Guidelines for Nutritional Care in the NICU: Author-Led Cases

✦ Course Transcript ✦

Course Introduction

Berthold Koletzko, MD, PhD: It's a great pleasure to welcome you to this exciting course on nutritional care of the preterm infant. The goals of this course are to present to you current knowledge on preterm nutrition and its impact on the outcome of our patients. We are sharing the latest guidelines designed for implementation to the practice of nutritional care. They are provided by some of the leading international experts in the field.

Why are we focusing on this? Well, there is increased attention to nutritional care of preterm infants all around the world. It follows the wonderful developments of improvement of survival of preterm infants all around the world. You see in this slide data from China and the United States, where we have the same development over time—a marked improvement of survival. And in this situation, long-term outcomes get increased attention, and that leads directly to a greater focus on nutritional care, which we know markedly affects outcome.

This course is based on the recently developed new global guidelines on *Nutritional Care of Preterm Infants.* These recommendations, developed in 2021, were built on 3 previous editions since the 1990s, first coordinated by Professor Reginald Tsang, then in Cincinnati, who then handed over this exercise to me. The current guidelines were developed by leading global experts from all 5 continents. The recommendations are not only the recommendations of individuals, but they were critically peer reviewed in a very careful process, and they were adopted in a formal consensus process by all the experts that worked together.

In these new recommendations, we have a few changes, with more emphasis on parenteral nutrition starting from the first day of life, more emphasis on meeting protein needs with an early start of amino acid supply, an increased phosphor supply, [with an] emphasis on early supply of lipid emulsions, and higher intakes of long-chain polyunsaturated fatty acids, prioritization of mother's own milk with fortification, and more attention to feeding after discharge. So, look forward to all these details in different modules.

I want to thank the authors and presenters that helped make this course become a reality, and I want to thank you all for participating in this course, and for also translating the acquired knowledge and the skills into the practice with your patient care. To facilitate that, we also offer you case studies. I really encourage you to go to these case studies. I trust you will enjoy the exercise.

Nutrition, Growth and Long-Term Outcomes

Tanis Fenton, PhD, RD: Good day, everyone. My name is Tanis Fenton. I'm a professor at the University of Calgary in Canada. Today I'm going to talk about our chapter *Nutrition, Growth and Long-Term Outcomes.* I want to give a nod to my 2 coauthors who added very important contributions to this chapter. The subtitle of the chapter is *The Importance of Growth Monitoring*.

So, let's talk about preterm infants. They grow very fast. They actually grow twice as fast as the next fast-growing humans, which are term infants. Preterm infants can double their weight or even triple their weight in 2 or 3 months, where term infants take about 3½ months to double their weight. In this time of very rapid growth, preterm infants need nutrients, and the best estimate of the nutrient amounts they need are the amounts to replicate fetal accretion. There may be intelligence coming in the future with perhaps an even better rate of nutrient accretion, but at this point in time, fetal accretion is the best estimate.

Guidelines for Nutritional Care in the NICU: Author-Led Cases

Some infants grow slower than others. At birth, some are small due to genetics, and others are small due to factors related to the pregnancy they have just emerged from. There are many factors that contribute to their growth when they're in the NICU. Because there are various growth potentials, we really need to be aware of [utilizing] a 1-size-fits-all categorization to consider the growth of these infants.

I'll say a few words about commonly used growth charts, including the one that a colleague and I developed in 2013, and also a colleague's chart that was published in 2010. Both of these growth charts have segments based on the growth of the fetus, based on the size of infants at birth starting at 22 to 23 weeks, and then after term age. Both of the charts use the WHO [World Health Organization] growth standard. Both illustrate the growth goal, which is to grow similarly to the fetus and then similarly to the term infant.

These charts are usually used for growth monitoring, but they're also used to assign the size at birth in terms of small, appropriate, or large size at birth for their gestational age. Both our charts and the Olson charts can be used. Our charts can be used for this purpose from 22 to 36 weeks, and the Olson charts can be used for this purpose from 23 to 39 weeks.

Because of many requests for a more comprehensive age range for assigning size at birth, we've prepared our original meta-analysis up to 42 weeks. It extends from 22 to 42 weeks. This data and charts can be downloaded from our webpage at www.ucalgary.ca/fenton (Fenton with a small letter [f]). You can download that information for free. They range up to the full ranges of ages at birth.

To explain a bit more about my [Fenton] growth chart, it was developed using meta-analysis techniques based on 3.9 million births. Under [the] 30 weeks we had 34,000 births that occurred in Australia, Canada, Germany, Italy, Scotland, and the US between 1991 and 2007. We combined the curves from that 6-country meta-analysis with the WHO growth standard, using some smoothing based on a validation study we used with over a thousand very preterm infants. That validation study showed that infants do not slow down at term and have a weight loss after 40 weeks as term babies do.

These growth charts are available for download from that same webpage.

The Olson charts are very similar. They used original data, which is also included in our growth charts. But instead of smoothing at term, they left a gap between 39 and 40 weeks. You can see the differences between their original data and the growth standard and plot right across that interval.

One thing I'm going to talk about today is the concern that healthcare practitioners have about preterm infants being at higher risk of obesity compared to term-born infants. They've been concerned that preterm infants are at higher risk of obesity for 2 reasons. One is the hypothesis that's referred to as the developmental origins of health and disease. The second reason is that preterm infants have a higher percent of body fat at 40 weeks postmenstrual age.

Let's look at both of these factors in a little more detail. It's interesting, if you look at the weight status of preterm infants in later life, they aren't at higher risk of obesity, despite the concern they might be. I've cited 3 studies with preterm infants at ages 4 to 18 years where these infants were not at higher risk of [becoming] overweight compared to their term-born peers born in the same year.

These graphs by Hamatschek et al are a nice illustration of the data that have been reviewed with body composition of preterm and term infants around the time of birth and the first few months thereafter. Each of the dots on these graphs represent 1 study (a body composition study), and

Guidelines for Nutritional Care in the NICU: Author-Led Cases

the size of the dots refer to the sample size of the study. At a glance, you can see there have been more and bigger studies done on term infants than on preterm infants. This data is nice because they included all the studies they could find, and we can see they were able to draw curves showing the change, over age and over time, for preterm infants and term infants.

I'd like to draw your attention first to the postmenstrual age at 40 weeks. This is where there's been a lot of concern. You can see at 40 weeks the preterm infants have an average body fat percentage of about 16%. And you can see some of the bigger studies have been at that age. If we look at the term infants, there's a lot of data, and the average percent body fat is 11%. But at 40 weeks, preterm infants, on average, have a higher percent body fat. Let's look at 52 weeks, which is about 3 months of age, and you can see that the percentage body fat of the preterm infants is 24%, and the percentage body fat of term infants is about 25%. Now we don't have a lot of confidence in the 3-months' data on the preterm infants because there isn't a lot of data, but you can see that both groups—the preterm and the term infants—increase their body fat rather quickly after birth and then it levels off. And that's what you see, observing infants, as well. There is a phase of postnatal fat gain, and then it does level off.

I think we can conclude, looking at these 2 graphs, that the concern is a short-term effect, and to get a good understanding of body-fat percentage, we really need to look at what happens over time. So, rather than aiming for any kind of specific weight gain or body composition at 40 weeks for preterm infants, I believe a better goal is to support the infants to grow at rates similar to the fetus. That's the best guide we have now. It may change over time, but at this point, this is what we know.

Now I want to talk about the data that shows weight below a certain percentile, before or around 40 weeks, and whether it predicts poor cognitive scores. There are 7 studies that have addressed this question. They've usually looked at weight less than the third or the 10th percentile at around 36 to 40 weeks. Most of them have looked at Bailey scores, some of them have also looked at IQ scores, and all of these 7 studies found that having a weight below these percentiles around 36 to 40 weeks does not predict low cognitive scores. That's a pretty consistent finding across these studies.

Now I want to talk about growth goals for preterm infants. As part of the development of this book, we had consensus meetings among all the authors, and we developed some consensus growth goals for preterm infants, as listed on the slide. I'll read them out for you. Number 1, support preterm infants to grow at rates and accrete nutrients similar to the fetus. Number 2, aim for preterm infant growth to maintain weight, head circumference, and length growth patterns to aim for growth that is approximately parallel to growth chart curves. Number 3, increasing weight out of proportion to length does not confer developmental benefits. Number 4, gaining additional body fat postnatally appears to be a temporary event. Number 5, if an infant's growth pattern deviates importantly from expected growth patterns, first of all, ensure that nutrition is optimized and assess for possible contributing factors. And I think a point to add here is that if the child is genetically small, we don't need to get them up higher on the growth charts. And number 6, preterm infants are placed lower on growth chart curves after the postnatal weight-loss phase. And we recommend that the phrase extrauterine growth restrictions be retired and not used to diagnose infants with weight below the 10th or the third percentile around the time of discharge, because it's not predictive of adverse outcomes.

I'd like to talk now about the causal relationships for neonatal outcomes. You can see a couple diagrams on this slide. It's kind of a busy slide, but we have 2

Guidelines for Nutritional Care in the NICU: Author-Led Cases

sets of diagrams. The first diagram describes the problem, as assumed to be, that poor growth is the cause of poor cognitive outcomes. I think that's a message that we see quite a bit in the literature, but I argue that the problem may be that there are several factors that contribute to poor cognitive outcomes.

Ideally, we can work to improve all of these to improve poor cognitive outcomes. Some of these also contribute to poor growth, and it's questionable whether poor growth in units with good nutrition contribute to poor cognitive outcomes. I would argue that there are other factors, and these other factors are the social determinants of health, which affect the health status and outcomes of people in all age groups. Prenatal factors, which are beyond the control of neonatal healthcare practitioners. Inadequate nutrition can be a factor and certainly was in the early 1980s when people were learning how to nourish preterm infants. But in units with really good nutrition care, I would argue that inadequate nutrition isn't a cause of poor cognitive outcomes.

We know that NICU stress can affect the outcomes of these infants and neonatal morbidities can, as well. So, poor growth is more likely an outcome of these adverse circumstances that preterm infants can be dealing with and not the direct cause of suboptimal development.

So, you might question how can the social determinants of health influence preterm infant long-term outcomes? There's been some interesting work looking at infants and how they perform in terms of development related to their parental education level. The results are quite reassuring that there might be some modifiable factors that can improve outcomes of infants. One of the interesting studies showed that when infants had a severe neonatal brain injury, and if the mother has had a higher education level, they had better cognitive outcomes. So, it suggests there are some things parents can do to provide, perhaps, a more stimulating environment that might help the infant overcome the injury they received early on.

It becomes clear when you look for the social determinants of health in the literature that neurodevelopment is modified by the family's socioeconomic circumstances and their educational attainment, as well.

I wanted to talk a little bit more about the concern that nourishing these babies might make them obese. There's been an interesting set of 2 meta-analyses recently published out of New Zealand. They looked at early macronutrient supplements for preterm infants and what are the effects. These studies looked at preterm as well as small-for-gestational-age infants, and they looked to see what the effects are, the long-term effects when these supplements are given in randomized control trials. This is high quality information. It's not observational, but rather it is from randomized control trials. Now a meta-analysis like this is limited by what information is available, but I think you'll find the findings of value.

They found that there was improved motor function in toddlers, especially for girls, after these supplements [were given]. There wasn't a change in cognitive function in the toddlers and older children, but the data was limited. Then, of real interest, they didn't find any adverse effects on later metabolic outcomes. They looked at high- and low-density lipoproteins, cholesterol, fasting glucose, blood pressure, and body mass index. They also looked at triglycerides, which was interesting because the triglycerides were lower among the infants who had received the nutritional supplements. There was no evidence that these supplements led to any concerns in terms of metabolic syndrome. So, that is very reassuring.

So, the key takeaways include when infants' growth patterns deviate from expected growth patterns, first, ensure that their nutrition is optimized and

Guidelines for Nutritional Care in the NICU: Author-Led Cases

then examine other determinants of health and morbidities for possible contributing factors. I'll just add, it can be acceptable for infants to have growth that looks suboptimal if there's a reason for it, such as if a baby's born large for gestational age due to a mother having difficulty controlling diabetes during pregnancy. We wouldn't expect that baby to maintain their high birth percentiles. The second point is it's important for clinicians to optimize nutrition intakes to meet current recommendations, and then consider the morbidities of possible causes if an infant has poor growth velocity.

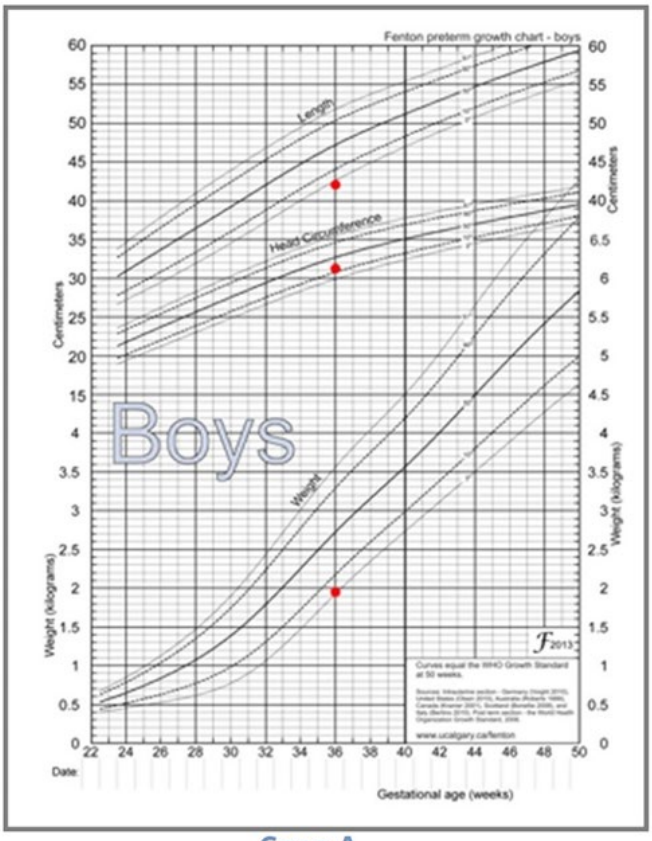
And then my overall recommendation is to aim for preterm infant growth to maintain weight, head circumference and length growth patterns, and to aim for those patterns to be parallel to growth-chart curves. As I mentioned earlier, increasing weight out of proportion to length does not confer benefits.

In terms of research priorities, they are numerous for this population group. We need more studies to identify the causes of adverse neurodevelopment so we can improve outcomes for these infants and their families. We need long-term follow-up studies beyond the first years of life so we can understand how different nutrition strategies can give us the best outcomes for these families.

Case Challenge

To assess preterm infant growth, serial weight measurements are needed, as well as measures of head circumference and length. It is helpful to know about the infants' prenatal, medical, and nutritional history, as well as parental heights.

Neonatology has been focusing on weight at approximately 36 weeks, using a criterion of whether or not weight is less than the 10th percentile to identify extrauterine growth restriction. This is problematic for several reasons.



Case A

Question 1: How would you assess this infant's growth?

A. Growth faltering based on weight <10th percentile at 36 weeks
B. Good growth
C. I can't assess using just 1 point in time

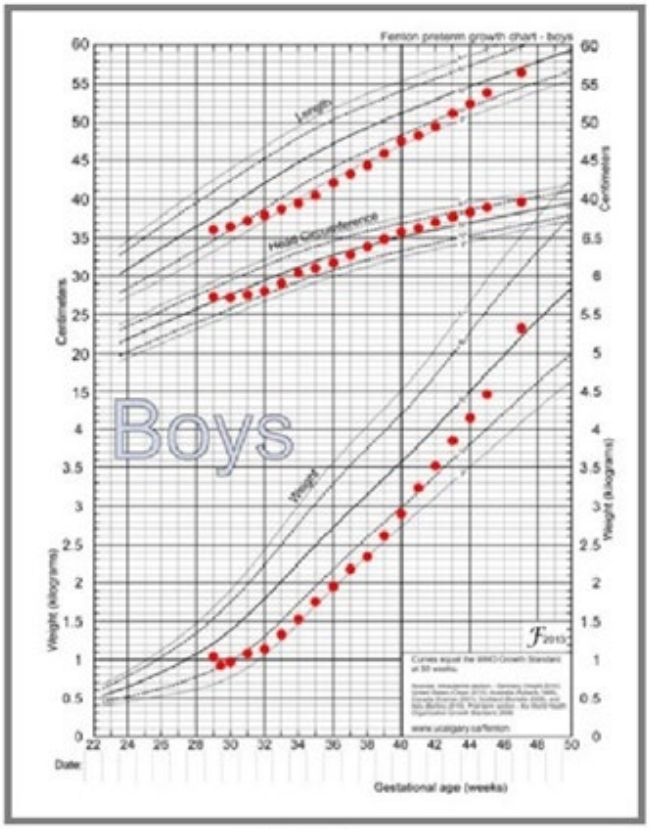
The best answer is C. I can't assess using just 1 point in time.

Let's look further at various infant histories that could have preceded the above infant measurements.

These weight, length, and head circumference points could have been reached after considerably different histories:

How would you assess these infants' growth patterns? ...

Guidelines for Nutritional Care in the NICU: Author-Led Cases



Case B

Question 2: How would you assess the growth pattern for infant B, focusing on his growth trends up to 47 weeks corrected gestational age? Relevant background details and medical history includes the following:

Both of the infant's parents are tall, suggesting his genetic potential for height is above average.

During pregnancy, his mother had elevated blood pressure that led to his delivery due to the fetus's growth lagging for a few weeks, ie, he had intrauterine growth restriction.

How would you evaluate his growth?

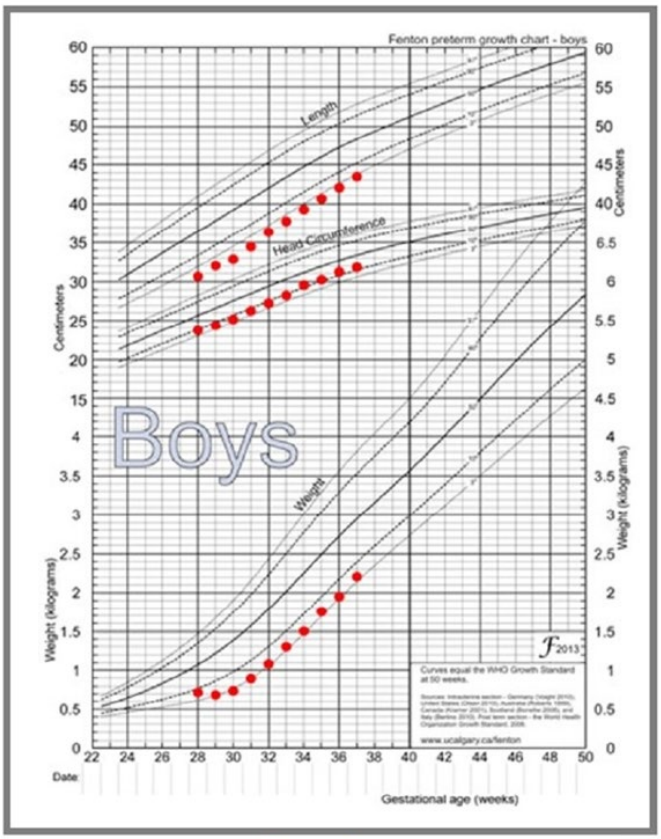
A. Growth faltering
B. Good growth

The best answer is B. Good growth

This infant shows gradual catch-up growth toward his genetic potential after prenatally induced growth faltering. Prenatally growth restricted infants sometimes regain their birth z-score even as early as before 40 weeks post menstrual age, while non-growth restricted infants seldom regain their birth z-score before 45–64 weeks. This infant's birth length was at the 30th percentile, but both parents are tall, so his genetic potential is likely to be higher in the percentiles.

This infant was growth restricted despite the fact that his weight exceeded the 10th percentile at birth. The 10th and 90th percentiles are arbitrary cut-off points, which will misclassify some infants at birth in both directions: (1) some growth restricted infants may weigh >10th; 2) some non-growth restricted will weight >10th; 3) some weigh >90th but have no excess weight; and 4) some have excess weight but do not weigh >90th. This baby achieved and exceeded his birthweight percentile by 45 weeks, his head birth percentile by 40 weeks, and his length birth percentile by 47 weeks.

Guidelines for Nutritional Care in the NICU: Author-Led Cases



Case C

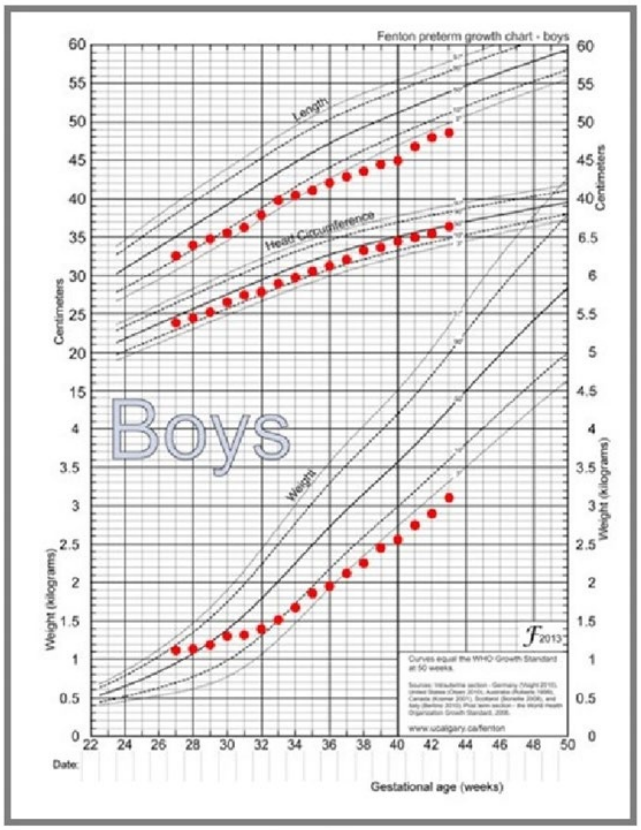
Question 3: How would you assess the growth pattern for infant C?

There was no evidence of intrauterine growth restriction for this infant, therefore his birth weight, length, and head circumference reflect his genetic potential.

A. Growth faltering
B. Good growth

The best answer is B. Good growth

This infant stayed small because his genetic potential is to be small. His growth pattern is appropriate for an infant who was not growth restricted, which is growth that is approximately parallel to the growth chart curves.



Case D

Question 4: How would you assess the growth pattern for infant D?

A. Growth faltering
B. Good growth

The best answer is A. Growth faltering

This infant has apparent growth faltering because, for many weeks, his growth has been less than intrauterine rates, as shown by the growth chart curves. His healthcare providers need to sort out the following:

→ If nutrition has faltered, then nutrition support is a priority to improve his nutrition intakes;
→ If nutrition has been good, has he had a challenging NICU course? He needs more support and needs realistic growth expectations; and
→ If nutrition has been good and there are no other explanations for this growth pattern that continues to be less than intrauterine rate,

Guidelines for Nutritional Care in the NICU: Author-Led Cases

consult endocrine. It is possible he has a genetic cause of this growth faltering.

For preterm infants, the whole question of whether growth faltering is due to an organic (medical) vs non-medical (nutrition support or feeding ability) needs to be considered.

A problem with commonly used electronic medical records is that it is not possible to visualize a neonate's growth-chart weight concurrently along with length and head circumference.

Preterm Nutrition and the Brain

Sara Ramel, MD: My name is Sara Ramel. I'm an assistant professor and neonatologist at the University of Minnesota. I coauthored this chapter on *Preterm Nutrition and the Brain* with Dr. Mandy Belfort.

The brain undergoes enormous changes, not only increasing in size, but more importantly, in complexity throughout early development. Unfortunately, this rapid pace of development leaves the brain particularly vulnerable to stress and lack of critical nutrients during this time period. Oligodendrocytes are responsible for myelination in the CNS, are rapidly developing between 25- and 35-weeks' gestation and are extremely sensitive to energy deprivation. For this reason, optimized nutrition starting immediately after birth is critical.

Early growth patterns, especially prior to term, have been associated with long-term neurodevelopmental outcomes among preterm infants. Specifically, increased linear growth and fat-free mass accretion have been associated with faster speed of processing and higher scores on standardized developmental testing. Increased calories, fats, and protein have all been associated with improved growth and neurodevelopment. However, the optimal amount to provide during each stage of development is not entirely clear.

While all nutrients are important for brain growth and development, deficits in certain nutrients at particular times have especially large effects on the brain between 24- and 44-weeks post conceptual age—the time when we, as a healthcare team, are often making decisions about which nutrients to give and how much to give. Specifically, when deficits and nutrients that support basic neuronal processes are provided in insufficient quantities during times of rapid development within these neurologic systems, the brain is left particularly vulnerable to injury. This is true for inadequate provision of macronutrients including proteins, fats, and carbohydrates, as well as several micronutrients.

Brain areas that are rapidly developing during the last trimester have the highest metabolic rates and are at the greatest risk for metabolic disruptions. These include the hippocampus, [which is] important for learning and memory, myelin, which underlies speed of processing, and the cerebellum, which is important for balance, motor integration, and cognition.

We can all share stories of preterm infants overcoming amazing odds as evidenced by the significant amount of plasticity in the developing brain. However, vulnerability often outweighs plasticity, and therefore prompt, optimized nutrition is critical to optimizing outcomes. Additionally, this plasticity may not guarantee complete healing back to typical or normal functioning, as evidenced by the literature on early hypoglycemia, periventricular leukomalacia, and poorer outcomes long term.

Nutrient deficits that occur during times of rapid neuronal proliferation or differentiation can have long-term and potentially irreversible ramifications, specifically deficits in protein, energy, iron, zinc, and long-chain polyunsaturated fatty acids (LC-PUFAs) during early development can alter neuroanatomy.

Guidelines for Nutritional Care in the NICU: Author-Led Cases

Carbohydrates, particularly glucose, are the main fuel source for the brain, and while the typical newborn utilizes between 4 and 8 mg/kg permitted of glucose, preterm infants have low glycogen stores and poor gluconeogenic capabilities, causing them to need glucose-infusion rates of closer to 12 to maintain both normal glycemia and growth. A few clinical studies have confirmed the importance of early caloric intake, although most are small observational studies. More randomized trials are needed to determine the optimal early caloric intake for this vulnerable population.

Fats also play an important role in brain development, as they comprise a large percentage of the brain's composition. Fats are necessary for myelin synthesis, synaptosome formation, and cell-membrane fluidity, all of which are crucial for efficient neural processing. A large [amount of] literature on the role of a specific group of fats, the long-chain polyunsaturated fatty acids, has shown that supplementation is associated with more mature electroretinograms, short-term gains in neurodevelopment, and improved visual acuity out to 1 year of age. Although similar to other macronutrients, the optimal amount and timing of supplementation remains unclear.

Case Challenge

Early growth in very low-birth-weight preterm infants (VLBW), specifically prior to term corrected age, has been associated with improved neurodevelopmental outcomes later in life. Previously, growth monitoring focused specifically on weight gain; however, improved linear growth and fat-free mass (FFM) accretion are also associated with faster speed of processing and higher scores on standardized developmental testing. Many factors contribute to linear growth rates; however, nutrient provision is 1 factor that the care team can control.

A 1-month-old VLBW preterm male infant, who was born at 27 weeks with his weight at the 50th percentile and his length at the 25th percentile, is on full enteral feeds of maternal breast milk with human-milk fortifier to 24 kcal at 150 mL/kg/d. His weight is tracking along the 10th percentile; however, his linear growth is slow and is now below the 10th percentile. The team is discussing fortification and supplementation strategies.

Question 1: Which of the following additions to this infant's diet could improve linear growth and potentially in turn long-term neurodevelopmental outcomes?

A. Increased calories and protein
B. Increased protein supplement only
C. Iron supplementation
D. Choline supplementation

The correct answer is A. Increased calories and protein

While increased protein supplementation is associated with improved linear growth and considered safe up to 4.5 g/kg/d enterally, increased caloric provision has also been associated with improved linear growth and FFM accretion, and would be especially useful in this case where the infant has also had suboptimal weight gain. Iron supplementation has been linked to improved neurodevelopmental outcomes in preterm infants but not with linear growth. Choline supplementation is beneficial during pregnancy but has not been shown to improve either neurodevelopment or growth in preterm infants.

The decision was made to increase the fortification to 26 kcal as well as add a modular protein supplement to provide 4.5 g/kg/d of protein. There is some improvement over the coming weeks, however his linear growth remains below the 10th percentile despite adequate weight gain. The team has decided to add a micronutrient supplement to help augment linear growth.

Guidelines for Nutritional Care in the NICU: Author-Led Cases

Question 2: What supplement has been shown to improve linear growth and neurodevelopmental outcomes among preterm infants?

A. Selenium
B. Zinc
C. Copper
D. Iodine

The correct answer is B. Zinc

Preterm infants are at risk for zinc deficiency due to low stores, high requirements, and variable absorption. In a few small studies, zinc supplementation among preterm infants was associated with improved linear growth as well as improved neurodevelopmental outcomes. Zinc is also known to be associated with several different essential processes in brain development including neuronal proliferation, differentiation, and myelination. Additionally, suboptimal brain-zinc status may contribute to white matter damage in the preterm infant through its role in preoligodendrocyte differentiation. Current recommendations suggest supplementation with 2–3 mg/kg/d of elemental zinc.

Energy Requirements and Carbohydrates in Preterm Infants

Katie A. Huff, MD, MS: I am Dr. Katie Huff. I'm a neonatologist at Riley Hospital for Children and an assistant professor of clinical pediatrics at Indiana University in Indianapolis, Indiana.

I will be presenting the chapter I cowrote with my fellow authors, Dr. Scott Denne and Dr. William Hay, titled *Energy Requirements and Carbohydrates in Preterm Infants*. I would like to also thank Dr. Laura Brown, an author of the previous version of this chapter, for her contributions regarding nonglucose carbohydrate information, which will only be briefly touched on in this verbal presentation, given time constraints, but is more extensively covered in our written version.

When considering preterm neonate nutrition, it is important to know that our goal is to provide the necessary nutrition to approximate the rate of growth-body composition and nutrient concentration similar to that of a fetus of the same gestational age. In addition to this, I want to convey that energy requirements are influenced by an individual's age, weight, and other clinical factors. That energy balance influences not only weight gain, but also body composition.

In the clinical setting, weight gain is a reasonable surrogate marker for adequate energy intake in preterm infants. But we do know that, despite having adequate weight gain over time, preterm infants have altered body composition relative to term infants at term-corrected age. Glucose is an important energy source for preterm infants, given their large brain and heart overall weight ratio, which we'll discuss a little further in later slides, and preterm infants continue to produce glucose despite adequate glucose supplementation. This leads to their high risk for hyperglycemia development. It's important to consider that nutrient balance is essential, and both insufficiency and excess total energy intakes can be deleterious and should be avoided.

In the setting of glucose supplementation, preterm infants are at risk for both hypo- and hyperglycemia. And because of this, their glucose levels should be monitored closely, with adjustments made as needed. So, the energy recommendations outlined in this chapter—shown in our chart—are separated based on type of intake, whether it's parenteral vs enteral in addition to patient clinical state, whether it's early in life when patients are starting parental nutrition, or the stable patient who's on full parenteral nutrition or internal supplementation.

Guidelines for Nutritional Care in the NICU: Author-Led Cases

Recommended intake is also further divided based on patient current weight, which we thought was important to include in this version of the chapter. These recommendations were made considering other supplementation recommendations, including protein or amino acids and lipid supplementation that's outlined in other chapters. To point out, the enteral energy recommendations on the right side of the chart recommendations are increased compared to parenteral recommendations. This is to account, in part, for increased losses that occur via nutrient excretion in those patients who are receiving enteral nutrition.

When determining an individual patient's energy needs, it is important to consider that energy requirements vary based on multiple patient-specific factors. Lower enteral energy recommendations of about 110 kcal/kg/d should be adequate to ensure energy for growth, especially of the brain, and have been associated with decreased risk for such things as retinopathy or prematurity.

Higher requirements, even greater than potentially 130 kcal/kg/d may be needed in those infants who experience growth faltering, in particular, during the period of illness or instability when catabolic conditions may predominate. The most important point is that a patient's true energy needs and supplementation should be individualized based on that patient's overall growth and their current clinical status. Energy expenditure estimates vary widely from study to study with numerous factors influencing the energy expenditure of a preterm infant, and therefore their overall energy needs.

These factors can include such things as type of dietary intake, whether they're receiving formula vs breast milk, the patient's environment, if they're receiving thermoregulation medications, in particular caffeine, and their current clinical state, in particular, if they're experiencing sepsis. Numerous examples of these various conditions and their influence on energy expenditure are outlined in the table we've provided.

Glucose is the main source of energy of the body, especially of the heart and brain, and neonates have the same glucose needs as a fetus of the same gestational age. Because of this, they must either synthesize or receive adequate supplementation once they are born and no longer have the supplement directly from the placenta. A normal glucose utilization rate for a preterm infant is about 6 to 8 mg/kg/min, which is increased compared to term infants due to, again, their increased brain-to-body-weight ratio I mentioned previously.

It has not been well established, but the maximum glucose utilization rate for normal glucose oxidation is estimated to be around 11 to 13 mg/kg/min. In glucose supplement and above this maximum leads to concerns for increased fat synthesis, which is an energy-expensive process, and can lead to fat in such organs as the heart and liver, leading to further morbidities and complications for neonates. It is important to note when considering glucose supplementation, like I mentioned previously, that extremely preterm infants continue to produce glucose at a rate of about 2 to 3 mg/kg/min, despite adequate supplementation. This increases their risk for hyperglycemia and accounts for lower recommended glucose infusion rates or GIR [glucose infusion rate] over the first few days of life in this population.

If an infant does develop hyperglycemia, it is important to note that the first-line recommendation is to decrease the GIR stepwise, while closely monitoring glucose levels until hyperglycemia resolves or until a minimum GIR of about 3 to 4 mg/kg/min is reached. This minimum is recommended to account for continued glucose production in these neonates, while adequately supplementing and giving the needed glucose to

Guidelines for Nutritional Care in the NICU: Author-Led Cases

account for the needed glucose utilization in the neonate.

If still hyperglycemic despite the GIR minimalization, insulin infusion can be considered. In this setting, glucose levels should be monitored closely to avoid hypoglycemia, a common side effect of insulin use. For close monitoring, recent studies have shown that continuous subcutaneous glucose monitoring can be safe and well-tolerated in preterm infants and can improve their glycemic control. However, more information is still needed to understand how to apply this technology widely in our preterm infants, and also to understand the long-term effects of this use and this tight glycemic control in the preterm population.

Recommended glucose supplementation for this chapter is, again, divided by the type of intake as our energy recommendations were considering enteral vs parenteral, as well as patient clinical status—whether they're early starting parenteral nutrition or a patient who's stable on full parenteral or enteral supplementation. Again note, like I previously mentioned, that in those patients of the lowest weight, their GIR or glucose infusion rate is recommended to be lower compared to other patients because of their higher risk for hyperglycemia in their ongoing glucose production.

In addition, the recommendation for GIR, once on full parenteral nutrition, is based on the maximal glucose utilization rates I mentioned previously, in addition to balancing nutrient recommendations, such as intake for amino acids and lipids, and their overall energy recommendations.

As you'll note, the internal intake is labeled slightly differently here. Not in the form of GIR, and this is meant to account for the intake in breast milk, which is primarily lactose, in the form of the primary carbohydrate, which does, through its hydrolysis, provide glucose to the neonate.

Again, as was discussed with energy recommendations, the actual glucose supplementation prescribed to a patient should be individualized and should account for the patient's glucose tolerance, their calorie needs, glucose levels with close monitoring during times of glucose titration, and also change in patient clinical status.

So, the key takeaway for this chapter is that the patient's nutritional supplementation for both energy and glucose should be individualized based on the patient's growth while also accounting for their laboratory monitoring and clinical status.

Some other key takeaways include that energy needs are influenced by multiple patient-specific factors and should be individualized based on the individual patient needs. Glucose is an important source for energy, however, excess can lead to hyperglycemia, and this risk should be considered, monitored for, and treated appropriately.

Some research considerations regarding the topics of this chapter include determining the ideal ratio of macronutrients and energy supplementation to improve preterm infant body composition, more similar to a fetus of the same corrected gestational age, in addition to considering further studies to better understand the influence of tight glycemic control and use of such devices as continuous subcutaneous glucose monitoring on both the short- and long-term preterm patient outcomes.

Case Challenge

You are a member of the care team when a mother delivers a male infant at 27 weeks gestational age due to severe maternal pre-eclampsia. The infant has a birth weight of 800 g. The infant is stabilized and is currently in an appropriately heated and humidified isolette receiving continuous positive airway pressure (CPAP) at 6 mm Hg. For access, a central umbilical venous catheter (UVC) is placed with placement confirmed via X-ray.

Question 1: When considering initial fluid orders for this patient, you plan to order parenteral nutrition to be given the UVC. What would be appropriate

Guidelines for Nutritional Care in the NICU: Author-Led Cases

initial starting energy and glucose orders for this patient?

A. Energy: 100–115 kcal/kg/d; Glucose infusion rate: 7–10 mg/kg/min
B. Energy: 90–100 kcal/kg/d; Glucose infusion rate: 6–9 mg/kg/min
C. Energy: 110–130 kcal/kg/d; Glucose infusion rate: 11–13 mg/kg/min
D. Energy: 60–70 kcal/kg/d; Glucose infusion rate: 3–6 mg/kg/min
E. Energy: 60–80 kcal/kg/d; Glucose infusion rate: 8–10 mg/kg/min

The correct answer is D. Energy: 60–70 kcal/kg/d; Glucose infusion rate: 3–6 mg/kg/min.

For a patient who is 800 g soon after birth just starting parenteral nutrition, the recommendations for energy and glucose are 60-70 kcal/kg/d and 3-6 mg/kg/min. When considering actual nutrients to be given to a patient it is important to consider each individual patient's needs and medical status. Energy and glucose recommendations for all weight groups are noted in the tables below.

Advisable Parenteral and Enteral Energy Intakes for Preterm Infants by Current Weight

Current weight	Parenteral energy [a], kcal/kg/day		Full enteral energy [a], kcal/kg/day
	Starting [b]	Stable patient [c]	
500–1000 g	60–70	100–115 [d]	110–130
1000–1500 g	60–70	90–110	110–130
1500–2000 g	60–70	90–110	110–130
2000–2500 g	45–70	90–110	105–125

a. Calorie intake should be individualized based on patient clinical status and growth. Depending on a patient's energy expenditure, calorie needs may be increased or decreased.
b. Based on IV infusion rates for amino acids of 2.5 g/kg/day, lipids of 2 g/kg/day, and dextrose of 6–8 mg//kg/min starting in the 1st 24 h after birth.
c. These values should be considered minimum values during the transition from parenteral to full enteral nutrition to avoid cumulative deficits in energy and protein if parenteral rates are reduced faster than enteral rates are increased.
d. Based on IV infusion rates for amino acids of 4 g/kg/day, lipids of 4 g/kg/day, and dextrose of 10 mg//kg/min for the most preterm, lowest birth weight infants. Lower amounts of protein are appropriate for more mature infants.

Recommended Starting (upon admission to NICU) and Full Parenteral Glucose Infusion Rates and Full Enteral Carbohydrate Intakes in Preterm Infants by Current Weight

Current weight	Starting parenteral glucose [a]		Full parenteral glucose [a]		Full enteral carbohydrate, g/kg/day
	g/kg/day	GIR, mg/kg/min	g/kg/day	GIR, mg/kg/min	
500–1000 g	4–12	3–6 [a]	10–15	7–10 [b]	11–13 [c]
1000–1500 g	6–12	4–8	10–15	7–10	11–13
1500–2000 g	6–12	4–8	10–15	7–10	11–13
2000–2500 g	6–12	4–8	10–15	7–10	11–13

a. GIRs should be increased or decreased in response to frequent plasma glucose concentration measurements to maintain normoglycemia.
b. Higher values up to 9–12 mg/min/kg might be needed based on larger brain/body weight ratio in very preterm and asymmetric SGA infants and IUGR/SGA infants with hyperinsulinism-like disorders.
c. Based on a feeding rate of 160 mL/kg/day.

GIR, glucose infusion rate; SGA, small for gestational age; IUGR, intrauterine growth restriction.

Question 2: On the following morning the patient is noted to have a glucose 300 mg/dL. You confirm this was an appropriately drawn sample with a repeat value on capillary sample of 305 mg/dL. Which of the following is the most appropriate course of action for this patient?

A. Start insulin infusion and continue the current glucose infusion rate.
B. Decrease the glucose infusion rate while trending glucose levels.
C. Keep the glucose infusion rate the same and plan to frequently monitor glucose levels.
D. Stop all glucose containing fluids and monitor the patient.
E. Do not be concerned, this is an appropriate value for this patient.

The correct answer is B. Decrease the glucose infusion rate while trending glucose levels.

This patient has hyperglycemia. While the true value at which a patient is hyperglycemic may be controversial and vary amongst studies, it is often defined as a glucose of greater than 150 – 200 mg/dL. Based on this definition, this patient is hyperglycemic. While insulin infusions have been associated with increased carbohydrate infusion tolerance and decreased weight loss in the first week of life, they have also been associated with an increased risk of lactic acidosis, hypoglycemia, and possible increased risk of mortality. In this setting, it is considered safest to first decrease the glucose infusion rate (GIR) in order to treat hyperglycemia. The speed and degree of GIR decrease is dependent on the etiology, degree of hyperglycemia, and patient response. However, an initial decrease of 1 mg/kg/min should be reasonable. In this setting with a change in GIR, glucose levels should be monitored frequently (every 3-4 hours) until stable. Concerns have been raised regarding decreasing the GIR and ability to deliver appropriate calories. Additional strategies

Guidelines for Nutritional Care in the NICU: Author-Led Cases

to improve glycemic control include increasing the dosage of amino acids (to increase endogenous insulin release) and decreasing lipid infusion rates (to decrease substrate competition for oxidation). In the setting of sudden change in glucose levels, the overall clinical context of the patient should be considered. Other conditions, such as sepsis, which is highly associated with hyperglycemia, should be considered if no other explanation exists.

Over the first week of life the patient's glucose levels normalize and allow for titration of the glucose infusion rate. The patient remains clinically stable, and you are able to advance the patient on enteral nutrition and wean off parenteral nutrition. At 2 weeks of age, however, the patient becomes clinically ill with worsening respiratory distress and feeding intolerance. They patient has a positive blood culture and is diagnosed with sepsis. They receive appropriate antibiotics and are intubated and placed on mechanical ventilation with stabilization of blood gas values.

Question 3: Given the patient's feeding intolerance you are concerned for an ileus and decide to hold enteral feeds at this time. In this setting, what should be the plan for this patient's nutrition?

A. Give glucose containing fluids only. It will likely be only 1-2 days and this patient should be fine over this period.
B. Give fluids.
C. Place the patient on parenteral nutrition, but limit the contents, especially the glucose given the patient's history of high glucose.
D. Place the patient on parenteral nutrition and plan to individualize the content based on the patient's clinical status including frequent lab checks. The patient's needs will be altered by the change from enteral to parenteral nutrition, their sepsis, as well as their change in respiratory status.
E. Place the patient on parenteral nutrition and use the last parenteral nutrition order the patient was receiving.

The correct answer is D. Place the patient on parenteral nutrition and plan to individualize the content based on the patient's clinical status including frequent lab checks. The patient's needs will be altered by the change from enteral to parenteral nutrition, their sepsis, as well as their change in respiratory status.

A patient's nutrition order should always be individualized based on the patient's current clinical status, type of feeding needed, and overall growth. The patient in this scenario has had a change in their clinical status for many reasons. They have sepsis and have worsened respiratory distress, both of which may increase their overall calorie needs. They also have an ileus and need parenteral nutrition in place of their enteral nutrition, often with fewer calories needed for growth in this setting. In addition, this patient does have a history of hyperglycemia and may be prone to a recurrence of this. With these changes, and considering this patient's history, the best plan is to check the patient's laboratory values, including glucose, and alter their delivered nutrition based on their close monitor and current needs. Alterations in their parenteral nutrition and nutrition in general may be needed as the patient clinically changes over time. While this patient may tolerate being treated with glucose- containing fluids only and receiving no fat or protein sources for a period of time, this is not ideal. In this setting, this premature patient would be using their body stores and worsening a deficit that may already exist when compared to a fetus of the same gestational age. In addition, using the patient's last parenteral nutrition prescription may not be ideal as the patient was in a different clinical state at that time.

Guidelines for Nutritional Care in the NICU: Author-Led Cases

Approaches to Growth Faltering

Frank H. Bloomfield, MBChB, MRCP, PhD: Hello, everyone. My name is Frank Bloomfield. I'm a professor of neonatology in Auckland, New Zealand and also director of the Liggins Institute, a research institute into mothers' and babies' health. I'm going to be talking to you today about the chapter on approaches to growth faltering, and I'd like at this point to acknowledge my coauthors, Brenda Poindexter and Barbara Cormack. Barbara is also from the University of Auckland.

My topic is *Approaches to Growth Faltering* in preterm babies. The first point I'd like to address is what do we mean by faltering growth? It's important to realize that faltering growth is dynamic, just as growth at any other point of the life cycle is dynamic. It's not determined by a given centile on a growth chart at a single point in time. So, when we read about the proportion of preterm babies who have suffered faltering growth using a definition of a certain centile at 36-weeks corrected age, or term corrected age, that really is not a definition of faltering growth. It's telling us about the size of the babies in that population or cohort, but not how they have grown since they were born.

Instead, faltering growth is a fall across centiles after birth. This defines the trajectory of growth, indicating that it's not up to the optimal level. When we're thinking about this, however, we do have to remember that there is a natural fall across centile shortly after birth, due to the contraction of extracellular fluid. The mid-gestation fetus is almost 80% fluid, and some of this is excreted after birth. Therefore, babies have a fall across centiles in the first few days. On average, this approximates to about 0.8 Z-scores for weight, and that is fairly consistent across preterm gestations.

The other reason we're interested in faltering growth is because it is very common, in both preterm and very low-birth-weight babies. This is important because as a population, preterm babies are already smaller than the gestational age match fetuses who go on to birth at term. So if, for example, we were to plot preterm babies at a given gestation on a fetal growth chart, instead of seeing the bell-shaped curve normal distribution that we see on our birth weight cross-sectional charts, we would see a skewed chart that skewed to the left, with a greater proportion of preterm babies being small. This is because preterm birth is linked to fetal growth. The other reason it's important is because at the time that preterm babies are born, they are undergoing a period of growth in the womb that is very, very rapid. In fact, probably the most rapid of any time of life, and therefore, they need fetal nutrient requirements to support that rapid growth. And matching these levels after birth is very challenging, both through the limited fluid requirements, while also trying to increase the amount of enteral nutrition these babies can tolerate.

So, when we are thinking about measuring growth, we have to remember that weight is a measure of mass and not of growth. Again, just as in any other pediatric measurement, we need to measure linear growth to determine growth. Weight, of course, could be a measure of fluid retention or of fat accumulation, or indeed of a mass, such as a tumor. This is why these other measures of growth are important. If we do measure all 3 parameters, we can see that in our preterm babies, declines in length and head circumference often exceed those of weight, because it is much more challenging to support a baby's linear growth than it is simply to help them put on weight.

So, what are the nutrient requirements of very preterm babies? Well, I won't go over this in great detail because this is covered in one of the other presentations, but I'd like to focus briefly on protein uptakes, just as an example. If we're thinking about a fetus at the same time as our preterm babies are

Guidelines for Nutritional Care in the NICU: Author-Led Cases

born, what are their nutrient uptakes across the placenta? Well, through active transport, the midgestation fetus acquires about 3.5 g/kg/d of amino acids via placental transport. However, in addition, the fetus is swallowing between 500 and 750 mils of amniotic fluid every day, and that contains about an additional half a g/kg/d of protein, which—[it] has been demonstrated—the fetus is able to utilize and incorporate into growing tissue. That means the preterm fetus is growing at about accumulating 4 g/kg/d of protein.

After birth, there is an obligatory protein turnover. This is due to the normal breakdown and resynthesis of muscle. It's obligatory, you don't have any choice. You can't turn that off. And this equates to about 1% to 2% of body protein per day, or about 1 to 1.5 g/kg/d of protein. So, this is the absolute minimum that a newborn preterm baby requires to avoid going into nitrogen deficit, which it would accumulate due to obligatory muscle turnover.

We're estimating that the minimum requirement in the first couple of days is about 2 g/kg/d, increasing after about a week to about 3.8 g/kg/d after this. It's important to note that we have to pay close attention to nutritional intakes. Although we might prescribe intakes that meet the recommended requirements, evidence has shown that babies often don't actually receive what we're prescribing.

Of course, this can be for a number of reasons. It may be that the fluid we prescribe—whether parenteral or enteral—is not received for certain reasons. If it's parenteral, it may be that the fluid intake is taken up by other infusions, such as inotropes, sedatives, pain relief, etc. Or the intravenous infusions may be interrupted for a period of time, such as for antibiotic administration. And this can add up to 1 to 2 hours per day, which is a significant period of time. Enteral intakes may be decreased because of perceived feed intolerance, or actual feed intolerance. There may be concern about whether the baby's tolerating the nutrition, for example, through measuring serum urea concentrations. Although it's very important to note that there is no evidence that elevated serum urea concentrations have any adverse effect. Similarly, there's no evidence that ammonia concentrations are significantly related to protein intakes. So, probably the most important reason for measuring serum urea is to see whether protein intake is sufficient or inadequate.

There may be increased energy requirements, for example, through bronchopulmonary dysplasia or congenital heart disease. And there might be micronutrient depletion, but the most common are sodium and zinc. For babies who have a stoma, we need to be aware that there may be malabsorption, particularly if there's high output. And finally, we need to be particularly vigilant at the time of transition from intravenous to enteral nutrition, as we're titrating one against the other. This can lead to a period of decreased nutritional intake.

This is shown on this graph here. This graph shows you the protein intake, again, just as an example, in 3 different scenarios during the transition from parental nutrition through to enteral nutrition. The parental intake is shown in the black bars, and protein from human milk is shown in the pale-gray bars. In the first example and the second graph, A and B, the parental nutrition is stopped when the enteral intake, which is 120 mL/kg/d. This is commonly done so that indwelling central venous catheters can be removed as quickly as possible, reducing the risk of associated sepsis.

You can see in Graph A that if this is the approach that is taken, then as enteral intakes increase from 120 mL/kg/d to 180 mL/kg/d, protein intake is less than 2 g/kg/d, which really is not sufficient.

In the middle graph, Graph B, fortifier is added when enteral feeds are 5 mL per feed. You can see that this mitigates this decrease in enteral nutrition, but it does involve adding a fortifier. In the graph on

Guidelines for Nutritional Care in the NICU: Author-Led Cases

the right, the approach is to continue the parental nutrition until the baby is on, in this case, 180 mL/kg/d, which might be regarded as full feeds. And again, you can see that this approach mitigates that dip in protein intake. So, these are all different strategies that can be used to try and prevent this nadir.

Again, I won't go into human milk fortification in great detail because this is covered in another chapter, but just to make the point that the high nutritional requirements of preterm babies mean that human milk given in quote "usual" volumes may not be sufficient. Usual volumes may be 150 to 180 mL/kg/d, but as shown in the previous graph, this doesn't provide the protein intakes that are currently recommended, and it may be necessary to increase volumes to 200 mL/kg/d or more, which often are tolerated well by preterm babies to support adequate growth.

An alternative approach is to add human milk fortifiers, and these do lead to short-term improvements in growth. But it's important to note that evidence for long-term benefits either on growth or on neurodevelopment, is lacking. The other point to note is that donor human milk has significantly lower nutritional value than mother's own milk. So, an infant receiving donor human milk likely will need nutritional supplements of some sort to ensure they have adequate nutrition.

The important thing is to be aware of the risk of growth faltering, and then to monitor for it. If we address growth faltering early, then this can be prevented. As pointed out, length and head circumference are just as important, and actually are a better measure of quality of growth than weight, but they do need to be measured accurately. This now is relatively straightforward. With head circumference, it can benefit from using a non-stretch measuring tape rather than paper tapes. And there are now a variety of devices available for measuring length inside incubators, even on babies who are ventilated or with CPAP. A neonatometer is a little more complex and expensive, but length boards are inexpensive and readily available, and there's a whole variety of these that can be obtained.

Growth should be measured on growth charts, for all 3 parameters, weight, length, and head circumference. If it's possible to convert them to Z-scores, which can be done by a simple algorithm, this does allow a very simple and regular evaluation of Z-score change, which gives you an ongoing longitudinal measure of how a baby's growth is progressing. This also controls both sex and gestational age.

So, what are common causes of growth faltering? Fluid restriction. For example, if a baby has patent ductus arteriosus, one approach in some jurisdictions is to restrict these baby's fluid intakes, and this can lead to inadequate nutrition. Similarly, a higher stoma output is essentially similar in the loss of nutritionals through the stoma rather than inadequate intake. The protein intake may be inadequate, and this can be assessed through measurement of blood sugar and nitrogen, which, if less than 1.6 mmol/L, or 4.5 mg/dL, does indicate that protein intake is inadequate to support growth.

There is a chapter on energy intake, and this also will lead to inadequate growth. Then 2 important micronutrients would be whole-body sodium depletion, which can be measured through urine sodium output, and zinc, particularly after 4 to 6 weeks postnatal age. And this can be simply measured by using a serum zinc. Malabsorption, both of fat and carbohydrates, is less common, but also would lead to growth faltering. Gastroesophageal reflux is often considered as a cause of growth faltering, but unless the baby is vomiting up milk, this is unlikely to be a significant cause. In fact, the latest evidence suggested there's no indication for measuring gastric residuals

Guidelines for Nutritional Care in the NICU: Author-Led Cases

routinely. This doesn't add any value. Then, as mentioned previously, there may be an increased energy requirement through either bronchopulmonary dysplasia or congenital heart disease.

So, what are the possible intervention strategies? Well first, it would be to increase the nutrient intake. This can either be by increasing enteral volume. And as mentioned previously, we shouldn't be shy of increasing volumes to 200 or even greater, mL/kg/d. These can be increased as far as the babies who tolerate them. There are now human milk-derived fortifiers that are available, in some jurisdictions. They're not available everywhere. And of course, whether or not they're affordable will depend on the model of care in that jurisdiction.

Multicomponent bovine-derived fortifiers have been around for a long time, either as a powder or as a liquid, and do provide additional nutrition intake, but of course, are not derived from human milk. Then there can be individual components, protein, lipid, and fat. The important thing to consider here is whether there is evidence that an individual multinutrient should be added rather than a multicomponent fortifier. For example, as alluded to earlier, it's very easy to increase weight by giving additional energy, such as carbohydrates as a glucose polymer, but this may not be promoting optimal growth unless the deficit is one of energy.

So, what are the key takeaways from this talk? First is that we need to be measuring quality of growth and not just weight. That means measuring length and head circumference, doing so at regular intervals, and monitoring them on an appropriate growth chart. We need to be considering baby's growth as a trajectory over time, a dynamic measure, not just a position on a growth chart at a given point in time.

And finally, prevention, of course, is always best, but when it does occur, prompt recognition, identification of the underlying factor and appropriate intervention can mitigate any adverse effects.

What are the key areas of uncertainty? Well, we don't really know the optimal growth trajectory that supports neurodevelopment. We don't know yet how a bigger deficit in growth has adverse effects, although, it is clear the associations between poor growth and neurodevelopment have been around for a long time. Secondly, we really need large trials to determine if fortification of human milk improves long-term outcomes without short-term costs.

Thank you very much.

Case Challenge

You have been attempting to transition a 4-week-old infant born at 25 weeks' gestation to full enteral feeds with mother's own milk. She tolerated feeding increases well, and the percutaneous central venous catheter was removed at 3 weeks of age when she achieved 120 mL/kg/d (ratio alternatively labeled: $mL.kg^{-1}.d^{-1}$) well, and the percutaneous central venous catheter was removed at 3 weeks of age. Enteral feeds are slowly increasing due to challenges with maternal milk supply keeping pace with requirements and have now reached 135 mL/kg/d. Her weight, length, and head circumference at birth were all on the 50th percentile; her weight now lies on the 20th percentile, her length and head circumference are on the 9th percentile.

Question 1: Which of the following courses of action is the most appropriate for this baby?

A. Continue to increase enteral feeds with mother's own milk, as permitted by supply, as growth is adequate
B. Add a multicomponent fortifier to the breast milk to increase calorie, protein, and micronutrient intake while continuing to increase enteral volumes

Guidelines for Nutritional Care in the NICU: Author-Led Cases

C. Increase milk supply with pasteurized donor human milk to 150 mL/kg/d
D. Reinsert a percutaneous central venous line and restart parenteral nutrition to provide increase calorie, protein, and lipid intake

The correct answer is B. Add a multicomponent fortifier to the breast milk to increase calorie, protein, and micronutrient intake while continuing to increase enteral volumes.

The baby's growth is faltering, with length and head circumference falling significantly. Weight alone is not a good measure of growth. The period of transition from parenteral to enteral feeds is often a time when macronutrient intakes fall significantly before increasing again once full enteral feeds are attained. 135 mL/kg/d of mother's milk is unlikely to provide adequate nutrition for a baby this premature and continuing to provide only this amount will lead to further decline in growth. Pasteurized donor human milk contains fewer nutrients than mother's own milk, and while it will increase the nutrient supply somewhat from current levels, this level of nutrition will still not be adequate. Reinstating parenteral nutrition could supply the additional nutrition required, but it is interventional and carries the risk of infection, and it is not needed when there are other enteral options available.

A multicomponent fortifier can be added well before full enteral feeds are attained and will increase macronutrient intake to levels that may better support growth.

A multicomponent fortifier was added, and enteral feeds continued to increase to 180 mL/kg/d over the next 10 days. Weight, length, and head circumference stabilized on the 25th, 15th, and 20th percentiles, respectively. At 8 weeks of age, her weight was on the 15th percentile, but her length and head circumference had decreased to below the 5th percentile. On examination you note mild generalized edema, mild abdominal distension (the baby is receiving bubble CPAP), and her stools have become looser than before but are of normal color. Her medications include thiazide diuretics and spironolactone because she has a persistent patent ductus arteriosus and chronic lung disease.

Question 2: Which of the following investigations is most appropriate?

A. Serum zinc concentration
B. Steatocrit and fecal chymotrypsin for fat malabsorption
C. Urinary reducing substances for lactose intolerance
D. Echocardiogram to determine whether cardiac failure is responsible

The correct answer is A. Serum zinc concentration

The baby's growth is faltering again, with linear growth falling. Weight is maintained, but this is likely due to edema. She is at the age when zinc deficiency is likely to manifest. Her risk factors are preterm birth, thiazide diuretics, and a period of insufficient nutrition. In the absence of acholic stools, significant fat malabsorption is unlikely. Similarly, having tolerated milk feeds for >6 weeks, carbohydrate malabsorption is unlikely. Zinc deficiency can cause diarrhea and, if severe, skin lesions in babies. A serum zinc <10 µmol/L demonstrates zinc deficiency, which is associated with poor growth. Whether supplementation plays a role in improving neurodevelopmental outcomes is unclear. A plasma zinc concentration <10 µmol/L requires supplementation with 2–3 mg/kg/d elemental zinc.

Guidelines for Nutritional Care in the NICU: Author-Led Cases

Recommended Nutrient Intake Levels for Preterm Infants

Berthold Koletzko, MD, PhD: Hello, I'm Burt Koletzko, a professor of pediatrics at the University of Munich. It's a great pleasure to introduce you to the development of reference nutrient intakes for preterm infants and the new global guidelines on nutrient needs.

How do we define reference nutrient intakes? The goal is to meet the physiological requirements of an infant to maintain normal growth, development, and health. It's obviously based on a review of the scientific evidence and literature. In the case of preterm infants, unfortunately, for several nutrients we still lack conclusive studies. So, we need to remember that there are still some considerable uncertainties on the number of adequate intakes. Importantly, for several nutrients, the needs are related to weight-gain velocity, so we describe the nutrient needs as daily intakes per kilogram [of] body weights. We also provide data for nutrient levels per hundred kilo calories of intake, which is important when you feed a baby, to look at what is in your supply. This is based on the calculation from an energy supply of 100 to 110 kcal/kg/d considered to be the minimum of an adequate range of a healthy, growing preterm baby.

We derived these in the new global guidelines by having a group of leading experts from all around the world review the evidence. Individual groups drafted text and recommendations, which were critically peer reviewed, carefully revised, and then submitted to a formal consensus process. You [can] see on the slide, the level of consensus defined by the percentage of supporting votes. I can say that for all nutrients we have strong consensus or consensus.

The next table shows you a comparison of the new reference nutrient intake values compared to the previous edition of this exercise published in 2014. For some of the nutrient recommendations, the levels have remained the same, for others, they have changed. You see, for example, the range of lipid intakes has become wider. The recommended phosphorous intake has gone up to higher levels, and I'll come back to the reasons why we chose to do so. But before doing so, let's just go back to defining the concept of reference nutrient intakes. It's based on the concept that there is a normal distribution of requirements, with the median being the estimated average requirements, plus and minus 2 standard deviations define the range of most of the population with a lower threshold intake, and the reference routine intake being defined at the amount that covers the needs of all the population.

On the other hand, there is an upper safe level of intake. Levels above these are generally avoided because there is concern of untoward effect. So, what we try to achieve as an acceptable range of intakes is anything between the reference nutrient intake and an upper safe level of intake.

However, these are values for groups of infants. The needs of an individual preterm infant may actually differ from what is defined in the tables that we provide, depending on, not only gestational age but conceptional age, but also birth weight and, thereby, body stores at birth, and the rate of weight gain or current weight and, therefore, the amount of nutrients that are required for growth and any particular disease conditions. For example, the child with a heart defect [or] with severe lung disease will have markedly changed nutrient needs.

Let's look at the importance of timing of supply, the importance of early supply right after birth. The fetal amino supply via the placenta amounts to about 3.5 to 4 g per day. If we want to achieve fetal accretion, we need to provide amino acids from the day of birth—from the first day of life—and if we achieve that in a good way, then we would match

Guidelines for Nutritional Care in the NICU: Author-Led Cases

the protein balance in utero, approaching accretion of about 2 g/kg/d. However, if you would give a preterm glucose infusion only, then not only do we not achieve protein accretion, but we also reach a protein oxidation to meet energy needs, and within only 1 week, about 22% of body protein would be lost. Obviously, that's a nutritional emergency because if you lose one fifth of your body protein, you have markedly adverse effects, also on the composition and function of your organs.

The protein requirements of preterm infants depend on current body weight. You see it in this table between 500- and 1500-g body weight. We recommend 3.5 to 4.5 g/kg/d, with enteral feeding and up to 3.5, with parenteral nutrition between 1500 and 2000 g, 3 to 4 g with enteral nutrition. And with a body weight between 2 and 2.5 kg, an intake of 2.5 to 3.5 g/kg/d.

We want to give human milk as much as possible, but we must be aware that human milk doesn't meet the protein requirements of a preterm infant. The protein content in mother's own milk is too low to reach the needs of the preterm infant. We try to achieve a protein supply of 2.5 g/100 mL of milk, also it falls markedly over time. So, to achieve a good protein supply in infants fed milk, we need to add extra protein; we need to fortify. It's also important to remember that the milk of donor mothers tends to have an even lower protein content than mother's own milk, and that is because donor milk is typically collected at a later stage of lactation when the protein content has fallen.

Another important group of nutrients are the polyunsaturated fatty acids and, particularly, long-chain polyunsaturated fatty acid, DHA, and arachidonic acid (AHA). They are not synthesized by the preterm infant. The long-chain PUFAs ARA and DHA in amounts are needed for growth. If we calculate what is accreted in utero, we conclude the DHA intakes of about 1% of fatty acids along with arachidonic acid are required to match accretion. This is important because some randomized control trials report considerable benefits of providing DHA and arachidonic acid for visual and mental development and for risk reduction of retinopathy of the preterm infants.

If we don't provide DHA and arachidonic acid in preterm infants, then we see a very rapid fall of the plasma concentrations, both of DHA and arachidonic acid. Again, that has been associated with adverse effects on function and outcome.

If you provide human milk, then we not only give a supply of DHA but also arachidonic acid. Interesting enough, arachidonic acid and DHA are correlated in newer milk, both in term infants and in preterm infants. In these 2 studies from Europe and North America, interestingly enough, the mean ratio between arachidonic acid DHA was very similar, 1.8. In other words, human milk typically provides twice as much arachidonic acid as DHA.

Preterm infants deposit large amounts of DHA and arachidonic acid in the brain and other tissues with apparent functional importance. If you want to match that, then preterm infants need much higher amounts of DHA and arachidonic acid than we typically provide to a healthy term baby. Preterm infants need about 30 to 65 mg/DHA/kg and 50 to 130 mg/AHA/kg/d. If mothers provide breast milk, in order to achieve a high DHA level in their breast milk, we advise them to eat oily fish at least twice a week and take DHA supplements, for example, about 1 gram per day. Infants receiving preterm formula should get a formula ideally that provides 0.5 to 1% of DHA, and at least the same amount of arachidonic acid as DHA.

The next table summarizes the overall recommendations for lipids supplied to preterm infants. Medium chain triglycerides should not exceed 40% of fat. DHA, again, 0.5% to 1% of fatty acids. The ratio between DHA and arachidonic acid should be 0.5 to 1. In other words, more or at least

Guidelines for Nutritional Care in the NICU: Author-Led Cases

as much arachidonic acid as DHA. We also provide recommendations for choline and L-carnitine.

Phosphorus has changed in the recommendations, as I alluded to before. Phosphorous is not only important for bone health, but it's also essential for cellular energy metabolism and important for cardiac, respiratory, and neurological function. It is incorporated in a large portion to the skeleton but is also part of all cells of all tissues as part of cell membranes, nucleic acid, glucose metabolism, energy metabolism, and also oxygen-hemoglobin dissociation curve. With any tissue growth, we need phosphorous for deposition. Phosphorous deficiency is defined as a serum concentration below 4/mg/dL, and severe deficiency below 2.5 mg.

Phosphorous needs depend on growth, and growth depends on protein supply. So, with a higher supply of amino acid and protein from birth onwards, as we recommend today, there's increased phosphorous deposition in the tissue, and that means we need higher phosphorous supply to prevent hypophosphatemia with an increased amino acid supply. The recommended phosphorous supply is in the table: 1 to 2 mmol/d, the first postnatal days IV, then after 1.25 to 3. Although oftentimes in the real world, it's difficult to go above 2 due to the solubility of molar ratio with calcium. With enteral feeding, we aim at a higher intake, 2.3 to 3.9 mmol/kg/d.

Here is a table with more data on the daily enteral nutrient intakes. You can look up the details in the guideline. I don't want to go through the whole table, but I want to encourage [and remind] you that all this information is available. So, go back to the tables [in the book] and look at the details if you have any questions.

How do we in practice approach meeting the recommended nutrient intakes in very preterm infants? Again, we need supplemental parenteral nutrition starting from day 1 with 1.5 to 2.5 g/amino acid/kg/d, increasing rapidly in the next few days to 3.5 g. Along with sufficient other macro- and micronutrients, including phosphorous. Enteral feeding should be started early, within the first 48 hours, preferably with mother's own milk plus fortifier, again reaching at least 3.5 to 4 g/protein/kg/d, along with other sufficient micronutrients. If children show growth faltering, we need to increase the protein intake up to 4.5 g. Parental amino acid intake should not be tapered before we achieve a sufficient enteral intake of at least 75 mL/kg/d.

Let me come to the take home messages. Reference nutrient intakes (RNI) refer to stable growing preterm infant populations and are based on current body weight. For most nutrients, needs are proportional to growth with few exceptions, including water and fat. Nutrient intakes below the RNI, however, may be appropriate during the early postnatal phase prior to full enteral feeding, and also during critical illness. And again, needs of individual preterm infants may need to be adjusted because they can deviate from the population reference intakes.

We have a number of open questions, therefore there are research opportunities to reduce the knowledge gap on nutrient needs in different subgroups of preterm infants. Today we have methods and technologies available that can limit the burden of preterm infants participating in such studies. They've become more feasible than ever, and therefore we think neonatologists and other researchers, as well as funding agencies, should invest in such studies to advance this solid knowledge on optimal nutrition of preterms, supporting the optimal health and development.

Thank you very much indeed for your kind attention.

Guidelines for Nutritional Care in the NICU: Author-Led Cases

Case Challenge

A baby boy is born at 27 weeks of gestation with a birth weight of 600 g. His Apgar scores are 5 at 1 minute and 6 at 5 minutes. He shows respiratory distress and is given a first dose of intratracheal surfactant within the first hour of life. Respiration remains insufficient, and the infant is treated with intermittent positive pressure ventilation (IPPV).

Question 1: Which of the following describes the best option to provide postnatal nutrition for this infant?

A. Provide intravenous amino acids 0.5–1 g/kg/d
B. Aim to increase intravenous amino acid supply to 1.5–2.5 g/kg/d by day 3 of life
C. Do not provide intravenous lipids because of respiratory distress
D. Wait with starting enteral feeding until about day 5 or until the respiratory situation has improved
E. Aim to start milk feeding with 24 ml/kg/d before 48 hours of life, and aim to increase the volume daily by 24 ml/kg

The correct answer is E. Aim to start milk feeding with 24 ml/kg/d before 48 hours of life, and aim to increase the volume daily by 24 ml/kg

Current recommendations suggest initiating an intravenous amino acid supply of 1.5–2.5 g/kg/d on day 1 with an energy supply from glucose and lipids of about 65 kcal/kg/d, and to increase parenteral amino acid supply to 3.5 g/kg/d in the following days. Intravenous lipids can begin within the first days of life, even in infants with respiratory distress and those requiring mechanical ventilation. Enteral milk feeding should not be delayed and should be started within the first 48 hours after birth.

This male infant received a parenteral amino acid supply of 2.2 g/kg/d on day 1, which was increased to 3.4 g/kg/d up to day 4, along with intravenous provision of glucose, a lipid emulsion, sodium, potassium, calcium, and chloride. Donor human milk was started on day 2 at 12 x 1 ml and increased to 12 x 3 ml on day 4. The infant was stable, tolerated enteral nutrition, and respiratory support could be downgraded from intermittent positive pressure ventilation (IPPV) to continuous positive airway pressure (CPAP). Laboratory analysis on day 4 revealed hypophosphatemia (serum P 1.4 mmol/L [4,3 mg/dL]), while other serum electrolytes were normal.

Question 2: Which of the following statements is LEAST correct?

A. Increasing donor milk supply will quickly correct hypophosphatemia
B. A high amino acid supply from birth increases lean body mass deposition which goes along with enhanced tissues phosphorus accretion
C. The normal range of serum phosphorus concentration is 1.8–2.6 mmol/L (5.6–6.1 mg/dL)
D. An adequate intravenous phosphorus supply during the first postnatal days of life is 1–2 mmol/kg/d (31–62 mg/kg/d)
E. An adequate intravenous phosphorus supply after the first postnatal days of life is 1.25–3 mmol/kg/d (39–93 mg/kg/d)

The best answer is A. Increasing donor milk supply will quickly correct hypophosphatemia

The recommended high postnatal amino acid supply along with knowing what this infant received prevents postnatal protein breakdown and induces the desired enhanced protein synthesis and lean tissue accretion; this, in turn, correlates to tissue deposition of potassium and phosphorus. This infant received an intravenous sodium, potassium, calcium, and chloride supply along with the macronutrient supply, but no phosphorus, which induced hypophosphatemia. The recommended intravenous phosphorus supply is 1–2 mmol/kg/d (31–62 mg/kg/d) during the first postnatal days of life and 1.25–3 mmol/kg/d (39–93 mg/kg/d) after

Guidelines for Nutritional Care in the NICU: Author-Led Cases

the first postnatal days. Human milk has a relatively low phosphorus content, which does not meet the needs for the desired rapid lean tissue growth of very low birth weight infants. Therefore, neither donor human milk nor mother's own milk are suitable for correcting hypophosphatemia. A human-milk fortifier for preterm infants is needed to provide additional phosphorus.

Human Milk Fortification for Preterm Infants: A Review

Berthold Koletzko, MD, PhD: Hello, I'm Bert Koletzko, professor of pediatrics at LMU University of Munich. It's a great pleasure to share with you today new global guidelines on feeding preterm infants with fortified milk. Obviously, feeding mother's own milk fortified with extra nutrients is the preferred choice for preterm infants. It is associated with faster establishment of full enteral feeding, with protection against infection, [enhanced] parental bonding, and better cognitive outcomes, as well as other benefits. While most of these effects are associated in observational studies, we have very strong and conclusive evidence from randomized trials with respect to risk reduction for necrotizing enterocolitis. The next best choice after feeding mother's own milk is using donor human milk from a milk bank with established safety standards. But I will show you later in this presentation that this does not have the same benefit as mother's own milk.

Here is the result of the Cochrane review on the effect of human milk feeding on necrotizing enterocolitis risk. You can see that the risk of developing NEC with formula feeding is almost twice as high as feeding with human milk. The number needed to treat for 1 NEC case prevention is 33.

As I said before, donor milk is the second-next choice, but it's not the same as mother's own milk. In this study, for example, you can see that while donor milk achieves faster feeding advancement, the overall weight is not as good as in infants with no donor milk. Donor milk led to lower weight gain. The same is found in this study in 342 very preterm infants, where for each 10% more of donor human milk [given] compared to mother's own milk, there was 2.2 g/less weight gain/kg/d, and there was also less head circumference growth.

Why is that? Presumably because donor milk, on average, has a lower nutrient concentration, in particular lower protein concentration because it is generally collected at a later time of lactation. There's also this study from Boston that reported that cognitive outcomes are worse in infants at 1 and 2 years [of age] who were previously fed donor milk as compared to mother's own milk. Again, this may relate to a different nutrient composition of [the] donor [milk].

So, mother's own milk is the preferred choice of feeding. In order to have mother's own milk available, we should encourage initiation of milk expression soon after birth. A randomized trial indicated it doesn't matter whether it's within the first hour or within the first 6 hours, but clearly soon after birth, we should start with this. We should encourage frequent milk expressions, at least 4 to 7 times a day, which was shown to have a longer duration of milk production and greater milk volumes.

We should certainly discourage informal milk sharing because of the associated risks. In order to make this a reality, we need to establish NICU protocols and invest in parent education on pumping, handling and cleaning, milk storage, and handling and transport.

Human milk is great, but it doesn't contain enough protein to meet the high protein requirements of preterm infants up to 4.5 g/kg/d in the infants with the lowest body weight. So, if we want to meet this

Guidelines for Nutritional Care in the NICU: Author-Led Cases

amount of protein intake, we need to add protein-rich fortifiers.

You see here the rapid decrease of protein content in human milk from the first week of lactation onwards with increasing duration of lactation (in green) in mother's own milk—much further below—is the quotient content in donor milk. This is much lower than what we need to achieve for the very preterm baby. We need to close the gap. What's more, there is quite a variation between mothers, between milk samples, so one and the same approach may not be leading to the best outcome.

Protein fortification of human milk works, as Cochrane review showed in 6 randomized control trials, and improved weight gain, length gain, and head circumference gain without adverse effects, in particular without any increase of NEC risk.

Why do we fortify and for whom? Why do we want to avoid postnatal growth faltering, avoid deficits in minerals and micronutrients, support linear growth in bone mineralization, and improve neuro cognition. The infants who need fortified human milk are the very preterm infants below 32 weeks, infants below 1800 g body weight, and, of course, infants requiring food restriction, and therefore a concentrated diet. The targeted outcomes are to meet nutrient needs, approach growth similar to fetal growth, and reduce growth faltering and the associated adverse effects.

Special challenges you want to avoid are low weight gain, which leads to a higher risk of later metabolic disorders and noncommunicable diseases, slow head growth, which is associated with delayed motor and cognitive development, and postnatal growth faltering.

We have a variety of products available to fortify or to supplement human milk. We have multicomponent fortifiers, in other words fortifiers that not only provide protein but also other important nutrients. For example, phosphorus and others, derived either from cow's milk or from human milk. We also have single-nutrient supplements providing only protein fat carbohydrates. These are not used for standard fortification, but for individual-targeted fortification of infants with special needs. Generally, we prefer to use multicomponent fortifiers. And, finally, we have formulas for preterm infants, which we can use to supplement human milk if there is only a limited amount of human milk available. Here we have a choice between preterm formula with higher protein and nutrient density or postdischarge formula, slightly lower density for larger and infants at a later point in time.

In terms of the type of fortifiers, we have powder fortifiers. We typically add 0.8 to 1 g/protein/100 mL; or liquid fortifiers, which tends to add slightly higher amounts of protein. There is a discussion where the liquid fortifier that could potentially have more untoward effects on diluting beneficial components of human milk, but this discussion has not come to a firm conclusion at the moment. We have fortifiers that use hydrolyzed protein. The potential benefits are still under discussion. And many human-milk fortifiers also add energy from carbohydrates and fats to increase energy content up to 80 kcal/100 mL.

When and how should we start fortification? There's no full consensus about the best time to start fortification. The general recommendation is to add full-strength fortification when the infant reached 50 to 100 mL/kg/d of enteral feedings. We should not wait until, or delay after that, because there's no benefit from a delayed start, but a risk of slower growth. Full strength, there is no demonstrated advantage of starting with diluted fortification, with less than full-strength fortification. We have a lot of data to show that this is safe, introducing early fortifications, and it is not associated with feeding intolerance nor with increased NEC risk.

Guidelines for Nutritional Care in the NICU: Author-Led Cases

The benefits of starting early are improved postnatal growth. Fortification is considered early when it is started at enteral feeding between 20 and 60 mL/kg/d. Starting before 60 mL/kg/d may be beneficial particularly for infants with a low weight, between 500 to 1250 g birth weight, and were associated with improved body weight and head circumference gain. Again, no increase in complications, such as feeding intolerance and NEC. And a Cochrane meta-analysis on fortification at 20 or 40 mL compared to 100 mL found no conclusive evidence to support or refute early human-milk fortification.

There have been fortifiers made available based on human milk and human-milk protein. The Cochrane meta-analysis concluded there's no demonstrated benefit for using human milk over cow's milk-based fortifiers in preterm infants. There is a low certainty evidence from 1 study in human milk for preterm infants. In fact, there's no change in risk of NEC mortality, feeding intolerance, infection, or growth. I guess more data are needed to have a large number of quality studies.

What fortification strategies should we follow? We have the option of a standardized fortification. In other words, every infant gets the same. We have 1 standard dose added to a certain amount of human milk. This was shown to improve postnatal growth and bone mineralization, but it does not achieve adequate growth in all very preterm infants. The alternatives are adjusted with targeted fortification. Adjusted fortification, basically adjusts the dose of the fortifier and the protein intake to weight gain and or metabolic markers, such as blood urine nitrogen. Studies reported higher weight and head circumference gains, if you use this approach compared to standardized fortification. The targeted fortification adjusts the dose to measured composition of human milk, which is now possible in the unit. It's safe and has an apparent benefit also over standardized fortification.

Let me show you a couple of examples. This is a study using targeted fortification based on human-milk analysis. If you look at the right panels, you see that with standard fortification you have a very large variation of intakes achieved because the human milk content of protein is so variable with a targeted fortification. You not only achieve a higher overall intake, but you also reduce this variation, and you avoid the very low intakes that you achieve with standard fortification in some infants.

Clustered fortification: here is a study that had a standard process to go up or down with the dose of the human milk fortifier depending on categories of blood urine nitrogen. You could see that with this adjusted fortification, this supply of protein improved—went markedly up. And along with that, the growth of weight gain and head circumference gain was improved.

In conclusion, we should always fortify human milk for very preterms or preterms below 1800 g. It is reasonable to start full strengths fortification at 50 to 100 mL of enteral feeding. Bovine protein multicomponent fortifiers can be recommended as a standard approach, because we have at this time no evidence for a greater benefit of the human milk-based fortifiers, which by the way are far more expensive. We aim at protein intakes of at least 3 g/kg/d in small preterm infants, and we recommend targeted or adjust fortification, because it has a better benefit than standard fortification.

Should we consider continuing fortification after discharge? Well, it's probably a good idea in human milk-fed very preterm infants with growth restriction at discharge or poor growth after discharge. Those that have high requirements because of continuing medical problems, particularly chronic lung disease. We can, in practice, do this by mixing expressed human milk with fortifier and feed part of the milk as expressed milk and some unfortified milk, for example, by

Guidelines for Nutritional Care in the NICU: Author-Led Cases

direct breastfeeding in half and half proportions. Alternatives are finger feeding of the solid fortifier along with breastfeeding or alternating breastfeeding with a preterm formula. We need to monitor growth in these babies with an appropriate growth chart, and we should probably continue this in infants at risk up to 40 to 52 weeks post-conceptual age, depending on the individual growth.

Let me summarize my key messages. Human milk with added fortifier is a preferred feeding mode for preterm infants, in that a greater proportion of infants achieve adequate growth. Delayed start of fortification increases the risk of growth faltering and therefore should be avoided. If we want this to happen, we should establish a written unit policy for promoting and supporting human-milk feeding and educating parents, and for implementing human milk fortification for preterm infants. We strongly recommend the use of targeted and adjusted fortification over standard dosage. And we think that continued fortification after hospital discharge may be beneficial, particularly for those infants that show growth faltering.

With respect to our research needs, we really would like to see more data on effects on outcomes. We know that multicomponent human milk fortification improves growth, or we would like to see whether it also has benefits on later neuro development. We need better evidence on the optimal timing of introducing the fortifier. We would like to see well-designed and adequately powered control trials that compare different fortifiers, particularly those based on bovine and human milk. And we need to evaluate further the use of purification with breastfeeding post discharge.

With this, I thank you very much indeed for your kind attention.

Preterm Nutrition and Pulmonary Disease

Fernando R. Moya, MD: Hello, I am Fernando Moya. I'm a practicing neonatologist, and I have the rank of professor of pediatrics and director of the division of Wilmington Pediatrics Specialties under the Department of Pediatrics, University of North Carolina. Today we are going to talk about, in specific terms, the content of the chapter Dr. Ariel Salas and I wrote for the Koletzko book [*Nutritional Care of] Preterm Infants*, namely *Preterm Nutrition and Pulmonary Disease*. As you know, preterm infants are at very high risk for developing chronic lung problems, especially if they undergo a process of growth restriction in utero. That process conditions the lungs for a variety of reasons, which are discussed in more detail in the book—to be at high risk for developing a transition and then established chronic lung disease. The more growth restricted infants are at higher risk of developing this, so you need to be attentive for that. Prevention or amelioration of this involves a variety of nutritional interventions that we're about to describe.

You need to start paying attention to the fluid intake. The abundant data shows that fluid excess may worsen the lung status of the baby and put him or her at high risk for lung disease, both acutely and chronically. The data about fluid restriction is not as clear in terms of lowering the risks for chronic lung conditions, especially because as you lower you also limit the ability to provide nutritional intake. However, we discuss starting points for babies who are less than 2000 g of 60 to 80 mL/kg/d. Perhaps a little more for babies who are much smaller and have increasing insensible water loss. So, the first step is trying to prevent free water overload.

You need to provide a balanced source in nutrition that is based primarily in carbohydrates, trying to avoid excess or very high glucose infusion rate because those have been shown to increase

Guidelines for Nutritional Care in the NICU: Author-Led Cases

respiratory quotient that has increased CO_2 production.

And in a baby with a limited ability—for instance, a baby on a ventilator or a baby on respiratory support—that may increase the baby's work to breathe. You want to balance that with adequate protein that you start around 2 to 2½ g/kg and progressively increase to about 3½ to 4 g/kg, depending on size and gestational age over the next several days. It's important to add, from the word go, or shortly thereafter, triglycerides intravenously because they need to be a source of long-chain polyunsaturated fatty acids like the docosahexaenoic acid, DHA, and we'll speak a little bit more [about that] in detail. It has become quite obvious that we also need to watch minerals from the first 24 hours onwards, as often, infants who are growth restricted may have specific deficiencies of calcium, but primarily phosphorus and potassium.

That deficiency of phosphorus, the hypophosphatemia, is particularly important because phosphorus is a form of energy storage and, therefore, if you are deficient in that, your respiratory function may suffer, and infants with hypophosphatemia are clearly at higher risk for staying on the ventilator longer. So, those deficiencies need to be ascertained and corrected.

Also, you need to be mindful about the potential effects, although not clinically very apparent, acutely, of the role of certain vitamins like A, D, E, and specific micronutrients like selenium and, particularly, zinc. We will refer to this a little bit later.

Regarding long-chain polyunsaturated fatty acids, especially DHA, but also arachidonic acid, they're very important. They're part of lipid emulsions that are now available. You should know that some of the commonly used intravenous lipid [soybean oil-based injectable lipid emulsion solutions, eg, Intralipid] do not contain a large amount of DHA or ARA. Others like SMOF [soybean oil, medium-chain triglycerides, olive oil, and fish oil] do contain variable amounts of DHA and ARA, and of course some [fish oil triglycerides injectable emulsions, eg, Omegaven] contain a larger number.

This is really important because the long-chain PUFAs are very important for the balance of inflammation and anti-inflammation. It's being a part of cell membranes. Their deficiencies have been associated with lung problems and elsewhere. There is data suggesting that maternal supplementation with DHA would be able to ameliorate or lower the risk of preterm infants developing chronic lung disease.

This was borne out from a study in primarily Australia and New Zealand where they supplemented moms who were breastfeeding with tuna oil, thereby increasing the concentrations of DHA in the breast milk. This was quickly followed by studies in which DHA, in particular, was given directly to infants. The amounts were extrapolated from the maternal supplementation of 600 mg. These infants were very preterm, who received 60 mg/kg/d of DHA alone. That study published in the *New England Journal* a few years ago, not only did not show any improvement in terms of progression to BPD, but perhaps a slight increase.

Another large study approached the issue again by supplementing the mothers with twice as much as the prior study had done. Moms who were about to breastfeed their preterm infants were given 1.2 g of the docosahexaenoic acid, the DHA, or placebo. In that study, they also showed no decrease in the risks of BPD, and perhaps a slight increase. So, for now, we need to know more about the intervention of providing this supplementation with DHA. A lot of the criticism has been borne out of the fact that perhaps you need to supplement not only DHA but arachidonic acid, as well.

For about 2 decades now, we have known that many preterm infants are vitamin A deficient at the time of birth, and that generally tends to get

Guidelines for Nutritional Care in the NICU: Author-Led Cases

exacerbated, as there's no increased amounts of vitamin A in the current formulations we provide. Also, the content of vitamin A in breast milk, which is the feed of choice nowadays, is not very high. There have been several trials that have suggested that administering primarily intramuscular high doses of vitamin A can reduce the risk of BPD. Those have been put together in systematic reviews that still suggest this, but the fact that the dosing has been intramuscular has made some people shy away from its use. There are still currently ongoing trials that are looking at larger doses of vitamin A, and also being given enterally, that hopefully will shed some light onto this.

Now, there has also been interest in other micronutrients in terms of their relationship to BPD, or [whether] they could be used therapeutically. There was some interest in selenium, however, there was a large trial that showed that at least giving extra selenium to infants did not reduce the progression to BPD. There's been some interesting studies with zinc. Zinc can be dramatically decreased in babies who are preterm because they did not accrue enough storage. Moreover, the chronic use of diuretics results in significant urinary losses. In a study from Cincinnati, they added extra zinc to preterm infants who had established BPD and did not have a normal pattern of growth and saw a substantial improvement in their rate of growth. This is currently being studied further in a much larger randomized control trial.

So, from a practical point of view, from the word go, avoid free water overload and avoid high glucose infusion rates, especially in infants who have restrictions to eliminate carbon dioxide.

Follow the phosphorus level early, as it is likely to be low, commonly in babies who are preterm, especially those who are growth restricted. Correct those efficiencies because advances in protein without correcting phosphorus might make it worse. Consider vitamin A supplementation if it's something that you believe the data has borne out to be useful. It is a safe intervention to use.

For infants who are commonly on respiratory support and have problems tolerating feeding, consider positioning the infants in prone position, as there's a lower energy expenditure in that position, albeit small. Then lung compliance and resistance tend to be better, avoiding abdominal distension with continuous feeding. If you do this, bear in mind that if you're using primarily breast milk, and you give that continuously, there's likely to be a substantial energy loss as the amount of fat will tend to adhere to the walls of the tubing.

Also, once a baby is either evolving to or has established chronic lung disease, and he or she is breathing fast, don't forget that could increase resting energy expenditure and effect growth. The way to overcome that is if you are ensuring an adequate protein intake, it generally adds more energy, usually in the form of fat, with something, for instance, like MCT [medium-chain triglyceride] oil. So, watch your infant, if he or she is tachypneic, initiate this intervention.

Some key takeaways for these preterm infants: As mentioned, avoid high glucose infusion rates, start a balanced parenteral nutrition, including amino acids and fat, especially fat solutions that contain DHA and advance dose progressively.

We have learned quite a bit about the role of nutrition in preterm lung disease, but there's still a lot more to know. Some research priorities ought to be large studies looking at either maternal or neonatal supplementation, of not 1 but both DHA and arachidonic acid, potentially to reduce the risk of bronchopulmonary dysplasia. In addition, the data suggesting zinc deficiency limiting growth is very intriguing. We need larger studies to see whether in those infants, perhaps earlier or while they have established lung disease, the intervention of adding additional zinc may promote

Guidelines for Nutritional Care in the NICU: Author-Led Cases

growth. Growth is very important, as long-term studies have shown that a lot of the lung improvement depends on progressive growth, particularly length growth of the infant.

This series will have a case attached in which you will be given descriptions of a scenario of a real, live premature baby who had a progression to chronic lung disease, and what things to ponder as you're managing that infant from a nutritional point of view. Thank you.

Case Challenge

A female infant was delivered through cesarean birth at 28+2 weeks due to poor intrauterine growth and intermittent absent end-diastolic blood flow. Mom was exposed only to 1 dose of antenatal corticosteroids. Her birth weight was 730 g (8%), length 33 cm (10%), and head circumference 24 cm (17%) on the Fenton growth curves. In the delivery room she was started on continuous positive airway pressure (CPAP) but developed significant retractions, and there was a need for supplemental oxygen, to 40%. She was given a surfactant via INSURE [INtubation-SURfactant-Extubation]. The umbilical catheters were placed in the umbilical artery (UA) and umbilical venous (UV), and she was started on "vanilla" hyperalimentation, containing 2% protein and D10W (10% dextrose in water), plus calcium at 80–90 ml/kg/d.

Question 1: Which of the following metabolic abnormalities is this infant at risk of developing?

A. Hypoglycemia
B. Hypernatremia
C. Hypophosphatemia
D. All of the above
E. A and B

The correct answer is D. All of the above

Growth restricted preterm infants are at a high risk for hypoglycemia, hypophosphatemia, and hypernatremia, especially with the administration of parenteral nutrition with protein plus calcium and no phosphorus. Also, the addition of a sodium (Na) load in the umbilical arterial fluids at a time when no added Na is needed often results in the elevation of serum Na.

This infant's early course was complicated by persistent hypoglycemia, requiring high glucose infusion rates (GIR), elevated triglycerides while she was receiving an intravenous lipid emulsion, which prompted their discontinuation, and a persistently elevated blood urea nitrogen (BUN). On day 15, she remains intubated on high ventilatory settings along with the need for 38% oxygen. Her most recent arterial blood gas (ABG) is pH 7.27, partial pressure of carbon dioxide (PCO2) 67, partial pressure of oxygen (PO2) 58, and a base excess (BE) of 8. Repeatedly, she has not tolerated gavage feedings of donor breast milk above 30 ml/kg/d given over of duration of 20 to 30 minutes. She receives hyperalimentation with D13W and a GIR of 13 mg/kg/min, protein of 4 g/kg/d, and no lipids.

Question 2. What adjustments might be beneficial in her nutritional management?

A. Lower protein intake because her protein/energy ration is not optimal
B. Lower GIR to potentially decrease CO2 production
C. Add a small amount of intravenous lipids to increase energy balance and provide essential fatty acids
D. Slow down feeds and use the prone position
E. All of the above

The correct answer: E. All of the above

This infant is getting excess unbalanced energy from carbohydrates and probably driving CO_2 production higher. Moreover, she is at risk for essential fatty acid deficiency if no lipids are provided for several days. The persistently elevated BUN most likely reflects a protein breakdown for energy as opposed to growth. Slowing down her

Guidelines for Nutritional Care in the NICU: Author-Led Cases

ANNENBERG CENTER FOR HEALTH SCIENCES AT EISENHOWER
Imparting knowledge. Improving patient care.

This activity was supported by an independent educational grant from **Mead Johnson Nutrition**.

feeds and the use of the prone position may facilitate better tolerance. One needs to keep in mind that the slower the feeds, the higher the potential for loss of fat if breast milk is the primary source of feeding.

The infant is now 35 days of age and was extubated after a course of systemic dexamethasone. She is on a nasal CPAP of 7 and FiO2 [fraction of inspired oxygen] 28% to 30%. Her saturations are in the normal range, but she breathes most of the time between 70 to 80 times per minute. She is on full gavage feeds of donor milk fortified to 24 kcal with a bovine-derived human-milk fortifier. Her total fluids are mildly restricted to about 140 ml/kg/d, and she receives intermittent loop diuretics. Her growth has been rather slow, weighing only 930 g. All measurements are below the 3rd percentile. Her present pertinent lab results show: Na 136, K 4.0, Cl 95, Total CO_2 28, BUN 6, Creat 0.5, Ca 8.7, P 4.8. Alb 2.6.

Question 3. What adjustments might be beneficial in her nutritional management at this stage?

A. Increase energy selectively
B. Increase protein selectively
C. Increase both energy and protein intake
D. Continue a similar approach

The correct answer is C. Increase both energy and protein intake

This infant probably has a much higher resting energy expenditure given her constant tachypnea. She would benefit from more energy in the form of fat. Moreover, her low BUN is indicative of not enough protein, and some of it is being catabolized for energy. The relatively low Ca/P [serum calcium/phosphorus] relates to a marginal albumin (Ca). Those levels of Ca and P support the fact that adding more energy, protein, and solutes (like increasing human-milk fortification) would be well tolerated.