Protein for Preterm Infants: How Much is Needed? How Much is Enough? How Much is Too Much?

William W. Hay*, Patti Thureen

Department of Pediatrics, Section of Neonatology, University of Colorado School of Medicine, Aurora, USA

Preterm infants require considerably more protein to achieve normal intrauterine growth rates than is commonly fed to them during their first postnatal days. Continuing protein nutrition to maintain normal growth rates often is not achieved until several weeks after birth. Most very preterm infants do not receive the protein necessary to produce the 2–3 kilograms of body mass over a 12–16 week period of NICU care and, as a result, end up growth restricted by term, in lean body mass more than fat. This article reviews the requirements for protein and amino acids necessary to achieve normal growth and development of preterm infants. Protein requirements at 24–30 weeks’ gestation are as high as 4 g/kg/day, decreasing to 2–3 g/kg/day by term. Individual amino acids are important not just as building blocks for protein synthesis and net protein balance, but also as essential signaling molecules for normal cellular function. Perhaps most importantly, brain growth and later life cognitive function are directly related to protein intake during the neonatal period in preterm infants. Data are reviewed that document successful increase in protein balance in preterm infants achieved with higher than usual rates of amino acid and protein nutrition, noting that positive protein balance requires at least 1.5 g/kg/day, but there still is increased protein balance up to 4 g/kg/day. Further research is necessary to determine optimal amounts and mixtures of protein and amino acids for both intravenous and enteral feeding to improve growth, development, and functional capacity of preterm infants.

1. Introduction: Special Requirements for Nutrition of Preterm Infants

Medical care and survival of preterm infants, even those born as early as 24 weeks’ gestational age and as small as 500–600g, have improved remarkably. As a result, a continuing and principal medical problem is the need to nourish these infants to achieve healthy growth, often as much as 2–3 kg of body mass over a 12–16 week period. While one objective of such nourishment is to achieve normal intrauterine growth rates as stated by the American Academy of Pediatrics,1 another is to produce healthy body composition and normally functioning cells, tissues, and organs.

2. Are We Providing Sufficient Nutrition to Meet Such Needs?

Increase in body weight of preterm infants clearly is not the best measure of nutritional success, as it...
ignores changes in body composition, and cell and organ development and function. Unfortunately, body weight remains the standard measure of neonatal nutrition; thus the true nutritional needs of preterm infants to optimize their growth and development remain elusive.\textsuperscript{2,3} Recent data from the US National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health and Development Neonatal Research Network\textsuperscript{4} show that preterm infants of nearly all early gestational ages still show postnatal growth delays. This is especially true for the smallest, most preterm infants who are taking longer and longer to start growing after their preterm birth, achieve normal rates of growth, and reach normal body size, even at term gestational age. Furthermore, growth in terms of achieving ideal body composition now is recognized as a major problem early in life, as most of these infants are fed more than sufficient energy for their energy expenditure, including for growth. Such excessive energy intake starts very soon after birth with relatively high rates of intravenous glucose and lipids as part of standard intravenous nutrition regimens. As a result, body fat content of growing preterm infants commonly exceeds that of normal in utero development.\textsuperscript{5} At the same time lean body mass is less well developed in these infants, evidence that considerably more amino acids and protein are required for growth of such tissues than these infants commonly have been fed and that excessive energy intakes do not produce more muscle and bone, only more body fat.\textsuperscript{6}

Such underfeeding of amino acids and protein in preterm infants occurs despite a large and consistent body of experimental evidence showing that increasing amino acid and protein intakes, even during the first day of postnatal life and in infants who are requiring significant medical and often surgical treatments, produces increased net protein balance.\textsuperscript{7-10} Furthermore, early intravenous amino acid and enteral protein feeding shows evidence of enhanced growth, including early head circumference growth and later brain size and neurodevelopmental outcome.\textsuperscript{11,12} As such evidence expands and becomes more generalizable, it increasingly demonstrates that increased nutrition, particularly of amino acids and protein, plays an essential role in improving growth and neurodevelopmental outcome of extremely preterm infants.\textsuperscript{13} Furthermore, growth of lean body components is particularly dependent on protein intake in organs such as the brain. Recent MRI studies have shown strikingly deficient growth of the brain by as much as 40% of total brain volume in preterm infants,\textsuperscript{14,15} findings which are now evident even into adolescence.\textsuperscript{12,16} Such relatively gross measurements fail to show reduced development of neuronal length and dendritic connections, but these have been known for many years to occur in animal models of fetal under nutrition. For example, under nutrition of the rat fetus at critical stages of development permanently limits brain size, brain cell number, and dendritic number and interconnections. Perhaps more importantly, such under nutrition of rat fetuses also leads to reduced later life interactive behavior and cognitive functions such as learning and memory.\textsuperscript{17} Such adverse patterns of growth and development are even more specific in regions of the brain, such as the caudate nucleus, that directly impact cognition. Since a large proportion of preterm infants have some cognitive deficits, it is not surprising that there is a direct relationship between the degree of under nutrition with its slower rates of growth and poorer cognitive function. Importantly for human and not just animal model development, recent studies indicate that very preterm infants, when fed more protein and energy, have remarkable capacity for improved growth, including that of the brain and essential regions in the brain that are particularly related to cognitive outcomes. Lucas’s group\textsuperscript{15} (noted above) followed their experimental cohort of preterm infants, first reported in the late 1980s, into adolescence and was able to correlate directly the amount of nutrition provided to these infants with their adolescent body stature, brain and caudate nucleus size, and cognitive function, even at such a relatively advanced age and stage of development. More research in this area clearly is needed, however, as these observations were true only in males, and only for verbal IQ, not performance IQ. Furthermore, it was not clear whether the beneficial effects of the “high” nutrient diet were due to greater total nutrient intake, greater protein intake, more energy, or a greater supply of some essential component, such as a particular amino acid (e.g., leucine) or a particular lipid (e.g., docosahexanoic acid or DHA).

3. **Does It Matter Whether We Meet the Amino Acid and Protein Needs of Preterm Infants That Would Match Fetal Requirements?**

As noted above, repeated observations have documented less than adequate growth of preterm infants.\textsuperscript{11,12} As such evidence expands and becomes more generalizable, it increasingly demonstrates that increased nutrition, particularly of amino acids and protein, plays an essential role in improving growth and neurodevelopmental outcome of extremely preterm infants.\textsuperscript{13} Furthermore, growth of lean body components is particularly dependent on protein intake in organs such as the brain. Recent MRI studies have shown strikingly deficient growth of the brain by as much as 40% of total brain volume in preterm infants,\textsuperscript{14,15} findings which are now evident even into adolescence.\textsuperscript{12,16} Such relatively gross measurements fail to show reduced development of neuronal length and dendritic connections, but these have been known for many years to occur in animal models of fetal under nutrition. For example, under nutrition of the rat fetus at critical stages of development permanently limits brain size, brain cell number, and dendritic number and interconnections. Perhaps more importantly, such under nutrition of rat fetuses also leads to reduced later life interactive behavior and cognitive functions such as learning and memory.\textsuperscript{17} Such adverse patterns of growth and development are even more specific in regions of the brain, such as the caudate nucleus, that directly impact cognition. Since a large proportion of preterm infants have some cognitive deficits, it is not surprising that there is a direct relationship between the degree of under nutrition with its slower rates of growth and poorer cognitive function. Importantly for human and not just animal model development, recent studies indicate that very preterm infants, when fed more protein and energy, have remarkable capacity for improved growth, including that of the brain and essential regions in the brain that are particularly related to cognitive outcomes. Lucas’s group\textsuperscript{15} (noted above) followed their experimental cohort of preterm infants, first reported in the late 1980s, into adolescence and was able to correlate directly the amount of nutrition provided to these infants with their adolescent body stature, brain and caudate nucleus size, and cognitive function, even at such a relatively advanced age and stage of development. More research in this area clearly is needed, however, as these observations were true only in males, and only for verbal IQ, not performance IQ. Furthermore, it was not clear whether the beneficial effects of the “high” nutrient diet were due to greater total nutrient intake, greater protein intake, more energy, or a greater supply of some essential component, such as a particular amino acid (e.g., leucine) or a particular lipid (e.g., docosahexanoic acid or DHA).

4. **Which Amino Acids and How Much Protein are Necessary for Normal Fetal Development?**

Amino acids and protein are essential for producing normal fetal growth and development, providing the scaffolding for growth of all cells, tissues,
and organs, as well as the structural links among cells (e.g., dendrites among neurons). Amino acids in particular also act as metabolic signals to regulate metabolism, especially to support growth. For example, both intravenous and dietary amino acids (particularly leucine and arginine), alone or in concert with glucose, stimulate insulin secretion, which augments amino acid stimulation of protein synthesis and protein accretion.\(^\text{18}\) Leucine also is an important oxidative substrate\(^\text{19}\) and arginine is the basic substrate for nitric oxide,\(^\text{20}\) which is important for vascular function and blood flow to growing organs. Essential amino acids also are fundamental for production of key regulatory products. Glutamate and serine and other non-essential amino acids, for example, uniquely promote placental and fetal metabolism.\(^\text{21,22}\) Less than normal supplies of amino acids to the fetus not only produce overall fetal growth restriction, but they also can result in life-long consequences of reduced muscle mass and short stature, as well as the likely potential for less than optimal growth of neural tissue, neural connections, and cognitive development (Table 1\(^\text{22}\)).

### 5. What Can We Learn From the Fetus About the Requirements for Amino Acid and Protein Nutrition?

A fundamental concept in nutrition of preterm infants is that nutritional requirements for metabolism and growth should at least match those of the healthy, growing fetus of the same gestational age. While there clearly are unique environmental impositions, medical and surgical interventions, and complicating diseases in preterm infants that might modify nutrient requirements, if a fetus requires a certain amount of protein to grow normal amounts of muscle and bone and other cells and tissues, then this should also be the goal for protein and amino acid nutrition in the preterm infant of the same gestational age.

Studies in animal models have shown that the normally growing fetus is accustomed to large amino acid uptake rates, certainly more than what is customarily fed to the preterm infant of the same gestational age. Such high amino acid uptake rates are necessary to support the uniquely high rates of fractional protein synthesis and growth rates, as shown in Figure 1\(^\text{23,24,26}\) for fetal sheep, which are several fold higher at gestational ages approximating that of 24–28 week preterm infants than they are at term.\(^\text{23,24}\) Amino acids are used for protein synthesis in the fetus, and protein synthesis and net gain of protein are dependent on amino acid supply and fetal plasma amino acid concentrations.\(^\text{25}\) To meet these high rates of amino acid utilization for protein synthesis and growth, amino acids are actively transported into the fetus by the placenta in excess of amounts necessary just for net tissue accretion. Importantly, the excess amino acids not incorporated into net protein balance are used for oxidative metabolism (energy production); in fact, amino acids are second only to glucose and its product lactate.
in their contribution to the consumption of oxygen for fetal energy production.\textsuperscript{19,27} As a result of such contributions to oxidative metabolism, rates of fetal urea synthesis and excretion normally are quite high, indicating that the same should be expected for preterm infants, including relatively higher plasma concentrations of urea nitrogen, who are fed sufficient amino acids and protein to produce fetal rates of protein synthesis, growth, and oxidative metabolism.

Additionally, growth is a highly complex process, not just one of producing more structural protein in cells and tissues, but of very high simultaneous rates of protein synthesis and protein breakdown. Interestingly, while more amino acids (as well as insulin and other anabolic growth factors) promote the synthesis of amino acids into protein, the high protein breakdown rates in the fetus are relatively resistant to suppression by additional amino acids or insulin. Furthermore, inadequate fetal nutrition leads to increased rates of protein breakdown. Thus, while growth is fundamental and requires large amounts of amino acids and protein nutrition for support, turnover of protein also is fundamental, allowing for the necessary remodeling of cells and tissues as they replicate, grow, and link together to form expanding tissues with increasingly interdependent functions.

6. What Happens After Birth to Amino Acid and Protein Metabolism and Nutrition?

Based on these observations of fetal amino acid and protein nutrition and their direct relation to fetal growth, does it matter whether amino acid and protein nutrition after birth is less than that of the normally growing fetus? First, all studies have shown that early postnatal provision of intravenous amino acids to preterm infants produces greater rates of protein synthesis and net protein balance.\textsuperscript{28} This is true up to 3.5 g/kg of protein intake. Since most preterm infants are not fed as much protein as they would have received \textit{in utero} by active placental transport of amino acids, it also is not surprising that nearly all preterm infants end up growth restricted at term gestation, whether determined by fetal growth curves or postnatal cross sectional growth curves.\textsuperscript{29,30} Of more concern is the equally consistent observation that such slower than normal growth is associated with later life neurodevelopmental delays and cognitive deficits.\textsuperscript{31} Fortunately, follow up studies\textsuperscript{11} now are consistently showing that early postnatal supply of amino acids and protein promote linear growth and growth of head circumference and a positive relationship between protein nutrition and neurodevelopmental outcome (see below).

7. Why Are Preterm Infants Not Fed More Amino Acids and Protein in Their Early Postnatal Diets?

It appears that misunderstanding of normal metabolism (mostly ancient history at this point) has limited the amount of amino acids and protein in the diet of preterm infants, particularly immediately after birth. Some investigators refer to older studies by Goldman et al.,\textsuperscript{32} who showed that extremely high protein intakes with formulas of less than optimal quality compared with milk and current formulas, produced metabolic acidosis, excessive ammonia concentrations, uremia, hyperaminoacidemia, growth restriction, and worse developmental outcome. Such observations, despite vast improvements in formula compositions and generally improved medical care of preterm infants, have carried over to current concerns for less than optimal amino acid metabolism, potential toxicity of individual amino acids, metabolic disorders such as uremia and metabolic acidosis, and the need for higher amounts of non-protein calories to support the use of amino acids for protein accretion. Recent research,\textsuperscript{10} however, has shown that such concerns are unfounded. The good news is that today preterm infants are in much better physiological condition than in the period of Goldman’s studies. Protein nutrient mixtures, especially those used intravenously, also are of much higher quality. Furthermore, even the highest rates of protein intake for preterm infants suggested in new studies today are half or more of the rates of protein fed to the infants in Goldman’s studies. It is unlikely, therefore, that Goldman’s studies provide more than a warning about what can happen when reason gives way to unacceptably and irrationally high protein intakes by anyone’s estimation.

7.1. Possibility that amino acids will not be metabolized well

Regarding the concern that protein and amino acids are not well tolerated by preterm infants and will lead to growth restriction, actually, the opposite is true. Recent studies have shown that protein balance in near term\textsuperscript{33} and extremely low birth weight, very preterm infants (most of whom are on oxygen, ventilators, catecholamine infusions)\textsuperscript{10} is improved with adequate amino acid intake (see, for example, Figures 2 and 3 from Thureen et al\textsuperscript{10}) and there is a direct correlation between amino acid supply and protein balance through at least 3.0 g/kg/day (Figure 3\textsuperscript{10}).
7.2. Possibility that amino acids will not be oxidized well

There also has been concern that amino acids won’t be oxidized, leading to high, potentially toxic concentrations of amino acids. In preterm neonates, as in the fetus, there has been concern that amino acids are readily oxidized as fuels (Figure 3).

7.3. Potential for toxic amino acid concentrations

Many have been concerned that higher amino acid/protein intakes will produce excessively high concentrations of certain amino acids that are potentially toxic (e.g., glycine, phenylalanine, methionine). Others have been concerned that excessive intravenous amino acid intake won’t be as well tolerated because the quality (the balance or mix of individual amino acids) of intravenous (IV) amino acid mixtures is not good enough. This would lead to an imbalance of levels causing decreased protein synthesis, interference with amino acid transport, abnormal brain/CSF concentrations that in turn might adversely affect neurotransmitters, and accumulation of toxic metabolites. In contrast, recent measurements of amino acid concentrations in preterm infants fed modern IV amino acid mixtures have lower concentrations of potentially toxic amino acids and, in fact, have concentrations of most amino acids approximating those found in normally growing, healthy human fetuses in both second and third trimesters from umbilical vein samples (Figure 4). However, concentrations of some essential amino acids, particularly lysine and threonine, both essential amino acids and thus regulatory for protein synthesis rates, still are less than normal fetal values (Figure 4) when fed IV with a common commercial IV amino acid mixture used in the USA. It is possible, therefore, that even further improvement in the quality of intravenous amino acid mixtures will promote better amino acid balance and improved growth. This improvement also might extend to enteral feedings as formula manufacturers continue to optimize protein quality in formulas and milk fortifiers (the latter aided by the need for developing simple, accurate, rapid, and inexpensive measures of protein concentration in human milk).

7.4. Possibly excessive uremia

Many also are concerned that higher amino acid/protein intakes in preterm infants will lead to excessive uremia and that uremia will cause harm to these infants. Such fear of uremia probably reflects very old experience with IV and enteral amino acid and protein mixtures that were not of appropriate quality for these infants. Many more such infants were in much worse physiological condition, receiving inadequate energy intakes to provide alternative oxidative substrate and having worse renal blood flow and glomerular and tubular function, than is the case for the majority of preterm infants today. Urea production normally is very high when there

Figure 2 Amino acid intake (expressed as protein intake), urinary nitrogen excretion (expressed as protein excretion), and resulting protein balance at low (1 g/g/d) and high (3 g/kg/d) amino acid intakes. Values expressed as mean ± standard error of the mean. Reproduced with permission from Thureen et al.

Figure 3 By regression analysis, there was significant correlation between leucine intake rate and leucine oxidation rate. Adapted from Thureen et al.
Figure 4  Plasma amino acid concentrations in preterm infants receiving Trophamine at 3 g/kg/d vs. those from normal human fetuses (via percutaneous umbilical vein sampling, data from Cetin et al\textsuperscript{36}) in the second trimester and third trimester. Reproduced with permission from Thureen et al.\textsuperscript{10} VAL = valine; LEU = leucine; ILEU = isoleucine; THR = threonine; PHE = phenylalanine; MET = methionine; LYS = lysine; HIS = histidine; SER = serine; GLY = glycine; ALA = alanine; PRO = proline; ARG = arginine; ORN = ornithine; TYR = tyrosine; GLN = glutamine; GLU = glutamate; ASN = asparagine; TAU = taurine.
are high rates of amino acid oxidation, which increases urea synthesis and excretion rates. The normal sheep fetus, for example, excretes approximately 800 mg/kg/day of urea, which is about equal to 100 mg N/kg/day or about 2.4 g/kg/day of amino acids. Similarly, the normal human newborn infant at term metabolizes less amino acids (per kg body weight) than very preterm infants, yet develops quite high urea excretion rates of about 600 mg/kg/day or about 80 mg N/kg/day (approximately 1.9 g/kg/day of amino acids).37

Furthermore, there is no credible evidence that uremia of the degree commonly seen in preterm infants causes harm (an interesting study, in fact, would be to correlate blood urea nitrogen (BUN) concentrations in preterm infants with neuronal development and neurological and cognitive outcomes). Also, a recent study38 showed that among the usual type of preterm infant, including extremely low birth weight infants with less than 1000 g in birth weight and 27 weeks’ gestational age, there was no correlation between amino acid intake and BUN and there were very few BUN values greater than 40 mg/dL. In fact, BUN only increased modestly (around 5 mg/dL) when amino acid intake was nearly tripled from around 1 g/kg/day to around 3 g/kg/day, which it should do, since amino acids are normal oxidative substrates19,34 that yield ammonia, the source of urea, as well as CO₂ (Figure 5).38

7.5. Potential for metabolic acidosis

Still others are concerned that excessive amino acid and/or protein intake can lead to metabolic acidosi. Most studies have not shown metabolic acidosis in preterm infants fed relatively higher rates of amino acids (Table 2).38 When such acidosis does occur, usually there are other reasons, such as reduced glomerular filtration rate and urine flow rate, severe fluid restriction as often done for hyperglycemia, or the opposite, dilutional acidosis from excessive fluid administration (Table 2).

7.6. Need for higher caloric intake to metabolize the amino acids

There are also those who continue to falsely assume that increasing energy intakes must accompany increasing amino acid/protein intakes or the amino acids and protein will not be incorporated into net protein growth. This is true only at lower non-protein caloric intakes of below 60 kcal/kg/day. Above that level, increased protein intake is the primary determinant of protein gain, while increased non-protein calorie intake (fat and carbohydrate) primarily enhances growth of body fat.41 Furthermore, in one study42 it was noted that increased energy intake improved nitrogen retention by enhancing amino acid reutilization for protein synthesis, a higher quality protein improved nitrogen retention by limiting protein breakdown, emphasizing the primary importance of protein for producing nitrogen retention and positive protein balance. Excessive caloric intake, therefore, does to a preterm infant just what it does to everyone—produces excess fat.

8. But There Always Is Reason for Caution

Infants with documented excessive uremia probably should have their energy intakes, and cardiovascular and renal systems improved before they are advanced beyond the minimum amount of amino acids (approximately 1.5 g/kg/day) needed to prevent

---

**Table 2** Randomized trials of early amino acid administration in very low birth weight infants8,10,39,40

<table>
<thead>
<tr>
<th>Study</th>
<th>Amino Acid Intake</th>
<th>Additional Fluids</th>
<th>BUN, pH, Base Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Lingen et al, 199239</td>
<td>2.3 g/kg/d</td>
<td>vs. control at beginning at 24 hr</td>
<td>Normal BUN, no difference in pH, or base excess</td>
</tr>
<tr>
<td>Rivera et al, 19938</td>
<td>1.5 g/kg/d</td>
<td>vs. glucose within 24 hr</td>
<td>No differences in BUN, ammonia, or CO₂ content</td>
</tr>
<tr>
<td>Van Goudoever et al, 199540</td>
<td>1.15 g/kg/d</td>
<td>vs. glucose immediately after birth</td>
<td>No differences in BUN, pH, or base excess</td>
</tr>
<tr>
<td>Thureen et al, 200310</td>
<td>1 g/kg/d</td>
<td>vs. 3 g/kg/d</td>
<td>No difference in BUN, or base excess</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen.
protein breakdown. In fact, excessive feeding of all substrates needs to be questioned when abundant data demonstrate increased hyperglycemia from too much glucose and obesity from too much energy (lipid plus glucose), as well as the now widely recognized concern that excessive weight gain, primarily of adiposity (and primarily abdominal adiposity that is characteristically found in overfed infants with growth restriction and infants of diabetic mothers), might lead to later life complications of obesity, insulin resistance, and Type 2 diabetes. These problems of obesity and diabetes have reached epidemic proportions internationally. Interestingly, however, there is little data yet that shows that overfed preterm infants who gain excess fat experience adverse outcomes of obesity and diabetes more than the average infant, unless their excessive weight gain continues beyond 6 months to 1 year of life.43 There also is no evidence that simply meeting the growth requirements of amino acids for preterm infants has any bearing on the adverse effects of overfeeding that probably are more related to excessive caloric intake and the earlier development of obesity.

Nevertheless, there have been examples from excessively high amino acid and protein administration to preterm infants that have shown significant problems of metabolic acidosis, growth failure, and reduced neurodevelopmental outcome. Furthermore, attempts to prevent or correct fetal undergrowth with maternal high protein diets actually increases fetal intrauterine growth restriction and fetal and neonatal mortality rates, which also can lead to reduced insulin secretion as adults. Maternal high protein diets can increase fetal intrauterine growth restriction and fetal and neonatal mortality rates and lead to reduced insulin secretion when such infants become adults. Recently, follow-up studies of offspring of pregnant women who were fed either a high protein, low carbohydrate diet or a “standard” diet44,45 showed that the group that ate the high protein/low carbohydrate diet produced infants who, as adults (now in their late 30s), have higher blood pressure, fasting blood glucose concentrations, plasma cortisol concentrations, and hypothalamic-pituitary axis activity, and they were more obese. Too much of a good thing is not always better!

How much protein is too much, however, still has not been determined, although current estimates are that this limit might be around 4 g/kg/day for preterm infants born around 24–28 weeks of gestation, while more mature infants progressively require less as their gestational age approaches term. Furthermore, there is clear evidence that overfeeding of non-protein calories produces more rapid than normal gain of weight at any gestational age; this largely is due to fat deposition in adipose tissue, which increases the risk of later life obesity, insulin resistance, and diabetes. There are limits to all nutrient supplies.

9. How Should We Feed Amino Acids and Protein to Preterm Infants?

Preterm infants need to be fed enough amino acids and protein, starting right after birth, to prevent protein breakdown and to promote the growth and remodeling of cells, tissues, and organs at rates and producing body composition of lean body mass that mimic the growth and body composition of healthy fetuses growing in utero. This means providing amino acids and proteins earlier and in greater amounts after birth than customarily have been provided. IV amino acids should be provided starting as soon after birth as possible at rates appropriate for gestational age: 3.5–4.0 g/kg/day for infants <30 weeks’ gestational age; 2.5–3.5 g/kg/day for infants >30 but <36 weeks’ gestational age; 2.5 g/kg/day for infants >36 weeks’ gestational age. IV amino acid infusion rates can be tapered as enteral feedings advance, keeping total protein intakes at the starting values until growth develops and protein requirements can be re-evaluated. As long as the amounts of amino acids and protein are supplied at rates necessary to support protein synthesis and net protein gain, adverse consequences of both too little and too much protein can be avoided.

Milk is considered highly desirable for feeding preterm infants, but generally needs supplements with protein and other nutrients. For example, estimates of milk protein content, with and without supplements, often are less than the measured protein content, leading to protein intakes that can be as much as 0.6–0.8 g/kg/day less than estimated.46 Without more accurate measurements of milk protein content, therefore, assumed protein intake in infants fed milk (supplemented or not) can significantly overestimate actual protein intake. To compensate for the limitation in protein intake in such milk-fed infants, one group has recommended the simple addition of 1 g of protein (as a high quality liquid or powder supplement) per 100 mL of milk to arbitrarily, but reasonably, increase protein content of supplemented or unsupplemented milk and thus protein intake.47 Very few studies actually have addressed whether protein supplements per se do promote growth in preterm infants. The NICHD Neonatal Research Network11 and the Pediatric organization48 attempted to address this issue by comparing growth in infants fed more protein a few days earlier in one group vs. another group. While these studies
did not show significantly improved growth in the group fed more amino acids earlier, they did not show adverse effects, similar to the many studies of providing greater amounts IV amino acids to such preterm infants and observing a consistent increase in protein balance. It still remains fundamental, therefore, that growth of lean body mass — muscle, bone, brain, and organ mass — cannot increase without more protein, since these structures are built on a protein matrix.

10. Conclusions and Suggestions for Further Research

Further studies are needed to determine and develop optimal mixtures of amino acids for both intravenous and enteral feeding, as well as optimal amounts of total amino acids and protein. Glucose and lipid intakes need to meet energy expenditure requirements, but this generally will mean providing less of these substrates than these infants usually receive. For glucose, maintaining normal glucose concentrations that match those of the normally growing fetus (>50mg/dL, <80mg/dL) might be important for neurodevelopment. Polyunsaturated fatty acids of the ω-3 variety, particularly relative to amounts of ω-6 fatty acids, might be more beneficial for neurodevelopment as well. Future studies also are needed to determine long term outcomes of different rates of growth of different body components, such as adipose tissue and muscle, and include evidence for the rate of development of obesity, insulin resistance, and diabetes, as well as much needed information on brain growth (cellular as well as overall volume) and neuronal, neurological, and cognitive outcomes. When coupled with other studies and reports that are showing little if any adverse metabolic complications, it appears that there is more than sufficient rationale for promoting new research and clinical practice to define the short and long term benefits (and risks) of more optimal nutrition of preterm infants, nutrition that actually meets the requirements for growth as well as maintenance metabolism of these very small infants, right after birth.

References

25. Liechty EA, Boyle DW, Moorehead H, Auble L, Denne SC. Aromatic amino acids are utilized and protein synthesis is


