Intrauterine-Like Growth Rates Can Be Achieved with Premixed Parenteral Nutrition Solution in Preterm Infants¹–³

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Abstract
Growth failure in neonatal intensive care units is a major challenge for pediatricians and neonatologists. The use of early “aggressive” parenteral nutrition (PN), with >2.5 g/(kg·d) of amino acids and at least 40 kcal/(kg·d) of energy from the first day of life, has been shown to provide nutritional intakes in the range recommended by international guidelines, reducing nutritional deficit and the incidence of postnatal growth restriction in preterm infants. However, nutritional practices and adherence to recommendations may vary in different hospitals. Two ready-to-use (RTU), premixed parenteral solutions (PSs) designed for preterm infants have been prospectively evaluated: a binary RTU premixed PS from our hospital pharmacy and a commercially premixed 3-chamber bag (Baxter Healthcare). These premixed PSs provide nitrogen and energy intakes in the range of the most recent recommendations, reducing or eliminating the early cumulative nutritional deficit in very-low-birth-weight infants, and avoiding the development of postnatal growth restriction. A further rationale for RTU premixed PSs is that preterm infants require balanced PN that contains not only amino acids and energy but also minerals and electrolytes from the first day of life in order to reduce the incidence of metabolic disorders frequently reported in extremely-low-birth-weight infants during the early weeks of life. J. Nutr. 143: 2066S–2070S, 2013.

Introduction
Early nutritional support of preterm infants is critical to sustaining extrauterine growth and development and long-term health and well-being. The aim of nutrition in the preterm infant is to provide adequate nutrition before term gestational age in order to prevent the development of cumulative nutritional deficits and postnatal growth failure (1–3). Surveys have shown that nutritional practices and adherence to international recommendations for preterm infants (4,5) may vary in different hospitals (6). A systematic review of all published surveys reviewing these practices is reported in this supplement issue (7).

One of the nutritional practices recently advocated is the use of early “aggressive” parental nutrition (PN)², from the first day of life, using PN either as a primary or supplemental nutrition source (8). Here, we review the importance of this approach in achieving well-balanced PN and intrauterine-like growth in preterm infants, and how recent developments in the availability of commercially premixed parenteral solutions (PSs) may help to support this practice.

The use of early “aggressive” PN, providing >2.5 g/(kg·d) of amino acids and at least 40 kcal/(kg·d) of energy from the first day of life, combined with adequate enteral nutrition (EN) thereafter, has been shown to improve nutritional intakes, reducing nutritional deficit and the incidence of postnatal growth restriction in very-low-birth-weight (VLBW) infants (8,9). An increase in the amino acid intake in the first days of life to 2.5 g/(kg·d) has been integrated in the most recent recommendations (4,5). Recent studies confirmed the beneficial effects of this increase

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in amino acids on nitrogen balance and lean body mass (LBM) accretion during the first week of life, with potential benefits on long-term development.

**Design and Composition of a New Commercial Ready-To-Use Premixed PS for Preterm Infants**

One of the ways in which PSs can be prescribed is as a ready-to-use (RTU) premixed PS (2) that contains fixed amounts of each nutritional component per unit volume and is designed to provide a formulation that meets most of the nutritional needs for stable biochemical and metabolic variables.

Most neonatal intensive care units (NICUs) provide a variety of fixed solutions to cover the nutritional requirements of premature infants. The advantages of these solutions are that they are readily available and contain all the essential nutrients in fixed amounts, eliminating the chances of inadvertent omission or overload. The disadvantage of such standard solutions is that they are not all designed by experts in preterm nutrition; some are binary solutions requiring the provision of lipids separately and they may need some minimal adjustments, particularly during the first days of life.

For adults, commercially manufactured RTU multichamber bags containing 3 sterilized macronutrient solutions (amino acids, glucose, and lipids) with or without electrolytes in separate chambers of a single, closed system are widely available and have been used for >10 y (10). An international group of experts in pediatric nutrition suggested that a standardized total PN solution in a multichamber bag system could provide nutritional support for pediatric patients, requiring minimal individualized adjustments (4,5). The first clinically available commercial RTU premixed 3-chamber bag (3-CB) system for pediatric patients (Baxter Healthcare) was designed specifically for preterm infants (12). These PSs containing amino acids, energy, electrolytes, and minerals provided nutritional intakes from the first days of life in the range of the most recent recommendations (Table 1) (4,5) and required only limited supplementation during the study.

The first study was a noninterventional, single-center cohort study in 102 VLBW infants (mean birth weight: 1005 ± 157 g; mean gestational age at birth: 28.5 ± 1.9 wk) who remained in the NICU for >3 wk (3,9). Infants received from the first day of life a standard RTU PS prepared by the hospital pharmacy. To achieve an amino acid intake of at least 2.5 g/(kg · d) during the first 2 d of life, an amino acid supplementation of 1.0 and 0.5 g/(kg · d) was necessary at day 1 and day 2, respectively. An intravenous lipid solution was also administered from the first day of life. Enteral feedings of human milk (or preterm infant formula if human milk was unavailable) were initiated early on the first or second day of life, when the infant was clinically stable. The individualized fortification of human milk was initiated when 50 mL/(kg · d) was tolerated (13). Nutritional intake was in line with recommendations, with a mean amino acid intake of 2.5 g/(kg · d) and 45 kcal/(kg · d) on the first day of life, increasing to an amino acid intake of >3.5 g/(kg · d) and >100 kcal/(kg · d) at the end of the first week. The mean sum of the enteral and parenteral intakes during the first week of life was 3.15 g of protein and 80 kcal/(kg · d). At 6 wk of life, the mean cumulative energy and protein intakes/(kg · d) were higher than those in previous studies (14,15) and were similar to the recommendations for VLBW infants given 3.8 g of protein and 120 kcal/(kg · d) (3,9). This indicates that PN support with a high protein:energy ratio provides the opportunity to rapidly reach the recommended intakes. Postnatal weight loss of 6% of birth

<table>
<thead>
<tr>
<th>Nutritional component/ (kg body weight · d)</th>
<th>Recent recommendations for VLBW infants at the end of the first week of life2</th>
<th>Binary RTU premixed PS2</th>
<th>Commercially premixed 3-CB4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids, mL</td>
<td>—</td>
<td>165</td>
<td>128</td>
</tr>
<tr>
<td>Energy, kcal</td>
<td>90–120</td>
<td>118</td>
<td>117</td>
</tr>
<tr>
<td>Protein5, g</td>
<td>3.5–4.0</td>
<td>4.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Glucose, g</td>
<td>13–18</td>
<td>18.8</td>
<td>17.1</td>
</tr>
<tr>
<td>Fat6, g</td>
<td>2–4</td>
<td>3.07</td>
<td>3.2</td>
</tr>
<tr>
<td>Sodium, mmol</td>
<td>2–7</td>
<td>2.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Potassium, mmol</td>
<td>2–5</td>
<td>2.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Chloride, mmol</td>
<td>2–7</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Calcium, mmol</td>
<td>1.3–4.0</td>
<td>2.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Phosphorus, mmol</td>
<td>1.0–2.5</td>
<td>2.7</td>
<td>1.6</td>
</tr>
<tr>
<td>Magnesium, mmol</td>
<td>0.2–0.4</td>
<td>0.25</td>
<td>0.55</td>
</tr>
</tbody>
</table>

1 PS, parenteral solution; RTU, ready-to-use; VLBW, very-low-birth-weight; 3-CB, 3-chamber bag; —, not applicable.
2 Source: references 4 and 5.
3 Source: references 3 and 9.
4 Numeta G13%; Baxter Healthcare.
5 Primene 10%; Baxter Healthcare.
6 ClinOleic; Baxter Healthcare.
7 Lipid provided separately.
weight was limited to the first 3 d of life, with a mean return to birth weight of 7 d. Further decreases in weight Z-score were not generally observed after 3 d, except in the infants with the lowest gestational age, those with the highest need for ventilation support, and infants with the more severe clinical disorders, requiring >12 wk hospitalization. In all, at birth and at discharge, the same proportion of infants exhibited growth restriction (20%), suggesting that postnatal growth restriction could be prevented by optimization of the early nutritional program using PN.

To our knowledge, this study was the first to show that cumulative nutritional deficit and postnatal growth restriction could be abolished, even in extremely-low-birth-weight infants (9). Compared with data from previous studies (14–16), the results of this study (3) showed improvements of protein and energy intake with use of the most recent recommendations, a standard RTU PS, and improvement of EN support (3) (Fig 1).

The second study was a multicenter, noncomparative phase III trial in infants <37 wk gestational age (mean birth weight: 1382 ± 520 g; mean gestational age at birth: 31.2 ± 2.5 wk) requiring PN that provided at least 80% of their total estimated nutritional needs at study entry (12). Participants were grouped according to their postnatal age at inclusion (birth to 3 d old, n = 34; 4–7 d old, n = 35; >7 d old, n = 28). Infants received a commercially premixed 3-CB for 5–10 consecutive days (mean PN duration ± SD: birth to 3 d old, 8.4 ± 2.0 d; 4–7 d old, 8.7 ± 1.8 d; >7 d old, 9.4 ± 1.3 d). Depending on the individual patient’s needs, the lipid compartment of the bag could be activated and the volume of PS adjusted with additional supplementation when necessary. EN increased progressively throughout the study. Ten infants received additional amino acid supplementation to reach the required amino acid intake of >2.5 g/(kg · d) during the first 2 d of life, 7 infants received additional glucose supplementation, and 4 infants had lipids provided through a separate perfusion rather than by activating the lipid component of the 3-CB. Sixty-five infants required additional electrolyte (mainly sodium) and mineral supplementation. Mean protein and energy intakes over the course of the study are shown in Table 2 and were in the range of nutritional recommendations for VLBW infants (4,5). Weight gain during the period of PN, also shown in Table 2, was positive in patients included close to birth and at the upper end of fetal weight gain in those enrolled after the third day of life, suggesting that PN from the premixed 3-CB promotes growth and may reduce postnatal growth deficits. In addition, the premixed 3-CB was well accepted by nurses, pharmacists, and neonatologists with a visual analogic score for practical handling and ease of use significantly higher than that of RTU compounded bags and tailored premixes. No serious adverse events occurred that were considered to be related to PN infusion.

### Need for Well-Balanced PN from the First Day of Life in VLBW Infants

Recent studies have confirmed that this early increase in amino acid intake and the amino acid:energy ratio reduces the initial body weight loss of between 5% and 10% of birth weight and improves some electrolyte disorders. However, this early increase in amino acid intake can also induce new metabolic disturbances during the first few days of life as a result of imbalanced mineral and electrolyte supplies, making a case for revising the existing guidelines (17–19). For example, early provision of calcium intake from the first day of life is necessary to reduce the incidence of hypocalcemia, resulting from the abrupt interruption of placental transfer. However, a high amino acid supply in the presence of calcium, but without adequate phosphorus intake, induces hypophosphatemia (phosphate concentrations <1.6 mmol/L), which is deleterious for bone metabolism, energy metabolism, and acid-base status. It has also been suggested that hypophosphatemia can potentiate nosocomial infections (19–22). Therefore, calcium and phosphorus are necessary components of PN from the first day of life in VLBW infants. The desirable molar calcium:phosphate ratio of the P5 is related to the calcium intake.

### TABLE 2 Weight gain and protein and energy intakes in preterm infants receiving PN via a commercially premixed 3-CB (Numeta G13%;E; Baxter Healthcare) for 5 to 10 consecutive days

<table>
<thead>
<tr>
<th>Age at study inclusion</th>
<th>Weight gain, g/(kg · d)</th>
<th>Protein, g/(kg · d)</th>
<th>Energy, kcal/(kg · d)</th>
<th>PN + enteral nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–3 d (n = 34)</td>
<td>10.0 ± 9.5</td>
<td>2.50 ± 0.59</td>
<td>71 ± 16</td>
<td>3.36 ± 0.46</td>
</tr>
<tr>
<td>4–7 d (n = 35)</td>
<td>21.5 ± 10.2</td>
<td>2.74 ± 0.63</td>
<td>79 ± 18</td>
<td>3.64 ± 0.51</td>
</tr>
<tr>
<td>&gt;7 d (n = 28)</td>
<td>22.3 ± 9.4</td>
<td>3.16 ± 0.69</td>
<td>90 ± 19</td>
<td>3.84 ± 0.44</td>
</tr>
</tbody>
</table>

Values are means ± SDs over the duration of the study. Adapted from reference 12 with permission. PN, parenteral nutrition; 3-CB, 3-chamber bag.
and the nitrogen retention induced by the amino acid intake. According to the more recent guidelines for amino acid intake, the recommended calcium-phosphate ratio in PN would be reduced to a value close to, or slightly lower than, 1:1 (21).

Existing guidelines for PN in VLBW infants (4,5) recommend that electrolyte supplementation be postponed to the second or third day of life to reduce the incidence of hypernatremia and nonoliguric hyperkalemia, which is frequently observed in pre-term infants (23,24). The recommended amino acid intake [>2.5 g/(kg·d)] not only prevents nonoliguric hyperkalemia, it may also in turn be associated with relative hypokalemia (17,18). Potassium is the main intracellular cation and the provision of adequate amounts of nitrogen, potassium, and phosphorus are required to achieve rapid cell growth and LBM accretion. In VLBW infants, it is thought that the balance between potassium and phosphorus is closely linked to the amino acid supply and nitrogen retention, as reported in EN (21,25).

The reduction in initial weight loss and the early LBM accretion improve the sodium homeostasis, suggesting that sodium, an essential part of the extracellular compartment of LBM, needs to be provided early. Indeed, a daily LBM gain of 10 g results in a net storage of ~1.0–1.5 mmol Na+/kg body weight·d (4).

Chloride is also essential for acid-base homeostasis but is frequently neglected at the time of PN prescription. Although sodium and potassium needs may be considered when ordering electrolytes in the NICU, chloride needs are often delegated to the pharmacist. During PN administration, chloride needs may be provided for by the chloride associated with amino acids, calcium, potassium, or sodium or by the chloride content of drugs such as dopamine and dobutamine. PN containing an excess of chloride could induce severe metabolic acidosis (24). Therefore, a relative cation excess is needed in the PS [Na+ + K+ − Cl− = 1–2 mmol/(kg·d)] to improve the acid-base status of VLBW infants.

In summary, this evidence showing the importance of high amino acid supply and its potential impact on important metabolic disturbances in the first days of life suggests that there is a need for a balanced PS containing amino acids, energy, minerals, and electrolytes suitable for use in the first day of life in VLBW infants. In conclusion, eradicating growth failure in NICUs is a major challenge for pediatricians and neonatologists. PN during the early weeks of life, combined with adequate EN thereafter, is key to reducing early cumulative nutritional deficit and postnatal growth restriction in VLBW infants. Increasing the amino acid intake up to 2.5 g/(kg·d) on the first day of life has been integrated into the most recent recommendations. Recent studies confirm its beneficial effects on nitrogen balance and thus LBM accretion during the first week of life, and potentially on long-term development. This new approach of high amino acid supply is also potentially able to stabilize some important metabolic disturbances in the first days of life. In view of emerging evidence from the use of more optimal nutrition, there appears to be a need to revise the PN guidelines and for the development of balanced PSs containing amino acids, energy, minerals, and electrolytes, suitable for use from the first day of life in VLBW infants. Results from the recent multicenter study suggest that the use of a RTU premixed 3-CB shows promise for providing nutritional intakes and in helping obtain weight gain within recent recommendations for VLBW infants. These findings need to be confirmed, especially in VLBW infants fed parenterally from the first day of life.

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Literature Cited

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