Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Nutritional Care of the Preterm Infant: International Guidelines

✦ Course Transcript ✦

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Nutritional Care and Long-term Outcomes

Berthold Koletzko, MD, PhD: You all know we have seen amazing progress in the outcome of preterm babies, particularly the very small ones, where all over the world mortality has declined and survival has increased. We see examples from China and the US, but there are many other data from all around the world. Along with this improvement in short-term outcomes, there is a shift of attention to what happens in the long term with these babies. That implies a greater focus on nutritional care because we have more and more evidence that nutritional care markedly affects outcomes for the short and long term.

But there is uncertainty as to what to do and how to do it, and therefore, we recently brought a great group of global experts together and developed a second edition of this global recommendation, *Nutritional Care of Preterm Infants*.

In this second edition, which is actually the fourth edition because it follows a great example of Reginald Tsang from Cincinnati who started this whole concept, we developed and revised new recommendations. And here are some of the changes where we put more emphasis on parenteral nutrition from day 1, with more amino acid acids and phosphorus, early provision of lipid emulsions with higher supply of the long-chain PUFA [polyunsaturated fatty acids] that you just heard about. More emphasis on meeting protein needs, [and] prioritize providing mother's own milk with sufficient fortification, and more attention to feeding after discharge. The goal that we had was to define adequate nutrient intakes to meet physiological requirements for growth, health, and development, and we based this on a systematic review of the scientific evidence. But as you can imagine, for a number of questions, the evidence is not as good as we would like it to be. So clearly, there are uncertainties for a number of nutrients, and we have more work to do.

For many nutrients, the needs are related to weight gain velocity, so we differentiated some of the recommendations based on body weight and what we considered a desirable weight gain at the different body weight categories.

Nutrient Intakes Range

We all know not every baby is equal. There is a range of different physiological conditions. That's how we conceptualize nutrient intake recommendations, which do not refer to the individual baby, but [rather] to the population of babies that has a normal distribution from an intake that causes deficiency, to an average requirement, to the reference nutrient intake, which is the intake that is supposed to meet the needs of all the populations.

Then there's an upper safe level of intake—a level that is considered safe and above. We are concerned about potential adverse effects of too much [intake]. What we try to do is provide intakes in this green range, the acceptable range of intakes between the level that meets the needs of basically all babies and the upper safe level of intake. Importantly, we have defined these for stable growing preterm infant populations, again based on their body-weight categories, but they are not applicable for each and every baby. Individual babies may have a different need from these population intake recommendations depending on their condition. We still need to use our brains and look at the individual baby and its disease

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conditions. We still have gaps, obviously. We have research opportunities to close these gaps in different subgroups of infants. We have had great progress in methodology and technologies that can further these research studies with very limited burden on babies. We think our profession and the funding agencies should invest in such studies to advance our knowledge in this area to promote optimal nutrition of preterms for the benefit of their long-term health and development.

Preventing Nutritional Emergencies

Why is this? Well, think of this 1000-g baby born at 28 weeks. If you look at, it is 85% water. It has 100 g of protein. It has 20 g of fat, and it is basically all non-exchangeable fat, it's structural fat, and it has basically no glycogen in its liver. So, this baby has no utilizable energy stores. You can see it—there's no subcutaneous fat. If you don't feed it, what will this baby need to do? It will need to burn its body's substance; it will need to burn its protein to sustain itself. So, this is what happens. On the green line, you see what this baby would do if it was still in utero. It would have a fetal accretion of about 2 g/kg/d of protein.

If we give this baby just a glucose infusion, as we perhaps did in the past, then this baby will not gain protein but will burn about 1.2 g protein/kg/d to meet its needs. In only 1 week it will have lost 22% of its body protein. Think about that, 22% of your lean body mass of your organ structure, of the structure for your brain, your liver, everything. That's what we call a nutritional emergency. We can't afford this to happen, particularly if you think about the critical organs like the brain, which for growth and development needs substrates; it needs energy, and it needs building blocks to grow and develop its potential. In fact, we have a number of studies that show if we provide more energy and amino acids in the first week of life, we have a benefit for outcome. This is an association of energy and amino acid intake in extremely low birth weight infants adjusted for confounders. And we see that for each 10 kg/cal/kg body weight intake, in the first week, more, the mental developmental index at 1½ years of age corrected, increased by 4½ points. And for each 1 g of amino acids, it increased by 8.2 points. It's plausible, if you think about it. If you malnourished a preterm baby, you malnourished its brain and the brain function.

It is not the energy; it is not the fat deposition. More glucose doesn't do the trick because it's the lean body mass that matters. As shown in this study, the lean body mass in these infants born before 33 weeks predicted brain volume, volume of the cerebellum, the white matter, and the white matter microstructure. But fat mass did not predict any of these outcomes. If you give more glucose, it won't do the trick.

The same here: this is a study from Boston looking at the variation in protein energy provision with human milk during the hospital stay. It predicts brain growth of these preterm babies until term. With more protein intake above the 80th vs below the 80th percentile, you have an increase of the brain volume by 36 mils; you have an increase of cortical gray matter, deep gray matter energy intake, [a] similar trend. So, what we do really matters for the development of this extremely critical organ.

Parenteral Nutrition

If we think about what we try to achieve, we try to match the fetal growth as much as we can. If you look at the fetal accretion, you see that between 500 and 1000 g of fetal weight, it's about 4 g/kg/d going down to a 3.5, between 2.2 and 3 kg. If you then calculate the energy intake, you see what large amounts of protein you need to match that intrauterine accretion. In the extremely low birth weight infants, you need 3.8 g/protein/100 kcal, and then it gradually goes down as a baby grows. That's difficult to achieve; that's a lot of protein to provide.

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There's good evidence for this, first for the parenteral amino acid provision early on, this is a Cochrane review comparing less than 2 to at least 3 g/amino acids/kg/d. You see that with the higher provision of intravenous amino acids early on, you have less SGA [small for gestational age] at discharge, you regain birth weight faster, you have a better head circumference gain, less hyperglycemia, even less retinopathy. So, [there are] strong arguments for giving at least 2 to 3 g/amino acids/kg/d. And that's what our recommendations are, to start intravenous amino acids from the day of birth at around 1.5 to 2.5 g/kg/d and increase within a few days to about 3.5 to 4 g. Aim to provide sufficient glucose and lipids with it, because if you don't provide the energy, then your amino acids are oxidized. It will not contribute to protein synthesis. Importantly, provide phosphate along with the amino acids, and we'll come back to that. If you have more lean tissue deposition, you also have more phosphate disappearing in your cells. We recommend not to taper IV amino acids before reaching enteral nutrition intake of about 75 mg/kg/d.

So again, if you increase the amino acid supply, you also need to increase the phosphorus, because with more accretion of lean tissue, you also have more phosphorus going from your circulation into the intracellular space. Here are the recommendations for the phosphorous supply. Basically, equimolar to calcium supply.

Start Enteral Nutrition Early

How long [should you provide] parenteral nutrition? In the past many have thought, let's wait to introduce enteral nutrition; it may be beneficial for reducing NEC [necrotizing enterocolitis]. We have learned that concept doesn't hold true. Again, a Cochrane review of 14 RCTs [randomized control trial] comparing delayed versus earlier introduction of progressive enteral feeds, delayed, meaning at least 4 days after birth. There's absolutely no benefit for NEC, for mortality, for feeding intolerance. The only effect that you see if you delay enteral nutrition is that you have more invasive infections, more line-related infections. So, clearly not the way to go. Start enteral nutrition early. Try to reduce parenteral nutrition as soon as you can.

Neurodevelopment Outcomes

What do we feed? We have these choices: mother's own milk, donor milk. We don't want informally shared human milk. I don't think I need to discuss that. We want to provide human-milk fortifier. We have preterm formula. We don't want to give a term formula to a preterm baby. Human milk is beneficial. The evidence is good, very good for reducing necrotizing enterocolitis. Here again, the Cochrane showing that with feeding formula compared to donor human milk in randomized trials, the relative risk for NEC is almost doubled. Clearly, [this is] a very strong argument to try to push human milk as much as we can.

There are also associations between provision of mother's own milk and neurodevelopment of school-aged [children] at 7 years. Higher intake of mother's own milk improved IQ, reading scores, math scores, and was associated with less attention deficit hyperactivity symptoms at 7 years. Better reading, better spelling [are associated] with longer duration of mother's own milk, and the association was particularly strong in the infants born below 30 weeks.

[There is] similar data here: neurodevelopment at 5 years, breastfeeding for at least 3 months, in the German neonatal network of 2,500 very low birth rate infants. Median GA [gestational age], 28 weeks, just below 1000 g, at least 3 months of breastfeeding increased full-scale IQ by 2.2 points; conduct problems, hyperactivity, inattention were all significantly reduced. Very strong data were obtained from association studies, not from randomized studies, obviously.

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Mother's Own Milk vs Donor Milk

However, we should remember that mother's own milk and donor milk are not the same. This is a warning sign from a study from Tufts that showed Bayley III cognitive scores at the corrected age of 1 year and 2 years were significantly better in babies fed own mother's milk than donor milk. And there's more data. There is a lot of data showing that infants don't grow as well on donor milk [as on] mother's own milk. In this study, a large group of infants from 22 to 36 weeks tend to regain birth weight at 36 weeks or at discharge. All are significantly worse with donor milk compared with mother's own milk.

Same in this study here. Very much the same story with more donor milk. There's less weight gain and, more importantly, also less head circumference. This is a very recent study from Canada showing the same from Meghan Azad's group from Winnipeg, with higher mother's own milk intake, there was higher weight gain and, interestingly enough, there was also a beneficial effect on the infant microbiota, and there was less gut inflammation indicated by lower calprotectin with mother's own milk compared with donor milk. This study, by the way, was designed to test the effects of human milk vs bovine milk fortifier where there was no difference in any of the outcomes. The type of fortifier didn't matter for weight gain, for microbiota, for other outcomes, but it really mattered whether they had mother's own milk or donor milk. Clearly the conclusion is we need to try our best to motivate mothers to provide their own milk whenever they can.

Donor Milk Limitations

Now why is the growth so much worse? One thing to remember is that donor milk is usually collected at a later stage of lactation, maybe 3, 4 months after births. Then the composition of the milk is very different. For example, if you look at the protein content, it is markedly lower at that stage of lactation than early on when the mother pumps her own milk for her own baby. (18:18) That may be 1 of the key elements why donor milk doesn't provide the same result.

Also, for other nutrients in this case. You just heard about the importance of omega-3 DHA [docosahexaenoic acid]. The global mean for term human milk is 0.3% [of DHA]. If you look at the DHA content in milk banks in the United States, it's much lower than the global mean and both are much lower than what we recommend today as an intake for preterm infants with milk to match intrauterine accretion, where we aim for 0.5% to 1%. If you provide donor milk, on average you will provide much less DHA than the baby should get.

ARA & DHA Brain Accretion

We heard it already from Christina [Valentine] before on the importance of arachidonic acid (ARA) omega-6 and DHA omega-3 for brain development. We know there's a lot of accretion in high rates both in utero and during the time of treating the preterm baby in hospital. We have a lot of data showing that matters. This is a recently studied randomized controlled trial from Australia where preterm infants were provided with an extra 60 mg/DHA/kg/d. You can see that there was a significant improvement of intelligence at 5 years. So, a high level of DHA is similar to what the baby would get in utero is really beneficial. Human milk provides not only DHA but also arachidonic acid. Interestingly, the ratio is pretty stable in your milk for term infants from our own recent study in preterm infants from Toronto that showed the

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same. In both cases the ratio between arachidonic acid with DHA was about 2:1. There's always more arachidonic acid than DHA in human milk. And for the time being, we think there is a biological reason for this. Infants need both arachidonic acid and DHA.

This recent study is very impressive from Scandinavia showing that if you supply the amounts of arachidonic acid and DHA to preterm infants that the baby would otherwise get in utero, you reduce the risk of severe retinopathy by one half—one half the risk of retinopathy and the risk is correlated with both arachidonic acid and DHA concentrations in the serum of the babies.

Preterm infants grow faster and need more DHA and arachidonic acid than [full] terms. They need about 30 to 65 mg/DHA/kg/d and 50 to 130 mg/arachidonic acid/kg/d. Mothers who provide breast milk should be encouraged to eat oily fish regularly. We just heard it, but in addition, [they] also need to take DHA supplements because realistically they won't eat enough fish; they won't be able to eat enough fish to bring the levels of DHA up to the desirable range of 0.5% to 1%. In the Australian studies it took about 600 mg/DHA/d to bring up the DHA in milk of preterm infants to the level that we think is desirable. Also, if we choose a preterm formula, we should look out for formulas that provide about that dimension of DHA and arachidonic acid, 0.5% to 1% of DHA, preferably with arachidonic acid matching at least the amount of DHA.

So again, mother's own milk is a preferred choice. It should be fortified. Donor milk from a milk bank is the second-best choice, but it's not the same as mother's own milk. Again, the key benefit is risk reduction for necrotizing enterocolitis. Plus, we have a lot of indications for other benefits. You just heard it: microbiota, brain development, and other outcomes.

Improving Growth

Now if we feed babies human milk, we still need to watch the enteral protein intake. With enteral feeding, also an intake of at least 3 g/kg enhances weight gain in this Cochrane analysis with no untoward effects, no effect that would scare us regarding risk of NEC, sepsis, or diarrhea.

Now, as I showed you before, human milk protein is viable, and it decreases over time. If we aim for about 2.5 g/[per deciliter]/protein/100 mg/milk, we need to fortify, and we need to fortify even more, the older the baby gets and the later the stage of lactation is. You see again the comparison with typical donor milk, which is in a very different dimension.

Enteral Protein Intakes

We aim for these high enteral protein intakes, and to do that we need to fortify. [There is] very strong evidence, Cochrane again, with protein fortification 6 randomized trials. We improve weight gain, length gain, and head circumference gain without adverse effects, no change of NEC. So, for whom [do] we fortify milk? For very preterm babies below 32 weeks, for infants below 1800 g. And for other conditions, we aim to avoid postnatal growth faltering, deficits in minerals and micronutrients, improve linear growth and bone mineralization, and also neurocognitive developments.

When to start? There's no consensus. We discussed this back and forth in the expert group and the data is just not there. A good guess is to start with about 50 to a 100 mg/kg/d. There's data that these smaller babies benefit more from an early introduction, but there is a lack of good evidence when that best time is. In reality, there's not 1 answer, but it may depend very much on the condition of the baby. But don't wait. If you delay introducing a fortifier, you have no benefit. The only effect is that you will have more growth faltering. There's no advantage to starting with a reduced dose. There's no reason not to start

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with full-strength fortification, and it is safe when introduced early with enteral feeds, not associated with feeding intolerance.

Fortification of Human Milk

There is a big discussion which fortifiers to use. The Cochrane analysis shows that human-based fortifiers have no benefit over cow's milk-based fortifier, multicomponent fortifier. There is low evidence from 1 study suggesting no change in risk of NEC, mortality, feeding intolerance, infection, or growth. If you look at the glossy brochures that you see, you need to watch out because often studies are cited that compare studies where infants were fed either human milk, human milk fortifier or human milk with a bovine fortifier and cow's milk formula. That's not a clean comparison. Obviously, we know if we feed cow's milk formula, we have a different outcome.

Evidence from comparing human milk fed babies who were fed only human milk and then randomized to cow's or bovine fortifier, like the 1 I just showed you from Meghan Azad's group or Debbie O'Connor's group in Toronto show no benefit at all from the human milk fortifier. So, there is no reason, at the moment, to go for one preferentially. I will skip this because I understand that we'll hear more in the next talk about adjusted and target fortification. So, I can go over this quickly.

To conclude, fortify human milk for very preterm and preterm infants below 1800 g. Start full-strength fortification at about 50 to 100 mg/kg. The standard should be the bovine protein multi-component fortifiers. Aim to reach protein intakes of at least 3 g/kg/d. We advise targeted or adjusted fortification, but we'll hear more about that in the next talk.

Research Needs

We still have a lot of open questions. We need to understand better the variability of human milk composition, the predictors, we know the diet is 1 of them, but it's not the only 1 and the effects of that variability. We need to have better evidence or intervention in mothers to improve diet, lifestyle, and related infant outcomes. We need to look at how we can improve the quality of donor milk, for example, by donor selection and by different ways of processing. Multinutrient human milk fortifiers have been shown to improve outcomes until discharge-like growth, but we have a lack of information on long-term outcomes where we would like to know more.

Again, we have uncertainty about the optimal timing to introduce fortifiers. We need more well-designed and well-powered trials to compare different fortifiers head-to-head, bovine vs human milk, intact vs hydrolyzed protein, liquid vs powder. We have a lot of open questions. Lastly, we want to evaluate options in the effects of fortification also after discharge for those infants who may benefit from it.

There is good preterm formula available, but I want to highlight that they are not all the same: composition varies. Here you see is 1 example with the protein density per energy, which is variable in different preterm formula. I told you before, the DHA content is variable. It is worth looking at the labels when you choose your formula and look at what you're feeding your babies.

We want to stress again, early introduction of nutrition, ideally between 6 and 48 hours after birth and rapidly advance it. There is randomized clinical trial evidence showing you can advance 24 to 36 mL/kg/d. That is well evaluated by RCTs. There's no reason for routine evaluation of gastric residuals. That has been very well studied.

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We want to compare the composition of fortifiers and preterm formulas and choose products that best approach meeting the high nutrient needs of our patients. Importantly, we need regular monitoring, evaluating growth measures and establishing a written unit policy with all the groups that work on the babies. Motivate and train them and audit what we're doing.

Feeding After Discharge

Finally, what do we do when the baby goes home? Typically, babies are discharged at about half of a term baby's weight. So clearly, they still have low nutrient stores and higher needs than the term infants. Oftentimes we put them on breastfeeding, and everybody's happy—the family's happy, the staff is happy, the baby is finally fed at the breast. Or we give them a term formula and that may not be optimal for meeting the nutrient and gross needs of these babies. So, we often see growth faltering after hospital discharge.

What do we do with them? Well, 1 option is to give more volume or add more energy. Some people add oil or maltodextrin, dextrin maltose to improve the weight gain. What happens then, you have a weight gain that is going up. But if you look closely, if you put the babies in the air displacement plethysmography system (Pea Pod™) that you just saw, you basically promote body fitness. If you give more empty calories, more energy without substance, and that's not what we want. We don't want excessive fat. We don't want overfeeding empty calories. Too low protein-to-energy ratio, also, after discharge, makes babies fat.

If you look at what the baby needs at up to 2.2 kg or between 2.2 and 3.3 kg, typical on mother's milk, this provides much less; donor milk even less. If we would fortify the own mother's milk or the donor milk, we get closer to what the baby needs. If you give a preterm formula after discharge, then we also get closer to the requirements.

And that has been nicely studied. This is a Cochrane review [with] 16 trials on post-discharge feeding. If you give babies preterm formula with more nutrient intensity, more protein, more nutrients compared to term formula, [you will] have a benefit not only for weight gain, but importantly for lean body mass gain, for length gain, for head circumference gain. Also, if you use a typical postdischarge formula, which has less nutrients in density than the preterm formula, you have a benefit for weight and length. The key driver in this systematic review of 31 studies was really the ratio between protein and energy.

After discharge, try not to fatten your babies—no overfeeding with empty calories. Try to aim at a good protein-to-energy ratio, support breastfeeding obviously, but consider human milk fortification, particularly in those babies that grow poorly. Again, advise fish and omega-3 intake for the breastfeeding mothers. If the baby's not fully breastfed, use a postdischarge or preterm formula. And don't forget to monitor the growth. Don't forget to follow up with the baby.

Thank you very much indeed for your time and attention.

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Abbreviations

ARA	arachidonic acid	**LC-PUFA**	long-chain polyunsaturated fats
DHA	docosahexaenoic acid	**NEC**	necrotizing enterocolitis
GA	gestational age	**SGA**	small for gestational age
IV	intravenous		

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