Early Aggressive Nutrition in Very Preterm Infants

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Abstract
Despite numerous advances in the nutrition of preterm infants, the increasing survival at lower birth weights is resulting in a new frontier of extrauterine nutritional support of these vulnerable infants. The extremely low birth weight infant has endogenous energy to maintain energy balance for only 3–4 days without an exogenous energy supply. Nevertheless, many clinicians are still hesitant to introduce substrates at high rates early in life secondary to concerns of intolerance and toxicity. Current feeding practices appear to be resulting in significant postnatal growth failure in very preterm neonates. Optimizing nutritional support in these infants is critical to avoiding adverse growth and neurological outcomes. There is a need for scientifically based feeding strategies to achieve normal in utero growth rates postnatally. Important areas for research include determination of safe and efficacious upper limits of energy and amino acid intake, identification of markers for protein toxicity, better characterization of the effect of various neonatal illnesses and the neonatal stress response on nutritional metabolism, development of enteral feeding strategies that will allow for more rapid enteral feeding advance while reducing the risk of necrotizing enterocolitis, and understanding the benefits and risks of both over- and undernutrition in the extremely low birth weight infant.

Rationale for and against Early Aggressive Nutrition

Despite numerous advances in nutrition of preterm infants over the past decade, the increasing survival at lower birth weights is resulting in a new frontier of extrauterine nutritional support of these vulnerable infants. Extremely low birth weight infants (ELBW, i.e. <1,000 g in weight) have unique metabolic substrate requirements, predicted by high protein turnover rates, high metabolic rates, and high glucose utilization rates. The ELBW infant has endogenous energy reserves of only about 200 kcal, enough to...
maintain energy balance for only 3–4 days without an exogenous energy supply. Nevertheless, many clinicians are still hesitant to introduce substrates at high rates early in life secondary to concerns of intolerance and toxicity. In addition, there have been few studies demonstrating significant advantages to an aggressive approach. Several arguments for an aggressive approach include: (1) preventing a decrease in nutrient supply to the nutritionally vulnerable ELBW infant, (2) there are data suggesting improved developmental outcomes with early protein intake [1], (3) nationally and internationally, nutritional strategies for very preterm infants are resulting in postnatal growth failure from which the neonate does not recover by hospital discharge [2–4] (fig. 1), and (4) this postnatal growth failure is associated with increased risk of poor developmental outcome in very preterm infants [5, 6].

A commonly recommended standard for providing comprehensive postnatal nutrition to very preterm infants is one that duplicates normal in utero human fetal growth at the same gestational age [7]. This long-standing recommendation by the American Academy of Pediatrics has not included guidelines about how this should be achieved, however, and there is no data in the literature to support or refute this recommendation. Based on the significant variation in clinical practice, attaining a targeted rate of weight gain in very preterm infants is likely to be accomplished by very different nutritional strategies and without consideration of ‘quality’ of weight gain [8, 9].

**Fig. 1.** Longitudinal growth of hospitalized very low birth weight infants [2, with permission].
Replicating body composition of the fetus of the same gestational age as the preterm infant may be a more desirable nutritional goal. However, this necessitates an appreciation of the differences between normal fetal nutrition and commonly used postnatal nutritional practices in very preterm neonates. Amino acid uptake by the fetus is far in excess of that needed to meet accretion requirements; the excess amino acids are oxidized, contributing significantly to fetal energy production. However, amino acids are delivered to the preterm neonate in the first several weeks of life at low rates that are significantly less than required to provide for normal rates of fetal protein accretion. Glucose delivery to the fetus is determined by the maternal glucose concentration and occurs at a rate that reflects fetal glucose utilization for energy production. Fetal glucose utilization also occurs at relatively low plasma insulin concentrations. In the preterm newborn glucose usually is administered at higher rates than the fetus receives in utero, frequently producing hyperglycemia and plasma insulin concentrations that are significantly higher than those seen in the fetus. In addition, high glucose delivery rates to the preterm infant are likely to contribute to fat deposition. At 50–60% of gestation there is little fetal lipid uptake and this only gradually increases towards term. In contrast, in the very preterm newborn infant lipid is commonly provided as an energy source in amounts that exceed in utero delivery rates, contributing to adipose tissue production much earlier in development and in excess of rates that occur gradually over the third trimester of fetal development.

Clearly, current nutritional practices in preterm infants (high energy intakes of lipid and glucose accompanied by low protein intakes) contrast with the nutrient supplies that the normally growing fetus receives (high amino acid uptake with just sufficient uptake of glucose and lipid). The risks and benefits of these different nutritional patterns for the very preterm infant are not known.

**Strategies for Delivering Parenteral Substrates to ELBW Neonates**

**Protein**

Maximal weight-specific protein gain throughout life occurs prior to 32 weeks’ gestation. Thus, amino acid requirements are high in the fetus and very preterm infant in order to provide for the exceptionally high fractional protein synthetic and growth rates at this early developmental age. Infants who receive only supplemental glucose lose 1% of protein stores each day, and this may be even greater in very preterm newborns. If the target nutritional intake in the very preterm newborn is to achieve fetal protein accretion rates, then early amino acid administration is critical to avoid protein malnutrition. The quantity of postnatal amino acid administration that is required to produce fetal
rates of protein accretion has not been determined, but appears to be at least 3–4 g/kg/day [10].

Protein accretion is also affected by energy intake. Energy is required for both protein metabolism and deposition. Not only are relative protein accretion rates higher in the ELBW infant, but also are relative protein synthetic and breakdown rates, both of which are energy-dependent processes. Synthesis-to-gain ratios in ELBW infants may be as high as 5:1. It has clearly been shown in preterm infants that at the same protein intake, increasing energy intake increases protein accretion rate up to a maximal energy intake of 100–120 kcal/kg/day. This relationship, however, is curvilinear, with most of the effect of energy on protein gain taking place at less than 50–60 kcal/kg/day [11]. In contrast, increasing protein intake leads to increased protein accretion at nearly all energy intakes above 30–50 kcal/kg/day. Such observations support the need for much higher protein intakes than these infants normally receive and indicate that protein gain will be greatest with protein, not energy, intake.

\textit{Energy}

In order to prevent breakdown of endogenous energy stores, enough energy must be given to at least provide for energy expenditure. From data collected in ventilated ELBW infants in the first days of life, resting metabolic rate is approximately 40 kcal/kg/day. Approximately 20% of basal metabolic rate is accounted for by protein metabolism, or about 4–5 kcal/g protein. The energy cost of protein accretion is the sum of the energy stored (4 kcal/g) plus the metabolic cost of protein gain, which is estimated to be approximately 10 kcal/g protein. Therefore, energy intake to meet energy requirements for protein accretion should be at least 10 kcal/g protein gained. Studies indicate that protein growth in most ELBW infants probably occurs when amino acid intake rates are at or above 1.0–1.5 g/kg/day. Therefore, minimal total energy intake should equal resting metabolic rate plus 10 kcal/kg of infant weight for each gram per kilogram of protein intake above 1 g/kg. For a relatively stable, ventilated ELBW infant in the first days of life, this would give a minimal energy requirement of approximately 50 kcal/kg/day of energy intake at an amino acid intake of 2 g/kg/day, and 60 kcal/kg/day at an amino acid intake of 3 g/kg/day. This theoretical calculation supports the clinical observation that most infants will be in a positive protein balance at 2 g/kg/day of protein intake when given at least 50–60 kcal/kg/day of energy.

In the absence of protein intake, glucose is likely a more effective energy substrate in preventing protein breakdown than is fat, though the impact of the composition and amount of the energy source on protein metabolism remains controversial in ELBW infants. Optimal glucose/lipid intake ratios that maximize protein accretion have not been determined in the neonatal population. However, it is worth considering that the fetus at comparable gestational age to the ELBW infant uses primarily glucose and not lipid as a
nonprotein energy source. Furthermore, as discussed above, the fetus also takes up at least twice the amino acid load that it requires for net protein accretion and the balance is oxidized, providing energy. However, it is not clear if amino acids can be used as an energy source in ELBW infants in early postnatal life.

Glucose

In terms of maximal glucose intake, the general consensus has been to avoid hyperglycemia. The upper limit of the normal glucose concentration has not been defined in preterm infants, although many references use the value of 7 mmol/l (126 mg/dl). Common clinical practice is to tolerate glucose concentrations of up to 8.3–11.1 mmol/l (150–200 mg/dl), but the safety and consequences of this practice are unknown. The most common reason given for avoiding significant hyperglycemia is the risk for osmotic diuresis with secondary dehydration and metabolic instability. However, a recent review suggests that this is relatively uncommon [12]. In infants who are normoglycemic, we consider the upper limit of glucose administration to be that which meets the maximal glucose oxidative capacity. This is the glucose intake above which glucose exceeds the energy needs of the body and the excess glucose is converted to fat. Glucose conversion to fat is an energy-inefficient process that results in increased energy expenditure, increased oxygen consumption, and increased carbon dioxide production. This is an undesirable effect in all parenterally fed very preterm infants, but a particular concern in infants with existing lung disease. Chessex et al. [13] have shown that ventilated preterm infants with early and mild bronchopulmonary dysplasia receiving increased glucose intake do increase their carbon dioxide production, but this is compensated for by increasing their respiratory drive. However, this may not occur in infants with significant lung disease. The rate of glucose administration that exceeds the maximal glucose oxidative capacity is not completely known in neonates, but probably is above 11–13 mg/kg/min (~18 g/kg/day) [14, 15].

Lipid

Minimal intravenous lipid intakes should be targeted to prevent essential fatty acid (EFA) deficiency particularly in view of their critical role in postnatal brain development. Preterm infants have very limited endogenous lipid stores [16]. EFA deficiency develops by 4–5 days after birth if exogenous fat is not given and can be prevented with as little as 0.5 g/kg/day lipid (estimates range from 0.25 to 1.0 g/kg/day). Other benefits of intravenous lipid include its role as a high-density energy source (which can be provided by the peripheral venous route due to its isotonicity with plasma) and as a vehicle for facilitating delivery of fat-soluble vitamins. Optimal intravenous lipid intake above that which prevents EFA is controversial and has resulted in different lipid administration strategies among neonatal intensive care centers. Early use and/or rapid advancement of lipid emulsions in the preterm infant has been
cautious, however, because of concerns for potential development of several possible complications, including lipid intolerance, potential interference with immune function, impaired bilirubin metabolism and adverse effects on pulmonary function. There has been no recent evidence, though, that these concerns have been seen with the modest infusion rates of 0.5–1.0 g/kg/day that are commonly used today. A recent review comparing ‘early’ (≤5 days of age) versus ‘late’ (>5 days of age) initiation of parenteral lipids, which included 5 studies in 397 neonates, demonstrated no significant statistical differences between groups in the primary outcomes of growth rates, death, and chronic lung disease or the secondary outcomes, including several pulmonary disorders [17]. The authors concluded that early parenteral lipid administration could not be recommended for benefits of short-term growth or prevention of morbidity and mortality. However, there appears to be no clear contraindication to starting intravenous lipid infusions within the first day of life in most preterm infants, and there is a benefit in terms of ameliorating or preventing EFA deficiency. Clearly there is a critical need for more definitive information regarding the conditions under which intravenous fat administration should be limited.

**Early Parenteral Nutrition Studies in ELBW Neonates**

The first comprehensive, prospective, randomized, controlled trial of ‘aggressive’ versus ‘conservative’ nutrition in 125 relatively sick neonates weighing <1,500 g at birth was conducted in the 1990s by Wilson et al. [18]. Infants in the aggressive intake group were sicker, were started on earlier enteral nutrition (day 2 vs. day 5 in the control group), parenteral amino acids (day 1 vs. 3), and parenteral lipid (day 2 vs. 5). Nutrients were advanced more quickly and to higher maximal intakes in the aggressive nutrition group, and insulin was used if hyperglycemia developed. In terms of outcomes, there were no differences between groups in survival, hospital stay, days to full enteral feeding, and incidence of necrotizing enterocolitis (NEC), bronchopulmonary dysplasia, sepsis, cholestasis, and osteopenia. There was a significant improvement in weight gain at discharge from hospital in the aggressive intake group, though both groups demonstrated significant postnatal growth failure with discharge weight less than the 10th percentile of their standard growth curves.

A number of studies have focused on early protein administration in preterm infants. These studies have demonstrated that infusion of amino acids with glucose as early as the first day of life decreases protein catabolism. In general, 1.5–2.0 g/kg/day of protein intake is sufficient to avoid catabolism in neonates. In terms of the upper limits of protein intake, if the goal is to achieve intrauterine rates of protein deposition, then requirements of up to 3.8–4.0 g/kg/day of protein intake just to provide sufficient amino acids for protein accretion
have been estimated for ELBW infants [19] (table 1). In a randomized trial of early ‘low’ versus ‘high’ parenteral amino acid intake, it was shown that increased parenteral amino acid intakes for approximately 24 h produced short-term increases in protein growth in preterm infants [20]. This prospective, randomized study included 28 infants (mean weight 946 ± 40 g; SEM) who received either 1 g/kg/day (low amino acid intake) versus 3 g/kg/day (high amino acid intake) in the first days of life. Efficacy was determined by protein balance, and was significantly lower in the 1 versus 3 g/kg/ day amino acid intake groups by both nitrogen balance and leucine-stable isotope methods.

Table 1. Estimated nutrient intakes needed to achieve fetal weight gain

<table>
<thead>
<tr>
<th>Body weight, g</th>
<th>500–700</th>
<th>700–900</th>
<th>900–1,200</th>
<th>1,200–1,500</th>
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<td>Fetal weight gain&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>g/day</td>
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<td>16</td>
<td>20</td>
<td>24</td>
<td>26</td>
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<tr>
<td>g/kg/day</td>
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<td>20</td>
<td>19</td>
<td>18</td>
<td>16</td>
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<tr>
<td>Protein (Nx6.25), g</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Inevitable loss&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Growth (accretion)&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>2.5</td>
<td>2.5</td>
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<tr>
<td>Required intake</td>
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</tr>
<tr>
<td>Parenteral&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
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<td>15</td>
<td>15</td>
<td>20</td>
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<tr>
<td>Growth (accretion)&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>32</td>
<td>36</td>
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<td>39</td>
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<tr>
<td>Required intake</td>
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<tr>
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<td>108</td>
<td>119</td>
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<td>128</td>
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<tr>
<td>Protein/energy, g/100 kcal</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parenteral</td>
<td>3.9</td>
<td>4.1</td>
<td>3.5</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
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<td>3.8</td>
<td>3.7</td>
<td>3.4</td>
<td>3.1</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Because nutrient needs are closely related to body weight and weight gain, the nutrient needs apply to all postnatal ages. All values are per kg per day [19, with permission].

<sup>a</sup>Based on data of Kramer et al. [31].

<sup>b</sup>Urinary nitrogen loss of 133 mg/kg/day [32, 33] and dermal loss of 27 mg/kg/day [34].

<sup>c</sup>Includes correction for 90% efficiency of conversion from dietary to body protein.

<sup>d</sup>Sum of loss and accretion.

<sup>e</sup>Same as parenteral but assuming 88% absorption of dietary protein.

<sup>f</sup>Energy accretion plus 10 kcal/kg/day cost of growth.

<sup>g</sup>Assuming 85% absorption of dietary energy.
In terms of potential toxicity with the higher amino acid intake, there were no significant differences between groups in the amount of sodium bicarbonate administered, the degree of metabolic acidosis, or the blood urea nitrogen (BUN) concentration. When compared with plasma amino acid concentrations of normally growing 2nd and 3rd trimester human fetuses who were sampled by cordocentesis the normal fetal amino acid concentrations for both essential and nonessential amino acids were equal to those in the 3 g/kg/day group (except for threonine and lysine, which were significantly lower than seen in the fetus), but were at least twice the concentrations in the 1 g/kg/day group. More recently, in a large cohort of infants <1,500 g (n = 135 infants) te Braake et al. [21] compared 2.4 g/kg/day amino acids starting on the first day of life versus a stepwise increase over the first 3 days of life, and confirmed the safety (BUN and amino acid concentrations) and efficacy (nitrogen balance) of both strategies. Thus, in the short term it appears such amino acid delivery rates to the neonate are safe and beneficial, though the long-term effects have not been evaluated.

In the past several years initiation of 3 g/kg/day of parenteral amino acid intake in the first 1–2 days of life has become routine in many neonatal intensive care units. Nevertheless, a number of clinicians are hesitant to prescribe this rate of amino acid infusion because of concerns about potential amino acid toxicity. Currently there are no definitive clinical markers of toxicity from protein intake. In general, many clinicians follow BUN levels. However, a recent study in preterm infants showed no correlation between amino acid intake and BUN concentration [22]. Although gradually increasing amino acid intake over the first several days of parenteral nutrition is often advocated, there is no evidence that this specifically promotes tolerance of amino acids [21]. Clearly, further studies are needed to determine if even higher amino acid intakes are safe and efficacious when administered to very preterm neonates.

**Role of Insulin in Enhancing Growth with Parenteral Nutrition**

Exogenous insulin is most commonly used to control early hyperglycemia in very preterm infants. However, informal surveys suggest that there are a number of centers that use insulin in preterm neonates receiving parenteral nutrition for the purpose of enhancing growth. Insulin has been shown to successfully lower glucose levels and to increase weight gain without undue risk of hypoglycemia [23–25]. It is presumed that improved weight gain is secondary to both increased glucose utilization and improved protein balance in infants receiving parenteral nutrition. However, little is known about the effects of intravenous insulin infusions and relative hyperinsulinemia on the quality of weight gain and on counterregulatory hormone concentrations and the possible effects of these concentrations.
Administration of intravenous amino acids has been shown to decrease glucose concentrations in ELBW infants, presumably by enhancing endogenous insulin secretion. In the above study by Thureen et al. [20], an approximate doubling of insulin concentration occurred in the high versus low amino acid intake study group. The much lower incidence of neonatal hyperglycemia following the earlier postnatal introduction of parenteral amino acids was reported by Micheli et al. [26], and may be due to increased insulin secretion. It is known that enteral feeding also stimulates insulin release in infants. Since instituting a policy of early ‘high-dose’ parenteral amino acids, glucose intake rates at a maximum of 12 mg/kg/min and early minimal enteral feeding (MEF), we have virtually no significant hyperglycemia in preterm neonates, and insulin use is rare in our nurseries.

Contribution of Enteral Feeding to a Strategy of Early Aggressive Nutrition

An ‘early aggressive’ approach to nutrition benefits from early introduction of small-volume enteral nutrition (also referred to as MEF) in order to (1) provide trophic benefits of nutrient stimulation to the gut, (2) allow for a more comprehensive package of nutrient administration, and (3) avoid prolonged parenteral nutrition. The most common reason for delayed initiation and limited advancement of enteral feedings in preterm infants is the concern for increasing the risk of NEC. Clearly, there often is reason to cautiously initiate enteral feeding in very preterm infants soon after birth because of the known immaturity of a number of physiological and hormonal systems at early gestational ages. However, early enteral feeding prevents gut atrophy, stimulates maturation of the gastrointestinal system, may actually enhance eventual feeding tolerance, and may reduce the incidence of NEC, especially when colostrum and human milk are used. Most importantly, there is no evidence that MEF increased the risk for development of NEC [27]. Thus early MEF appears to have a role in early aggressive nutrition. Unfortunately, because of the concern for NEC, there is a paucity of definitive studies to guide early enteral feeding beyond the early use of MEF in very preterm neonates. Several small physiological studies give clues to best feeding practices, but do not provide comprehensive strategies for enteral feedings. Meta-analyses of enteral feeding practices are often not conclusive because there are an enormous number of variables in existing studies that make comparisons among studies difficult, and generalizations about safety and efficacy problematic. There are a number of enteral feeding trials with a decreased incidence of NEC as the primary outcome, but most of these are underpowered and not definitive. Clearly more research is needed in this area.
Aggressive Nutrition beyond the Early Neonatal Period: Is Postnatal Growth Failure Inevitable?

As noted above, a number of studies over the past 10 years would suggest that postnatal growth failure is unavoidable in ELBW infants. Many of the nutritional intervention studies to date have focused on delivering increased quantities of nutrients in the first 2–4 weeks of life. Clearly, this has decreased the catabolism seen prior to this type of intervention, and in some cases has resulted in improved weight gain. Growth faltering can occur at numerous time points during hospitalization, and solving the postnatal growth failure problem in this population will require different nutritional strategies at different time points. Figure 2 suggests there are at least three phases of growth faltering commonly seen in ELBW infants: (1) the several weeks immediately after birth when neonates are the most fragile, (2) the intermediate time period when infants are commonly slowly advanced to full enteral nutrition, but which could potentially represent an opportunity for significant catch-up growth, and (3) the postdischarge phase. There is currently little data regarding strategies to either prevent or reduce the incidence of growth faltering during these latter growth phases [28], and even less data regarding the risks and benefits of catch-up growth. Both human and animal investigations indicate that undernutrition, particularly insufficient protein intake, during critical development periods may adversely affect
long-term linear growth, neurodevelopmental outcomes, and general health. In contrast, overfeeding and/or positive crossing of growth percentiles may be associated with adverse later-life health outcomes such as obesity and type-2 diabetes [29, 30]. These contrasting responses to the amount (over- vs. undernutrition) and the timing of specific approaches to neonatal nutrition raise a number of as yet unanswered questions regarding postnatal nutrition of the very preterm infant.

References

Discussion

Dr. Rivera: What was the mean rate of growth and weight gain in those infants with early feeding? Were you able to measure the IQ of those babies with this type of approach?

Dr. Thureen: These studies were very short-term investigations that did not address long-term growth rates or developmental outcome. A more recent study we are doing indicates that early protein administration correlates with increased growth at 2 months of age. Poindexter et al. [1] recently showed that early amino acid administration to very preterm infants was associated with better growth and fewer infants with small head circumference at 36 weeks postmenstrual age. Clearly more studies are needed to assess growth and neurodevelopmental outcomes after early high protein administration to this population.

Dr. Fakhraee: We see some small babies <1,000 g who cannot tolerate D10W and usually we must use insulin. What is your opinion on that? With regard to minimal enteral feeding, what is the incidence of jaundice?

Dr. Thureen: We have seen a dramatic decrease in the incidence of hyperglycemia in our very preterm infants since starting early parenteral amino acids and early minimal enteral feeding, both of which likely stimulate endogenous insulin secretion. Clearly there are still a few infants who need exogenous insulin to treat significant hyperglycemia even with early amino acids and enteral feedings. We do not, however,
use insulin as a ‘nutritional adjuvant’ to enhance growth in infants without hyperglycemia since the possible adverse effects of such a strategy have not been sufficiently studied. Since the mid 1980s a number of studies have shown that minimal enteral feeding decreases the incidence and/or severity of jaundice.

Dr. Fakhraee: Actually I meant they cannot tolerate more than 4 mg/kg/min. We see it very often in the babies <1,000 g.

Dr. Thureen: The incidence of hyperglycemia varies dramatically and in different units it goes from 1 to 2% up to almost 100% of the infants, and in general those are infants who have high glucose infusion rates. Clearly you are talking about infants who don’t have high glucose infusion rates and I am not sure whether there are other stress factors that might contribute to hyperglycemia. We look at these infants on a case by case basis to really to try to decide what other factors are affecting this because you should not be having that degree of hyperglycemia in infants closed to 1,000 g. Clearly there is a lot of data on 24- to 25-week-old infants showing that no matter what you give them they still remain hyperglycemic. These infants are fed in most units and go on insulin to try to control the degree of hyperglycemia.

Dr. Fakhraee: You mentioned lipid infusion in severe infection. What is your definition of severe infection? What are the contraindications that you consider for minimal enteral feeding? Is there any contraindication to starting minimal enteral feeding?

Dr. Thureen: We didn’t go through each of those relative contraindications of lipid, but for infection there is a lot of evidence, at least in vitro, that lipid decreases neutrophil function and so there is some concern that giving high lipid intakes in a child who is septic could make things worse.

Dr. Fakhraee: Is there any contraindication to start early minimal feeding?

Dr. Thureen: We do not start minimal enteral feedings if an infant has significant hypoxic events, pressor support >5–10 μg/kg/min, clinical instability such as with significant sepsis, situations associated with decreased blood flow such as hypotension or clinically significant patent ductus arteriosus, or in infants with large aspires or recurrent abdominal distention. In infants who are IUGR or those who have had hypoxia we are starting to assess superior mesenteric artery blood flow patterns in response to test feeds of 1–3 ml/kg, and we hope this will help us define which infants are at risk with even a minimal enteral feeding.

Dr. B. Koletzko: In your study comparing amino acid intakes of 1–3 g that provide very valuable results, you chose to start providing amino acids only at about 24 h of age.

Dr. Thureen: We did not choose to start amino acids at 24 h of age but rather at birth. However, when we did that study, it took 24 h to order and receive that solution. Now we always have available a ‘stock’ amino acid solution that is stable and stored in the unit and we currently use this as the initial intravenous fluid after birth in all preterm neonates.

Dr. B. Koletzko: That may already answer my question because in the ESPGAN guidelines on pediatric parenteral nutrition published at the end of 2005 [2] we encourage people to start intravenous glucose with amino acids right from birth. Why do you use the wording ‘aggressive nutrition’ for safe and efficacious early enteral nutrition? As a pediatrician I have a problem with that. I wouldn’t call it ‘aggressive’ but just patient oriented and in fact probably less aggressive than starving a patient. Maybe if one would change terminology the practice could be even more widespread.

Dr. Thureen: When we started our study of 1 versus 3 g/kg/day of amino acid intake in very preterm infants early in life, most neonatologists around the world were starting infants on 1 g/kg/day of amino acids followed by a very slow advance of amino acid intake. Many clinicians considered 3 g/kg/day to be a dangerously high intake at which to start so we used the term ‘aggressive’ to acknowledge this concern. Now this
intake is widely felt to be safe and demonstrates a number of clinical benefits. But you are right, it is semantic, and I agree with your suggestion to call it ‘effective or intensive nutrition support’.

*Dr. Vento:* Could you comment on the conditionally essential amino acids, the L-cysteine, taurine or L-arginine which in certain circumstances, especially in very low birth weight infants or in low gestational age, could have some influence on their development?

*Dr. Thureen:* As you mentioned, there is a group of amino acids that may not be considered essential until there is a critical situation and they become ‘essential’. I believe we need a better understanding of the conditions under which these amino acids need to be supplied. The whole area of nutrition in specific diseases or during critical illness in preterm infants needs further investigation.

*Dr. Saavedra:* One of the difficulties that we have even after starting minimal enteral feeding is the rate of advancement that follows. There are two factors that we always see, mostly directed to this concern of potential NEC: using low concentration energy formulas and the apparent signs of intolerance. What is your position regarding concentration advancement versus volume advancement, bolus versus continuous gastric feedings?

*Dr. Thureen:* Unfortunately, all enteral feeding decisions are based on the fear of developing NEC. With the exception of hyperosmolar feeds, there is little evidence that certain feeding practices produce NEC. It is likely that many factors other than feeding contribute to NEC such as adverse alteration of gut flora secondary to excessive use of antibiotics, altered gut integrity, cytokine release, inflammatory responses and infections. I believe that the one thing that is becoming more evident is that the best enteral feeding to prevent NEC is breast milk. There is no evidence that dilute formulas prevent NEC, and in my opinion, they are contraindicated because they result in decreased caloric intake. Most ‘intolerance’ in very preterm infants is secondary to the poor GI motility seen in preterm infants, not to early NEC. Studies by Berseth and Nordyke [3, 4] suggest that giving feeds over longer periods (we use a ‘slow bolus’ over 30–60 min), breast milk and nondilute formulas, enhances gastric emptying and distal motor activity. In addition, bolus feedings stimulate a physiological pattern of hormone release that may not be seen with continuous feeds. We usually reserve continuous feeds for infants with reflux symptoms where smaller volume feedings are but one part of our strategy to decrease reflux. Data suggest that the rate of volume advancement has little to do with the development of NEC [5, 6]. Unfortunately, most studies regarding feeding strategies and the development of NEC are statistically underpowered to provide sufficient data on which to guide feeding practices.

*Dr. Dhanireddy:* The question of ‘good BUN’ and ‘bad BUN’ intrigues me. Frequently these extremely low birth weight babies have azotemia and we are struggling to decide whether it is too much protein. At what point would you cut back on the protein or slow down on progression?

*Dr. Thureen:* As I discussed in my presentation, our studies have not shown a significant correlation between amino acid intake and BUN levels [7]. Because of my concern with protein toxicity I have consulted with a number of metabolic and renal specialists. Their concern for toxicity focuses on encephalopathy, which occurs with BUN levels nearing 80–100 mg/dl. However, in neonatology our concern is that an elevated BUN level may reflect an inability to metabolize protein. My practice is to decrease amino acid administration when the BUN level approaches 35 or 40 mg/dl or when there is an unexplained significant metabolic acidosis since, although many things contribute to both a high BUN level and to metabolic acidosis, decreasing amino acid intake is one thing I can modify that could be having an adverse effect. Some of my colleagues tolerate BUN levels of up to 50–60 mg/dl. In my experience, BUN levels
above 40 mg/dl are unusual at 3 g/kg/day protein intake, but I know a number of neonatologists who are now starting to administer much higher parenteral amino acid intakes.

**Dr. Haschke:** As long as one has a continuous supply for the fetus or during continuous parenteral and enteral nutrition, it is clear that we do not have toxic concentrations of amino acids. As soon as we move to bolus feeding, it is quite different because here, the time between feeding and blood sampling for amino acid determination plays a big role. So sometimes one may miss a high amino acid concentration if blood is not taken at the right moment. We had this problem in one study when we were looking at high protein formulas for premature infants where the amino acid concentrations were taken exactly at a certain time point after feeding and it is clear that they vary considerably. There are differences, for example depending on whether blood sampling for amino acid determination occurs 1 or 3 h after feeding.

**Dr. Thureen:** I do very few enteral feeding studies and actually Dr. Cooke can address this much better than I can. It is a concern, especially as people start to advocate higher protein intakes in enteral feedings. It is an excellent point that we have to be careful with enteral feeding, especially when people are doing supplementation of enteral feeding. It is a very wide practice which could be dangerous without looking at amino acid levels for instance.

**Dr. Cooke:** In the absence of an inborn error of metabolism, we are unsure what plasma amino acids mean. Reference values are not fully established for the preterm infant. In effect, what is high, therefore what is acceptable or unacceptable remains to be determined.

**Dr. Cooke:** Can I comment on BUN. In the absence of associated anomalies, e.g. renal dysfunction, and/or metabolic anomalies, such as acidosis or hyperammonemia, we really don’t know how to interpret ‘high’ BUN. BUN is to total parenteral nutrition as gastric residuals are to enteral feeds, we get concerned but it alone is not a reason to discontinue parenteral nutrition.

**Dr. Fusch:** There is some effect of BUN on plasma osmolality. It is one of the most important contributors. As long as you have stable conditions it might be of less importance, but if BUN is changing quickly I don't know what will happen.

**Dr. Cooke:** It doesn't change that much. It is fairly consistent and we are talking about levels of 20, 30, 36 mg/dl. None of these children develop a BUN above 40 mg/dl or ~6 mmol and I think that is the crucial issue.

**Dr. Benavides-Hernandez:** The perinatal period is an important moment of metabolic programming. It is clear that aggressive nutritional support is beneficial in the short term and in neurologic outcome. I would like to know if you followed the patients or if you have any estimation of the long-term effect regarding overweight, renal function, and serum lipids?

**Dr. Thureen:** No, and I personally don’t do follow-up studies because the population at the hospital cannot easily be followed. But I think those are very important questions that need to be addressed, as well as those that Dr. Alan Lucas and others have put forth regarding nutrition and postnatal metabolic programming.

**Dr. Beaumier:** I would like to echo your reference about early protein and the benefit of having no more hyperglycemia because we have been doing that with 2.5 g and we have no more hyperglycemia. A question about lipids: what are your guidelines for advancement?

**Dr. Thureen:** We monitor triglyceride concentrations and try to keep them less than 150 mg/dl. There is evidence that the more gestationally immature infants, small
for gestational age infants, and infants with systemic infection have lower lipoprotein lipase activity and thus less lipid tolerance. Since triglyceride levels can be unpredictable in very preterm infants, we monitor blood levels with each advance in lipid volume to be certain the levels are at a safe range. We administer intravenous lipids over 24 h when possible because of evidence that lipids are better tolerated if given over a longer period of time.

*Dr. Heine:* We usually aim for a balance between carbohydrate and fat calories of about 50:50, in the older infants at least. In your experience, which proportion of glucose calories versus lipid calories do you apply?

*Dr. Thureen:* I think most neonatologists are still using 45–50% caloric intake as lipid. I am sure it is different in different institutions, but that is also our practice.

*Dr. Heine:* Does this also apply in very premature infants?

*Dr. Thureen:* We gradually advance lipid as tolerated in this population up to 45–50% calories as lipid.

**References**


