/kg per day in VLBW infants.

39.3.2.4 Carbohydrates

Glucose contributes to most of the osmolality of PN solution (510 mOsm/L for a 10% solution) by contrast to lipid solutions. An excessive glucose intake increases CO_2 production and may be responsible for hyperglycemia, cause lipogenesis, steatosis and may contribute to liver dysfunction. The maximum glucose intake should not exceed the glucose oxidation rate in parenteral nutrition of 13–18 g/kg/d and more than 60–75% of the non-protein energy during the stable growing period.

39.3.2.5 Lipids

Intravenous lipid emulsions are important constituents of total parenteral nutrition as they provide most of the energy intake and essential fatty acids (EFA). The CO_2 production is lowered compared to PN with a high proportion of carbohydrates and the nitrogen metabolism can be improved by adding lipid emulsions to PN. Lipid oxidation depends on the overall energy intake and consumption, intake of carbohydrates and triglycerides and the carbohydrate/lipid ratio. Lipid oxidation decreases as the carbohydrate intake increases and is replaced by lipid storage.

Maximum fat oxidation occur when lipid emulsions provide 40% of the non-protein energy in newborns so it is recommended that lipid intake should provide 25–40% of non-protein energy with a maximum of 3–4 g/kg/day (Koletzko et al. 2005). An increase in the concentration of plasma triglycerides is to be expected if the infusion speed of the lipid emulsion exceeds the speed of triglyceride hydrolysis that depends on lipoprotein lipase activity. In all cases, the triglyceride infusion dose should be adjusted to maintain a serum triglyceride concentration not exceeding 200–250 mg/dL, especially in ELBW or severely ill infants who may have limited lipid tolerance.

Concerns had been raised on the potentially adverse effects of lipid infusion on hemodynamics, infections or hyperbilirubinemia. It appears prudent to avoid high lipid supplies in infants with sepsis, impaired oxygenation, or severe hyperbilirubinemia and lipid emulsion infusion should be continued at least at 0.5–1.0 g/kg/day, which is sufficient to prevent essential fatty acid deficiency.

Lipid supply may result in enhanced lipid peroxidation and the formation of free radicals. An increased lipid utilization by reducing the carbohydrate/lipid ratio results in a reduction of lipid peroxidation and free radical formation. PN should be supplemented with multi-vitamin preparations including both vitamin C and vitamin E (alpha-tocopherol), which have anti-oxidative effects. Excessive exposure of the bottle to light should be avoided.

Carnitine is necessary for the transportation of long-chain fatty acids via the mitochondrial membrane and its oxidative metabolism. Because carnitine synthesis and storage are not sufficiently developed at birth, particularly in preterm infants, and because no commercial intravenous solution has carnitine, parenterally fed infants present low plasma and tissue carnitine levels that decline with postnatal age (Borum 2009). Although a meta analysis (based on 14 randomised, controlled studies) showed there to be no effect of carnitine supplementation on the metabolism of lipids, lipogenesis or weight gain (Cairns and Stalker 2000), a carnitine supplementation of 15 μmol/100 kcal could be advisible for infants on total parenteral nutrition for more than 4 weeks.

39.3.2.6 Minerals: Ca, P and Mg

Calcium and phosphorus cannot be provided through the same parenteral solution at concentrations needed to support in utero accretion, because of solubility. With a fluid intake range of 120–150 mL/kg/day, it is advisable to supply 65–100 mg (1.6–2.5 mmol) of Ca /kg/d, 50–78 mg (1.6–2.5 mmol) of iP and 7–10 mg (0.3–0.4 mmol/kg/d) of Mg, corresponding to a Ca/P ratio of 1.3:1 by weight and 1:1 by molar ratio in the TPN solution. It must be underlined that this quantity of calcium provided by parenteral route is about 55–80% of that deposited by the fetus during the last trimester of gestation (120 mg/kg/day) but similar or higher than that

obtained in enteral nutrition with the available preterm formula (see ▶ Chap. 41, "Calcium and Phosphorus Homeostasis: Pathophysiology").

39.3.2.7 Trace Elements and Vitamins

Vitamin mixtures for parenteral use have been available since the early time of parenteral nutrition and the amounts provided were (and are) determined to a large extent by the preparations available. Today, additives of all trace minerals for which a deficiency has been demonstrated are available. However, little definitive information is available concerning the parenteral requirements of either trace minerals or vitamins in VLBW infants. Research concerning the parenteral requirements of these nutrients by infants, of course, is hindered by the difficulties both of measuring plasma concentrations of the nutrients using small volumes of plasma and of interpreting the physiological significance of plasma concentrations.

39.4 Practical Aspects of Parenteral Nutrition in VLBW Infants

39.4.1 Basic Components Available for Parenteral Nutrition in Preterm Infant

39.4.1.1 AA Solutions

Considerable improvement of parenteral amino acid solutions have occurred from the late 1960s when the source of intravenous protein was casein hydrolysate. More specific pediatric amino acid solutions have been designed in the early 1990s with high essential/non-essential AA ratios and conditionally essential amino acid content for use in preterm infants. At least three different "gold standards" have been proposed for premature infants: (1) the amino acid concentrations from the umbilical cord obtained following fetal cord puncture or after birth, (2) the amino acid concentrations of rapidly growing preterm infants receiving their mother's milk or human milk supplemented with human milk proteins, (3) the amino acid concentrations of healthy breast-fed term infants. Nevertheless, despite the diverse composition of parenteral amino acid solutions used in pediatric care, nitrogen utilization does not change significantly (Fig. 1) (Rigo and Curtis 2004; Rigo 2005) (Table 2).

Therefore, optimal amino acid patterns for parenteral amino acid solutions in preterm infants still need to be determined and new solutions should be developed to potentially improve sulfur and aromatic AA imbalances and to provide additional glutamine. However, up to now, the use of cystein-HCl, acetyl-cystein, acetyl-tyrosine (Goudoever et al. 1994) and the supplementation with glutamine (Tubman et al. 2008) have not demonstrated beneficial effects. The recent data evaluating the effect of bypassing the intestine on individual AA requirements has not been translated to designing and evaluating new AA solutions.

39.4.1.2 Lipid Emulsions

Intravenous lipid emulsions consist of different oils (soybean, safflower, coconut, olive and fish oils), egg yolk phospholipids and glycerol [reviewed in 12, 14, 26, 27] (see Table 3). Intravenous lipid emulsions provide high caloric, isotonic solutions and can also be given through peripheral lines Traditionally, lipid infusions are prepared from soybean oil triglycerides emulsified with egg yolk phospholipids. Typical soybean oil contains about 45–55% linoleic acid (18:2n-6) and 6–9% linolenic acid (18:3n-3), but very little saturated or monounsaturated fat. Although clinically safe, experimental reports indicated that soybean oil based lipid emulsion could exert a negative influence on immunological functions. Those findings were related to its absolute and relative excess of ω-6 polyunsaturated fatty acids (PUFA) and the low amount of ω-3 PUFA and also to its high PUFA content with an increased peroxidation risk. The new lipid emulsion was basically designed in order to obtain balanced levels in polyunsaturated (ω-6 and ω-3), monounsaturated, and saturated fatty acids. They are differentiated by their fatty acid content, as well as fatty acid source of their origin, including soy, safflower, coconut, olive, and fish oil. Newer emulsions comprise physical mixtures of either a 20:80 mixture of soy ω-6 PUFA and ω-9 medium-chain monounsaturates (MUFA) from olive oil or

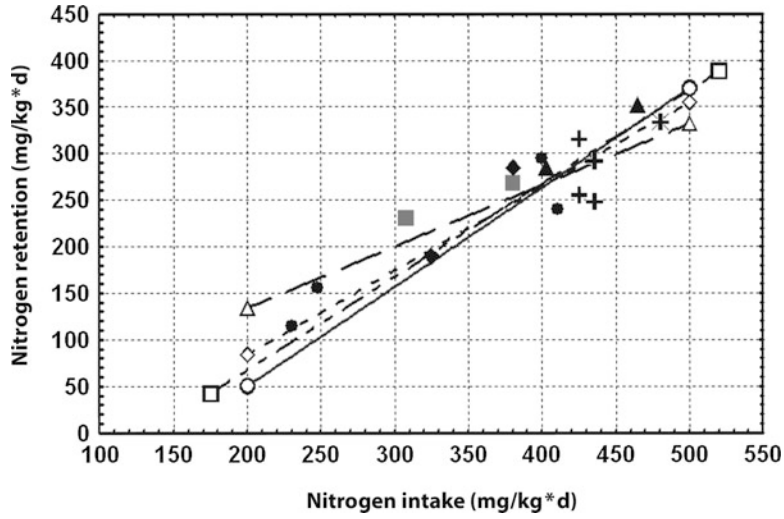

Fig. 1 Relationship between nitrogen retention and nitrogen intake in parenterally fed preterm infants computing of various studies (the different symbols represent individual studies)

Table 2 Main composition of commercial parenteral amino acID solutions for preterm infants

Product	%	Total AA (g/L)	EAA (%)	Cyst(e)ine (g/L)	Tyrosine (g/L)	Taurine (g/L)	Osmolality (mosm/L)	pH
Aminopäd	10	100	42	0.5[a]	1.1[c]	0.3	790	6.1
Aminoplasmal	10	100	42	[b]	0.4	–	864	5.7–6.3
Primene	10	100	48	1.9	0.5	0.6	780	5.5
Aminoven infant	10	100	51	0.5	4.2[c]	0.4	885	5.5–6.0
Vaminolact	6.5	65	44	1.0	0.5	0.3	510	5.2
TrophAmin	10	100	49	[b]	0.2	0.3	875	5.5

EAA Essential amino acID (n = 8)
[a]As acetyl-cystein
[b]Separately as cystein HCl
[c]As acetyl-tyrosine

Table 3 Oil content (%) in commercially manufactured intravenous lipid emulsions

Product	Soy (LCT)	Coconut (MCT)	Olive (MUFA)	Fish (ω3)
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

LCT long-chain triglycerides, *MCT* medium-chain triglycerides, *MUFA* mono unsaturated fatty acid

a 1:1 ratio of LCT with coconut oil-derived medium chain triglycerides (MCT). Structured MCT/LCT emulsions formulated from a random combination of triglycerides synthesized on the same glycerol carbon chain are cleared faster from blood in moderately catabolic patients. The newer lipid combinations with a smaller proportion of soy oil, have a much lower content of linoleic acid and linolenic acid, the potentially pro-inflammatory ω-6 PUFA, and less myristic,

palmitic, and stearic acids. These long-chain SFAs are believed to have increased cardiovascular risk and can also have acute effects on cell growth and apoptosis. In MCT/LCT emulsions, MCT may be preferentially metabolized under certain clinical conditions and structured MCT may have a reduced tendency to accumulate in the reticulo-endothelial system. The olive oil-derived ω-9 MUFA appears less immunosuppressive and may inhibit release of pro-inflammatory cytokines. They are also less susceptible to peroxidation and well tolerated in critically ill neonates. Fish oil emulsions are predominantly ω-3 long-chain PUFA. Alone, they lack EFA and are formulated as a supplement to be administered with other nutritionally complete lipid products, or are manufactured as physical mixtures (10% fish: 40% soy: 50% MCT or 30% soy:30% MCT:25% olive oil:15% fish). Fish oil-derived ω-3 PUFAs appear to alleviate symptoms of cholestasis, especially in neonates. Modern lipid products, based on olive, coconut, and/or fish oils, have demonstrable formulation and clinical benefits over traditional soybean and safflower IVLE and, when combined in the new multi-chamber bags, can also offer improvements in stability and safety (Hardy and Puzovic 2009; Diamond et al. 2009; Waitzberg et al. 2006).

39.4.1.3 Mineral Sources

In parenteral nutrition, calcium may be provided in the form of calcium gluconate, calcium chloride or calcium glycerophosphate. Due to aluminium contamination calcium gluconate was progressively abandoned by industry to meet the new FDA rule of 25 μg/L of aluminium in parenteral solution but remains frequently used in home-made hospital pharmacy preparations. Calcium chloride is easy to use but its high chloride content (2 mmol Cl^{-}/1 mmol Ca^{++}) limits its utilization in parenteral nutrition for VLBW infants (Poole et al. 2008; Bohrer et al. 2010). Calcium glycerophosphate with a 1:1 molar ratio is an adequate source of calcium and phosphorus, but is not registered for use in parenteral nutrition and needs to be prescribed from powdered anhydrous CaGlyP.

Phosphorus may be provided in inorganic (sodium or potassium phosphate) or organic form (glucose 1 phosphate, fructose 1–6 diphosphate, sodium glycerophosphate). Potassium phosphate is frequently preferred to sodium phosphate and used as the unique source of potassium in the parenteral solution. Potassium phosphate is easy to use but its high potassium content (1 mmol P^{3-}/1 mmol K for the monobasic form, 1 mmol P^{3-}/2 mmol K for the dibasic form or 1 mmol P^{3-}/1.7 mmol K for the mixed form) limit its utilization in parenteral nutrition for VLBW infants. Organic phosphorus in the form of disodium glucose 1 phosphate (Phocytan) is widely used in parenteral solution for VLBW infants. However, as for the use of sodium glycerophosphate, 2 mmol Na^{+}/1 mmol P^{3-}, or fructose 1–6 diphosphate (Esafosfina) the sodium content, 3 mmol Na^{+}/2 mmol P^{3-}, limits its utilization in VLBW infants particularly during the first weeks of life.

Magnesium is generally provided as magnesium sulfate in parenteral solution. Magnesium chloride has also been associated with the risk of inducing anionic-cationic imbalance in the parenteral solution.

39.4.1.4 Vitamins and Trace Elements

With the daily use of hydro- and lipo-soluble vitamins combined with trace elements clinical and biochemical evidence of deficiency were no longer reported.

39.4.2 Tailored or Standard Parenteral Solutions

Parenteral solutions can be prescribed using either of two formats: tailored or standard (Poole and Kerner 1992; Lapillonne et al. 2009). Tailored solutions are formulated specifically to meet the daily nutritional requirements of the individual patient, whereas standard solutions are designed to provide a formulation that meets most of the nutritional needs of the stable biochemical and metabolic parameters. Both of these methods have advantages and disadvantages associated with their use.

Tailored solutions are based on the principle that no single parenteral regimen can be ideal for all patients, for a wide variety of pathological processes, all age groups, or for the same patient during a single disease. The main advantage of tailored solutions is flexibility. Each solution is formulated for an individual patient and can be modified when the patient's nutritional needs and metabolic, electrolyte or clinical status changes.

The disadvantage of these solutions is linked to the time involved in calculation and label preparation, which today is nevertheless diminished with the use of specific computer programs. These solutions should be prepared with strict aseptic techniques, possibly in the pharmacy, not in the ward, and stored in a refrigerator at 4 °C. The solutions thus prepared are stable for 96 h and should be allowed to reach room temperature slowly and not warmed before infusion.

Standard solutions contain fixed amounts of each component per unit volume. In some hospitals there are a few types of fixed solutions to better cover the nutritional requirements of premature infants. The advantages of these solutions are that they include all the essential nutrients in fixed amounts, which eliminates the chances of inadvertent omission or overload. The disadvantage of standard solutions is their lack of patient specificity and the need of minimal adjustment particularly during the first days of life.

Very recently, it was suggested that the use of unique standard parenteral solution contribute to a significant improvement of nutritional support in both extremely and very preterm infants (Senterre and Rigo 2011b). In addition, ready to use industrially manufactured multi-chamber bags (MCB) containing the three sterilized macro-nutrient solutions (amino acids, glucose, and lipids), in separate chambers of a single closed plastic system were evaluated in multicentric study and provides similar benefits (Rigo et al. 2011). Their guaranteed sterility and longer shelf life are major technological advances that minimize the risks of inadvertent contamination during compounding and storage.

39.4.3 Nutrient Intake

Table 4 shows the composition of a ready to use parenteral solution for VLBW infants used in our NICU and the daily nutrient intake (kg/d) given by total parenteral nutrition according to the new

Table 4 Parenteral nutrition solution and daily nutrient intake (kg/d) of very low birth weight infants (<1500 g) in total parenteral nutrition according the "aggressive approach"

Day of life	Composition	D1	D2	D3	D4	D5	D6	>D6
		/kg/d	/kg/d	/kg/d	/kg/d	/kg/d	/kg/d	/kg/d
Parenteral solution (mL)	100	50	70	100	120	140	150	150
Glucose (g)	12.5	6.3	8.8	12.5	15.0	17.5	18.8	18.8
Amino acid (g)	2.7	1.4	1.9	2.7	3.2	3.8	4.1	4.1
Calcium (mg)	72	36	50	72	86	100	108	108
Phosphorus (mg)	55	27	38	55	66	77	82	82
Magnesium (mg)	8	4.0	5.6	8.0	9.6	11.2	12.0	12.0
Natrium (mmol)	1.6	0.8	1.1	1.6	1.9	2.2	2.4	2.4
Kalium (mmol)	1.5	0.8	1.1	1.5	1.8	2.1	2.3	2.3
Chloride (mmol)	2.0	1.0	1.4	2.0	2.4	2.8	3.0	3.0
AA supplement (g)[a]		1.0	1.0	0.5	–	–	–	–
Lipid emulsion 20% (g)[a]		1.0	1.5	2.0	2.5	3.0	3.0	3.0
Total fluid (mL)		65	83	110	132	155	165	165
Total energy (kcal)[b]	57	42	69	76	91	108	113	113
Total AA g		2.4	2.9	3.2	3.2	3.8	4.1	4.1

[a]ProvIDed separately in Y route

[b]Energy (kcal) = AA × 3.75 + Glu × 3.75 + lip × 9.3

practice of "aggressive nutrition" for VLBW infants. In any case nutrient intakes are always indicative and may be modified according to each patient, his/her clinical picture, biochemical data and tolerance to nutrient intake. Thus, this standard solution could be diluted with free water according to fluid requirement and sodium intake could be adapted after a few days of life.

These nutrient intakes are a mere indication and have to be modified according to the clinical picture and biochemical data of the single patient.

The following suggestions could be useful in the management of a parenterally fed VLBW infant.

- In the first days of life fluid intake should be increased if daily weight loss is >5%, total weight loss>12–15%, serum Na >150 mmol/L, urinary osmolality >350 mOsm/L and if the infant is under phototherapy or managed in a radiant incubator. On the contrary fluid intakes should be reduced if daily weight loss <2% or there is a weight gain and serum Na <130 mmol/L.
- Glucose should be routinely administered after birth and progressively increased with the objective to increase energy intake. When a glucose infusion rate of 6 mg/kg/min or less leads to hyperglycemia, the use of insulin is advised. Insulin should be discontinued as soon as glucose tolerance is established and the energy supply necessary for growth can be delivered without hyperglycemia. If insulin is used, strict blood glucose monitoring is mandatory to avoid hypoglycemia.
- The starting dose of AA in the first day of life should be higher than what is currently advised. Intake should never be less than 1.5 g/kg/d and the starting dose should preferably be 2.0–3 g/kg/d. When energy intakes reach about 70 kcal/kg/d and there is no enteral protein intake, the dose should be increased progressively to 3.5–4.4 g/kg/d.
- Although many neonatal intensive care units start lipid infusion only after the first days, it seems logical to start parenteral lipid within the first day in order to avoid a prolonged interruption of essential fatty acids and LC-PUFA. The starting dose of 0.5–1 g/kg/d should be gradually increased to 3–3.5 g/kg/d. The lipid infusion should be adjusted to maintain a serum lipid <250 mg/dL. Using a similar approach allows to reduce the cumulative nutritional deficit and limit or abolish postnatal growth restriction in VLBW infants (Senterre and Rigo 2011a; Lapillonne et al. 2009).

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