Nutritional Assessment in Preterm Infants

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Abstract

If the aim of nutritional assessment of preterm infants is to identify suboptimal (or excessive) provision of protein, energy and micronutrients, most currently available methods perform poorly. Assessment of body weight is limited by the confounding effect of fluid status especially in the first few days of life, and measurements of linear growth are relatively imprecise and slow to respond to nutritional changes. Growth assessment is hampered by the lack of an adequate reference standard. Comparisons to historical cohorts of preterm babies are inadequate. As most very low birth weight infants leave hospital below the 10th centile, use of these charts as ‘standards’ almost guarantees that preterm infants will have poor growth. Growth centiles based on data from newborn preterm infants have certain advantages. However, this is hardly normative data as preterm birth is always an abnormal event. Methods of assessing body composition are largely limited to the research setting, and it remains unclear whether the optimum composition of postnatal growth is one that mimics fetal growth or postnatal growth of the term infant. Biochemical nutritional assessments are of limited utility except in the highest-risk preterm infants, when nutritional inadequacy is likely (severe fluid restriction) or where intake is difficult to assess (use of human milk).

Introduction

Nutritional assessment covers two large and divergent areas. The first is the assessment of the adequacy of the nutrition provided to an individual preterm infant, whilst the second compares nutritional outcomes between different groups. The second is often concerned with assessing the effectiveness of an intervention as part of a research protocol, and may utilize complex outcomes. For example, since 2004 a number of studies have examined the effect of different intakes of glutamate or glutamine in preterm infants.
These studies have examined a variety of outcome measures ranging from growth [1] and plasma amino acid concentrations [2], to amino acid or urea kinetics [3, 4], whole body protein turnover [3], stress hormone and CPR levels [3], and compound functional outcomes such as feeding tolerance [5], necrotizing enterocolitis [1], sepsis [1, 5], and mortality [1]. The only of these measures that might be used to assess the glutamate intake in an individual infant are plasma amino acid concentrations, which are not in routine clinical use, or growth that is likely to be a late and nonspecific finding. The other outcomes are either too difficult or expensive to use (amino acid kinetics, protein/urea turnover), or affected by too many other factors (sepsis, mortality, necrotizing enterocolitis) to be useful in individual assessment. In this review, we will consider the first of these areas: the nutritional assessment of an individual preterm infant.

**Growth**

Growth is the most common, often the only, ongoing assessment of nutritional outcome in many preterm babies. It implies a coordinated, regulated change in body size and composition.

*The Importance of Early Growth*

Anyone who has cared for such babies is well aware of the usual pattern of weight change, with an initial loss of weight, followed by a return to positive weight gain, and birth weight being regained by 2–3 weeks of age [6]. In a recent review, Cooke [7] highlights the importance of this early weight loss. He imagines the growth of a hypothetical 27-week 1,007-gram infant who regains their birth weight by 2 weeks (or in a second example by 3 weeks) of postnatal age and thereafter grows parallel to their in utero growth curve. By 37 weeks’ corrected gestational age the infant would weigh more than 500 g less than their birth centile, and in the second case about 750 g less. These simulations are not unrealistic. Ehrenkranz et al. [6] examined the growth of 1,660 preterm infants cared for in 12 NICHD research centers in the mid 1990s. The average time to regain birth weight ranged from 11.6 days (SD 6.6) in infants weighing 1,401–1,500 g at birth, to 15.2 days (SD 12.2) in those weighing 501–600 g at birth [6]. In 27- to 28-week-gestation infants it took approximately 2 weeks to regain birth weight, by which time infants weighed approximately 450 g less than their birth centile. In 26- to 27-week infants birth weight was regained by 2–3 weeks of age by which time the weight deficit was about 450 g, a difference that increased to 750 g by 32 weeks’ corrected gestational age.

Embleton et al. [8] confirmed the importance of nutrition and growth in the first few weeks of life. In preterm infants ≥31 weeks’ gestation weight declined by 1 standard deviation score by 2 weeks of age, and thereafter remained relatively constant. In more immature infants (<30 weeks) weight
grew by 1.2 standard deviation score by 3 weeks and afterwards remained fairly constant. Maximum energy (335 kcal/kg) and protein (12 g/kg) deficits were reached by 1 week of age in more mature infants (≥31 weeks). In the less mature (≤30 weeks' gestation) infants similar energy and protein deficits were seen by 1 week of age (406 kcal/kg and 14 g/kg, respectively), but these continued to increase throughout hospitalization reaching 813 kcal/kg and 23 g/kg, respectively, by 5 weeks [8].

It also seems possible that early energy intakes have significant long-term effects. Brandt et al. [9] studied 46 small for gestational age very low birth weight (VLBW) infants. Sixty percent of the infants showed catch-up head circumference (HC) growth, and this was associated with better developmental outcome and higher energy intakes between day of life 2 and 10. Indeed, energy intake on days 2 though 4 were significantly associated with developmental quotient at 18, 24, 36, 48, 60 and 72 months of age.

Few prospective interventional studies have focused on early manipulations in nutrition. One exception is the study of Wilson et al. [10] who examined the effect of a variety of changes in nutritional practices, and compared the effect of ‘aggressive’ nutritional support versus the prior ‘control’ practice. This aggressive support included a variety of measures such as use of higher glucose concentrations, starting parenteral amino acids and lipid earlier, advancing to higher amino acid infusion rates, use of early low-volume trophic feeds, and more aggressive management of hyperglycemia.

The aggressive support led to higher energy, glucose, lipid and amino acid intakes but total fluid intakes were comparable between the two groups. Aggressive nutritional support also reduced the maximum weight loss (5.1 vs. 8.4%), reduced the time to regain birth weight (9 vs. 12 days), improved growth, and reduced the percentage of babies with a weight (38 vs. 56%) or length (33 vs. 57%) less than 3rd centile at discharge or death. Although the ‘aggressive’ support had an excess of sick babies at birth (judged by the CRIB score) there was no difference in most clinical outcomes between the groups, but for those infants that survived the first week, the odds ratio of bacterial or fungal sepsis was lower in the aggressive nutritional support group [10].

**Growth Assessment**

**Weight**

Weight can be easily measured and is the most usual (sometimes the only) growth parameter measured in preterm infants. Its accuracy can be improved by being carried out in as standardized a fashion as possible – naked, disconnected from the ventilator and immediately prior to a feed. However, even small errors can overwhelm ‘real’ changes in small preterm infants. The presence of an endotracheal tube or a full bladder may lead to larger weight changes than the real underlying growth of small infants.
Weight is affected by changes in hydration, a factor that is very important in the first few days of life where total body water usually decreases, or in sick septic babies where edema may be a problem. Term infants typically lose 10% of their body weight in the first few days, and preterm infants may lose 15–20% [11]. Although much of this reflects short-term changes in hydration, up to half the weight lost may be due to mobilization of lean tissue, glycogen and fat stores to compensate for inadequate nutrient intakes in the first few days after birth [11].

Although weight is typically measured daily it is important to consider the weight trend over several days. One way to do this is to calculate the rate of weight gain or weight velocity (in g/kg/day) over several days. This has the advantage that changes in weight velocity are much more sensitive in identifying changes in growth than examining weight plotted on growth curves [7]. Regular assessments of growth velocity averaged over the previous 5 or 10 days can help in the early identification of failure, and in monitoring the response to nutritional interventions.

**Linear Growth**

Measures of linear growth, such as crown–heel length (CHL), are generally considered the most sensitive measures of the adequacy of nutritional intake [7] and are relatively unaffected by changes in fluid status [11]. CHL is typically measured using a recumbent length board. The infant is placed supine on the board and their shoulders and knees gently pressed into the board. The head is held against a fixed headboard, and a moveable footplate that can slide up the board gently rests against the soles of the feet that are held at 90° to the length board [6, 11].

In a research setting the reproducibility of CHL measurement is good, with a co-efficient of variation of 0.41% and a 95% confidence interval of ±4.5 mm [12]. In other words, if a measurement of CHL is more than 4.5 mm greater than a previous measurement this would be due to chance in only 5% of instances. A difference in CHL measurement of this amount is, therefore, likely to represent real growth. As 4.5 mm represents between 3 and 4 days' CHL growth [6, 12], there seems little to be gained by carrying out CHL measurements more frequently than twice weekly. The reproducibility of CHL measurement in a clinical setting is likely to be worse, as few units have the luxury of having all CHL measurements made by the same team. Given this, the typical clinical practice of weekly CHL measurements seems reasonable.

Ehrenkranz et al. [6] reports serial CHL measurements in preterm infants, showing a steady increase from birth. The average rate of length gain was approximately 1 cm/week [6], significantly greater than the 0.69–0.75 cm/week increase seen in term infants in the first 3 months of life [11].

Due to the difficulties of measuring CHL in preterm infants, other measures of linear growth have been examined including foot length [13], elbow–wrist length [14], crown–rump length [15] and knee–heel length (KHL) [12]. The
reproducibility of KHL measurements in a research setting is poorer than CHL reproducibility, with a 95% confidence interval equal to 12–13 days’ growth in KHL. Reproducibility is worse in large more vigorous babies, but does improve with practice [12]. KHL growth appears to be nonlinear and to exhibit growth spurts of variable duration that are not related to changes in nutrition [16]. The same, however, may be true of other measures of ‘linear’ growth.

**Head Circumference**

HC is measured using a tape measure and is the largest occipital-frontal circumference measured above the brow ridges. Three measures are made, and the largest recorded [6, 11]. HC is a good measure of brain growth and is largely unaffected by changes in fluid status [11].

HC appears to increase at a rate of 0.89–1.00 cm/week in VLBW infants [6], rather more than the 0.5 cm/week seen in term infants during the first year of life. The rate of HC growth tends to increase with increasing postnatal age, with this effect being most apparent in the infants of lowest birth weight [6].

**Mid-Arm Circumference**

Mid-arm circumference (MAC) is a relatively infrequent measurement in preterm infants. However the data of Ehrenkranz et al. [6] provides useful reference data. MAC growth averaged 0.39–0.45 cm/week in infants weighing between 501 and 1,500 g at birth, although the rate was somewhat less for the 1,401- to 1,500-gram cohort (a pattern also seen for length and HC growth in this population) [6]. MAC decreases during the first 1–2 weeks of postnatal length, presumably reflecting either the changes in hydration or the suboptimal early energy intake seen in such populations. After this, MAC growth accelerates until it reaches a phase of linear rise. This stage is reached earlier in larger infants, beginning at approximately 3–4 weeks in 1,301- to 1,400-gram birth weight infants, but not until 10 weeks in 501- to 600-gram birth weight infants.

**Growth Standards for Preterm Infants**

In order to measure growth in preterm infants one needs a standard to which to make comparisons. There are three main choices of such a standard: (1) normal fetal growth, (2) growth of a peer group of (preterm) infants and (3) growth of term infants.

**(1) Fetal Growth Standards**

A variety of fetal growth standards exist, but there are many problems with them [7, 17]. Growth of the fetus can be assessed indirectly using ultrasound measurements, but these are prone to both ultrasound/operator errors as well as errors in the algorithms used to convert ultrasound parameters to weight measurements. Alternatively curves can be estimated using cross-sectional
data on the birth weight of ‘normal’ preterm infants. However, preterm delivery is a highly abnormal event and is often the result of fetal compromise (poor interval growth, signs of fetal distress, ascending infection, multiple gestations) or maternal illness (pregnancy-induced hypertension, HELLP syndrome). Many of these factors may impair placental function and fetal growth and distort the data used to construct growth charts.

Although the American Academy of Pediatrics [18] recommends nutrients to ‘approximate the rate of growth and composition of weight gain for a normal fetus of the same post-menstrual age, and to maintain normal concentrations of blood and tissue nutrients’ the definition of normal fetal growth is unclear [11, 17]. One of the earliest growth charts is that of Lubchenco et al. [19], based on 5,635 premature babies born at high altitude in Denver, Colo. Based on this dataset, fetal growth was estimated to be about 15 g/kg/day between 27 and 34 weeks’ postmenstrual age. Since then a number of other studies have questioned this value [see also 17], the three largest (each studying over 1 million births) are summarized above (table 1).

The more recent studies suggest that the growth rates from the Lubchenco data set are too conservative. It has been suggested that a more appropriate value is 16–17 g/kg/day [17]. Although there may appear to be little difference between growth rates of 15 and 17 g/kg/day these can have a substantial cumulative effect of growth. For a hypothetical 1,007-gram 26-week infant who regains their birth weight by 2 weeks, a growth rate of 17 g/kg/day will equate to a total weight more than 240 g greater by 37 weeks’ corrected age compared to if the growth rate had been 15 g/kg/day [7].

Term-born infants also lose weight after birth and take time to regain it; this is not taken in to account in the above calculations. We can calculate the growth rate for a 1,000-gram 27-week infant to catch up with a term-born infant by 44 weeks’ postconceptional age, by which time the average weight of term-born males is 4.4 kg [25]. By choosing this time as a target we can account for the initial weight loss that occurs in term infants. The growth rate required for the

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**Table 1.** Growth rates from three large studies of birth weight of preterm infants, compared to the data of Lubchenco et al. [19]

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size</th>
<th>Growth rate (27–34 weeks) g/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubchenco et al. [19]</td>
<td>5,635</td>
<td>14.9</td>
</tr>
<tr>
<td>Hoffman et al. [20]</td>
<td>1,164,871</td>
<td>11.2 (African American females)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.7 (African American males)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15.4 (Caucasian females)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15.7 (Caucasian males)</td>
</tr>
<tr>
<td>Arbuckle et al. [21]</td>
<td>1,087,629</td>
<td>16.3 (males)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.9 (females)</td>
</tr>
<tr>
<td>Alexander et al. [22]</td>
<td>3,134,879</td>
<td>20.0</td>
</tr>
</tbody>
</table>
preterm infant to catch up with the term-born infant will depend on the time it takes the preterm infant to regain its birth weight (table 2). If there is a period of poor growth, subsequent rates of weight gain will need to be higher to achieve catch-up, and the effects of this are larger the later the slow growth occurs. For example, if we consider our 27-week 1,000-gram infant who regains birth weight by 2 weeks, a growth rate of 14.21 g/kg/day will ensure catch-up with a term-born infant by 44 weeks. However, if this infant has 5 days without growth (say due to feeds being held for a septic episode) during days of life 40 through 45, the subsequent rate of weight gain to ensure catch-up by 44 weeks’ corrected age will be 15.18 g/kg/day. If the same insult occurs between 60 and 65 days of life subsequent growth will need to be 15.54 g/kg/day, 16.32 g/kg/day if it occurs between 80 and 85 days of life, and 19.35 g/kg/day if it occurs between 100 and 105 days of life.

We therefore have targets for postnatal growth ranging from 13–14 g/kg/day to as high as 20 g/kg/day. What is clear is that these lower targets will only be successful if they are achieved every day without fail. They do not allow for a few ‘bad days’ let alone bad weeks; e.g., when feeds are held for sepsis workup, growth is slow because the infant requires 200 ml/kg/day of fortified human milk rather than the 160–180 ml/kg/day that we expected to be sufficient, and because of the numerous other causes of suboptimal intake [8]. It is also clear that our current goal of growth of 15 g/kg/day is failing to prevent most preterm babies from having suboptimal growth in hospital [8] and being discharged home profoundly growth retarded. Increasing our targets for acceptable postnatal growth to 16–17 g/kg/day [17] seems the least we can do in response to this failure.

(2) Peer Growth Charts

These charts represent the observed growth of historical cohorts of preterm babies. One of the earliest was the growth grid of Dancis et al. [23] published in 1948. This was limited in the gestational age of infants studied (all >29 weeks) and the duration of the study (50 days). As with all such

<table>
<thead>
<tr>
<th>Time taken to regain birth weight, days</th>
<th>Required growth rate g/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>13.32</td>
</tr>
<tr>
<td>14</td>
<td>14.21</td>
</tr>
<tr>
<td>21</td>
<td>15.24</td>
</tr>
<tr>
<td>28</td>
<td>16.42</td>
</tr>
</tbody>
</table>

Table 2. Growth rate required for a 27-week 1,000-gram infant to catch up with a term infant by 44 weeks’ corrected age, depending of the time taken to regain birth weight.
charts it reflects the varied nutritional practices carried out at the time, and is
difficult to extrapolate to other populations and nutritional practices. A num-
ber of similar charts have been constructed [see 11], including the recent
large dataset of Ehrenkranz et al. [6] which included 1,660 VLBW (birth
weight ≤1,500 g) infants cared for at 12 NICHD research centers in
1994–1995. Although it provides considerable useful data it reflects nutri-
tional and neonatal practices from that period, and in those centers, that may
not be applicable now. In a similar NICHD cohort, growth failure (weight
<10th centile at 36 weeks’ corrected age) affected between 83 and 100% of
VLBW infants depending on birth weight and study center [24]; these postna-
tal growth standards can therefore at best be considered ‘typical’ growth
rather than optimum growth [11], as an infant growing along their centile line
on this chart is almost certain to leave hospital with growth failure.

One advantage of postnatal growth standards is that they allow the weight
to be plotted daily [11] and encourage caregivers to focus on growth as an
integral part of daily management. However, a baby that is consistently grow-
ing along a postnatal chart centile line is no cause for celebration; in the
absence of evidence of catch-up growth towards their birth centile, the baby
is extremely likely to leave hospital weighing less than the 10th centile.

(3) Term Infant Growth Charts

The US Centers for Disease Control and Prevention and the National
Center for Health Statistics have recently produced revised growth centiles
for males and females from birth to 20 years of age [25] (see http://www.
cdc.gov/growthcharts). Some preterm babies may remain in hospital beyond
their expected date of delivery, particularly those with severe chronic lung
disease or multiple anomalies. These infants can be plotted on the CDC
charts to allow comparison with term-born infants. Growth charts for weight
for age, length for age, HC for age, weight for length, and body mass index for
age are available for boys and girls between birth and 36 months. These
charts probably remain the best way to compare growth of VLBW infants to
their term counterparts [26].

Assessment of Body Composition

Much of the preceding discussion has concentrated on issues of weight
gain, which will prompt concerns that weight changes may reflect ‘only’
changes in fat mass or fluid status. The AAP reflects this concern by stating
that the goals for nutritional management of preterm infants are ‘to approxi-
mate the rate of growth and composition of weight gain for a normal fetus of
the same postmenstrual age’ (emphasis added) [27]. It is unclear whether this
goal is either achievable or desirable, and if so, how one can assess body com-
position in the clinical setting.
It is known that the composition of fetal growth changes, with more fat and lean tissue being deposited as gestational age increases [28]. In general, lower protein intakes and higher energy intakes lead to a relative increase in growth of fat mass – a pattern more consistent with the term infant than with the fetus [28]. It remains unclear however what composition of growth is more appropriate for the preterm infants. Unlike the fetus, the preterm infant is transitioning to a situation where considerable amounts of energy are expended on maintaining body temperature, and nutrient supply is changing from a continuous supply of calories to an intermittent supply of more fat-based calories [28]. Given that, it is possible that growth approximating the growth of the term infant (40% fat) is more physiologically sound than that approximating fetal growth (15% as fat). Definite data is, however, lacking. What is clear is that the composition of body weight change can vary widely in response to nutrient intake, even if changes in absolute body weight are very similar [28, 29]. When preterm infants are compared to the reference infant of the same age they have much lower lean mass, lower bone mineral mass but similar fat mass. If comparison is made to the reference infant of the same weight, they have normal lean mass, but increased fat mass and reduced bone mineral mass [30]. It seems likely, therefore, that current nutritional management leads to lower levels of bone mineral and lean tissue growth compared to the reference infant.

The different methods of measuring body composition in preterm infants are reviewed elsewhere [31], although most such techniques remain limited to use in research studies. There are few clinically applicable methods of assessing body composition in individual preterm infants, and those that have been used such as urine creatinine excretion (as a measure of lean mass) [32] and skinfold thickness (as a measure of fat mass) [31] remain unvalidated in preterm infants.

In clinical practice, ‘normal’ body composition is often assumed if weight, length and HC growth occur in parallel. Precise simple reproducible measures of lean mass and bone mineral mass might help identify interventions that might optimize both quantitative and qualitative aspects of growth, as well as help identify individual preterm infants who might benefit most from these interventions. Similarly, the ability to use methods such as dual X-ray absorptiometry might improve our nutritional management. However, the literature is unclear on what body composition is optimal for the growing preterm infant, and how effective interventions aimed at ‘correcting’ abnormal body composition might be.

Biochemical Assessments

A wide variety of biochemical measures have been used to assess nutritional adequacy in adults and older children. Some appear to work well in
preterm infants, for example serum copper slowly increases with age, and a low serum copper is a useful measure of copper deficiency. Other measures perform much less well, either because the appropriate ‘normal’ range is unclear, or because they are intrinsically poor measures of status in this age range.

Assessment of Bone Mineral Status

Serum calcium, phosphorus, and alkaline phosphatase are often measured to assess bone mineral status. Serum phosphorus is relatively responsive to dietary changes [33], more so than serum calcium which is under tight homeostatic control. Serum alkaline phosphatase is produced by bone, muscle and intestine. The bone isoform constitutes about 50% of total alkaline phosphatase, and is taken to be a marker of bone formation. Neither total, nor bone, alkaline phosphatase activity are particularly useful measures of bone mineral accretion, and they explain very little of the variability in bone mineral content [33]. Very high alkaline phosphatase levels are usually accompanied by radiological evidence of osteopenia.

One reason that alkaline phosphatase activity continues to be measured is that high levels (>1,200 IU) have been associated with long-term growth failure [18]. It is understandable, therefore, that clinicians would wish to respond to such a finding, for example with calcium and phosphorus supplementation. It is not known, however, whether doing so has any long-term effect on growth.

Routine measurements of calcium, phosphorus, and alkaline phosphatase are probably of limited value. Anecdotally, abnormal findings are rare in most preterm infants (>28 weeks’ gestation) who are receiving appropriate levels of preterm formula without fluid restriction. These measurements may be more useful when mineral intakes are less certain (e.g. human milk feeding, fluid restriction).

Assessment of Protein Status

Blood urea nitrogen (BUN) and serum albumin have traditionally been used as a measure of protein status. However, serum albumin has a half-life of 2–3 weeks and a turnover too slow to be a useful way of monitoring the response to nutritional interventions. Theoretically, prealbumin (with a half-life of a few days) and retinol binding protein (with a half-life of about 12h) would be more responsive. Indeed in a research setting, BUN [34] and retinol binding protein [30] reflect changes in protein intake, whilst serum albumin and total serum protein do not [34].

Routine monitoring of BUN and of serum proteins rarely produces abnormal values in larger (>28 weeks’ gestation) formula-fed preterm infants. It is possible that measurement of BUN, serum retinol binding protein or prealbumin may help to identify suboptimal protein intake in subjects whose intake is questionable (e.g. severe fluid restriction) or unclear (human milk-fed infants).
Acknowledgements

This work is a publication of the US Department of Agriculture (USDA)/Agricultural Research Service (ARS) Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Tex. This project has been funded in part with federal funds from the USDA/ARS under Cooperative Agreement No. 58-6250-6-001. Contents of this publication do not necessarily reflect the views or policies of the USDA, nor does mention of trade names, commercial products, or organizations imply endorsement by the US government.

References


Discussion

Dr. Rivera: When talking about in utero weight gain we are also ideally talking about weight gain in relation to growth, because the fetus and the newborn don’t come from a necessarily healthy environment. Many of these infants, especially preterm babies, come from an environment in which several factors affect in utero growth. From your point of view what would be ideal?

Dr. Griffin: We know that our babies ex utero are growing at a very different rate than they are in utero, which may mean that the appropriate composition of their body growth has to be different than it would be in utero. Clearly in babies born preterm their growth may not be representative of the growth of a healthy normal fetus, but also their body composition may be different. Because they start at a different developmental stage than the healthy normal fetus, the ideal composition of their subsequent growth might also need to be different.

Dr. Cooke: Should we be talking about growth in absolute terms, grams per day, or as a function of body weight, grams per kilo per day? Current recommendations are
that infants gain at a rate which parallels that in utero, i.e. \( \sim 17 \text{ g/kg/day} \) \[1\]. Yet, when body weight is suboptimal, e.g. the small for gestational age or postnatally growth-retarded infant, the infant falls progressively away from the intrauterine curve despite a gain of \( \sim 17 \text{ g/kg/day} \). Growth rates should be expressed in absolute terms at a rate which at least parallels that in utero, perhaps even greater if an infant is to achieve their original birth weight percentile.

**Dr. Griffin:** Historically the reason for expressing growth in grams per kilogram per day was the Lubchenco data that say that the number was pretty consistent from 27–34 weeks. You are right, grams per day may be more appropriate but the targets are constantly moving. As it is much easier to remember 15 g/kg/day than 8 or 10 different targets depending on what week of life the baby is. Practically I think we need to make a compromise and stick with grams per kilogram per day.

**Dr. Cooke:** Maybe this is one of the reasons we don’t do so well. Growth is not consistent throughout gestation, in either rate or composition \[2\]. Averaging it over a period, then relating needs to suboptimal body weight, may ensure that the infant receives too little or too much at the wrong time, hence poor growth that is commonly observed in these infants.

**Dr. Griffin:** That is right but even if we take relatively conservative goals for protein and energy intake and goals that are much lower than Dr. Ziegler presented early on, we are consistently failing to meet those intake goals, as your data from Newcastle show \[3\]. I think our first goal should be to meet those intake goals and then see if we still have the problem.

**Dr. Cooke:** Preterm infants fed a nutrient-enriched formula after hospital discharge achieve a rate and a composition of growth similar to the term infant at the same corrected age \[4, 5\]. Whether it is possible to achieve this earlier in life is not clear. Until the protein and energy requirements are better defined we are unlikely to do so.

**Dr. Putet:** You showed us the weight gain composition of the fetus between 25 and 30 weeks gestational age and in this composition there is a lot of water, 75–80%. Does postnatal growth need this amount of water? As far as there are protein deposition and lean mass, the same as in utero, can we accept the idea that the premature infant may grow on his own curve, minus 2 deviation standards up to 36 weeks for instance? At this time the water content of the weight gain composition of the fetus is much less and the baby will catch up by that time. Your aim was to wait for up to 44 weeks. What do you feel about this?

**Dr. Griffin:** You are right, if our goal is to match the body composition of the fetus then all our babies need a lot more total body water and I don’t think that practically or clinically it is anything that any of us want to do. Comparing ex utero with in utero is more helpful.

**Dr. Saavedra:** What should our targets be? Whatever the target we aim for, should it be a minimum or an ideal target? To what extent is the conservative approach to increasing feedings related to falling short of reaching our targets, particularly given the fear of necrotizing enterocolitis? Many people are convinced that either going too fast or giving a high caloric density is associated with the risk of necrotizing enterocolitis. Does this actually contribute to this very slow increment of feedings in the first couple of weeks?

**Dr. Griffin:** Necrotizing enterocolitis is the disease that neonatologists have an understandable fear about: in the morning the baby is completely well, and 2 h later the entire bowel is dead; this fear modifies everybody’s behavior to feeding. Neonatologists are also very attached to specific numbers and one of these numbers is 20 ml/kg/day, which is how much you increase feeds. Of course there are now randomized control data that advancements of 30 ml/kg/day are probably just as safe
and lead to full feeds sooner and more rapid reattainment of birth weight [6] as 20 ml/kg/day. But this number is just so engrained in neonatologists that I don’t know of anybody who is doing 30 g/kg/day. I also think that because of the fear of necrotizing enterocolitis this cautiousness could well be counterproductive. Fear of feeding the baby for the first 4 or 5 days of life (or even longer) will result in a sick gut as well as an ailing baby, and it would not be a big surprise that feeding is then sometimes not successful.

**Dr. Dhanireddy:** You have shown various ways of plotting growth. Can you recommend a growth chart or should we ask the obstetrician to send his intrauterine growth chart and continue to follow that? Maybe our goal should be to match intrauterine growth rather than use the Lubchenco growth charts or various others.

**Dr. Griffin:** I think a lot of those fetal grids are based on preterm baby cohorts. I don’t really think that they are very informative as it gives a false sense of security. Calculations of growth velocity and particularly trying to project those forward in time to say growth continuation at this rate is what is wanted at the time of discharge, or at the time of term, will perhaps give us a clearer idea.

**Dr. Dhanireddy:** There is no growth velocity chart?

**Dr. Griffin:** No there isn’t, but it is easy enough to calculate.

**Dr. Hentschel:** You mentioned several biochemical markers of how to follow infants that are poorly growing. Does amino acid analysis play a role in a poorly growing infant if you consider keeping that infant on parenteral amino acid solutions?

**Dr. Griffin:** I don’t think amino acid concentrations are useful except in very rare circumstances – very high protein intake (to avoid toxicity) or as a research tool.

**Dr. Cooke:** In children and adults, when protein intake is low so is blood urea nitrogen (BUN), unless renal or fluid status is compromised [7]. Although the situation is less clear-cut in preterm infants [8], a more recent study by our group suggests that there is a clear relationship between protein intake and BUN in the otherwise normal preterm infant [9]. In effect, BUN can be used as a measure of the adequacy of protein intake, an area that has recently been addressed by Ziegler et al. [10]. I wonder if Dr. Ziegler would like to comment?

**Dr. Ziegler:** The relationship between protein intake and BUN in premature infants unfortunately is not very tight. We used it anyway because monitoring BUN has its advantages. If the BUN is very low, one can be sure that protein intake is inadequate, and if the BUN is very high, it would be prudent to reduce protein intake.

**Dr. Haschke:** Now I am confused. What is a good reference for BUN? Is it the breastfed infants during the first 2 months of life, the healthy term breastfed infant? What should it be?

**Dr. Cooke:** I really was thinking of an adequacy of protein intake in relationship to BUN. What do we use in the preterm infants? We know that BUN in the first 48–72 h of life probably is a better reflection of renal function and it changes with time. Later on, when we vary protein intake in preterm infants there is a linear relationship. A cut-off is chosen, and as you well know working with Dr. Ziegler for a long time, nobody could decide whether we should be aiming for 2–4 mmol. We saw a large group of preterm infants receiving fortified human milk, and their BUN ran at 1–2 mmol which to me is low. Translating that into milligrams per deciliter, I am thinking of 6 mg/dl less. By using this arbitrary cutoff, I increase intake in these babies and the BUN increases and the growth velocity improves.

**Dr. Ziegler:** We don’t have standards for urea concentration in the first 2 or 3 weeks of life for the premature infant. There are many factors that influence BUN. The glomerular filtration rate starts very low and increases gradually so by 3 weeks on average infants reach a normal glomerular filtration rate. Hydration status and protein intake are just some factors that influence BUN. So we don’t have standards, but we
know that if BUN is very low, the interpretation is inadequate protein intake, and if it is very high then we would reduce protein intake, regardless of the actual reason for the high BUN. But the real question that I want to ask is how do you increase protein intake in practice?

**Dr. Griffin:** In practice we would give more energy and protein – more formula in formula-fed babies or more fortified breast milk (or more multi-component supplementation) in human milk-fed babies. We would rarely increase protein independently of energy so usually they would both go together and it’s a moot point whether energy or protein is the issue because our response to that is going to be the same. For babies who are profoundly fluid restricted we would occasionally use modular protein supplements but overwhelmingly the response would be to increase the volume or density of formula or fortified expressed breast milk.

**Dr. Fusch:** Skin-fold thickness is not so bad for preterm and term infants and can be easily made and the measurements are quite reliable. It seems that nutrition is more or less adequate or approaching adequacy. In the data from Ulm a large variation exists between different neonatal units in Germany regarding when and at what body weight children are discharged. There are considerable differences even if the discharge age is standardized. What is the current practice in the different units for adjusting the amount of feed? Often the amount of feed the baby should get enterally is not calculated everyday but if the amount has been the same for 3 consecutive days then the staff is alerted and feeding is increased. I would like to know how often this happens and if this can explain some of these effects, especially in infants growing stably who have a reduced risk of necrotizing enterocolitis?

**Dr. Griffin:** When we write feeding orders, we do it everyday but that is not optimal because we make rounds in the morning and the baby was measured the night before. So we are always half a day behind their actual weight but it is a consistent half a day. If we think we should give 120 kcal/kg/day that is mostly based on yesterday’s weight, not on today’s weight.

**Dr. Putet:** I agree that urea is a very good marker when it is low. When the premature infant is getting 130 kcal/kg/day we do not increase the volume; we just increase the protein intake if urea is below 2 mmol because we believe that it is really the protein which is deficient. We use only human milk fortifier.

**Dr. Cooke:** I was thinking about your question on weight. Should we use actual or expected weight to estimate nutrient intake? Many preterm infants are growth retarded, either at birth or postnatally. Intakes and target growth rates related to a suboptimal weight will always underestimate the needs and growth potential of these infants [11]. Perhaps what we should be using is expected rather than actual weight as Dr. Griffin points out.

### References