Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Global Guidelines for the Nutritional Care of Preterm Infants

2022 Symposium

✦ Course Transcript ✦

Overview

Berthold Koletzko, MD, PhD, and Brenda B. Poindexter, MD, MS, are lead expert contributors to the updated and expanded 2nd edition of the global guidelines for the Nutritional Care of Preterm Infants.

Improved care for premature infants has increased survival rates in very low and extremely low-birth-weight infants. Recent evidence related to nutritional requirements contributes to improved long-term health outcomes for premature infants. In this course, filmed at a live symposium, Dr. Koletzko and Dr. Poindexter present key nutritional needs, new lipid and protein requirements, and how to approach human milk fortification in premature infants. They discuss guidance for clinical application, while highlighting continued research opportunities to advance nutritional care of preterm infants.

Target Audience

This activity was developed for pediatricians, neonatologists, nurses, advanced practice clinicians, registered dietitians, and other healthcare providers involved in childhood health.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Apply expert nutrition recommendations for very low-birth-weight infants in your clinical practice based on 2021 preterm infant nutritional guidelines.
- Identify areas in your clinical practice that will benefit from the latest preterm infant nutritional guidelines for enteral nutrition in very low-birth-weight infants.
- Identify research opportunities to advance nutritional care of preterm infants.

Faculty

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Faculty

Berthold Koletzko, MD, PhD
Speakers Bureau: Mead Johnson Nutrition, CAE Healthcare
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Spouse Employer: Pfizer

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The estimated time to complete the activity is 1.5 hours.

This activity was released on May 27, 2022 and is eligible for credit through May 27, 2024.

Obtain CE/CME credit at pnce.org/Preterm-Guidelines

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Editor's Note: This is a transcript of a live symposium presented in Denver, Colorado on April 24, 2022. It has been edited and condensed for clarity.

NUTRITIONAL NEEDS AND RECOMMENDED INTAKES FOR PRETERM INFANTS

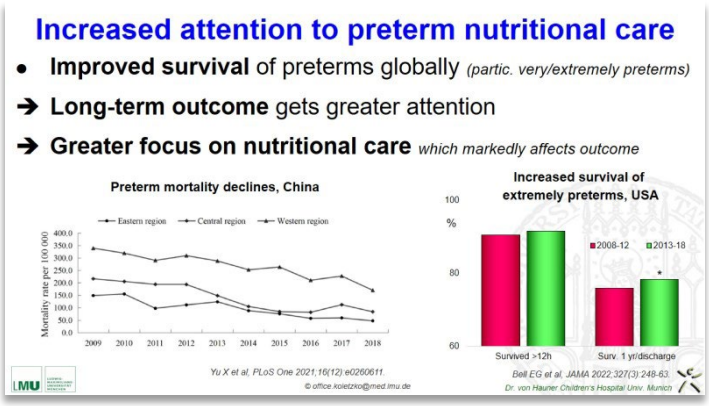
Berthold Koletzko, MD, PhD: I can't tell you what a great pleasure it is to be, jointly with Brenda, here at a face-to-face meeting. We wish, so much, to share with you some of the highlights of the exercise that we performed trying to review the current knowledge, the current evidence on preterm nutrition, and bring this together in a global consensus for recommendations for practical application.

It builds on the previous great work that Reginald Tsang has provided. Many of you will know his books he produced since the 1980s, and we've been following his tradition, trying to translate science into practice. We had great support from Reginald Tsang, who wrote a chapter in this book, as well, on the historical perspective.[1]

This is what we are going to touch upon: the nutritional needs, the protein requirements, lipid intake recommendation, what's new in iron and vitamins, human milk and fortifiers, the practice of enteral nutrition, the need for multidisciplinary approach and audit, and feeding after discharge. We can only highlight some of the key points, but you will have the book available to look at in more detail when you go out at the end of the symposium and pick up a copy.

Nutritional Needs

Let's start with nutritional needs and recommended intakes. Why are we so worried about this? We see there is increased attention to nutritional care of preterms. We've seen encouraging improvements in survival of preterms all over the world. You see here examples from China and the United States.[2] You can go anywhere in the world and see these positive developments. With that, the shift of our attention is moving. When I was starting my training in the NICU, our concern was survival and avoidance of acute complications. Pneumothorax was still a big thing at the time, or NEC [necrotizing enterocolitis], and now we are moving more and more to asking what is going to be the long-term quality of life and health of these babies. That gives us a greater focus on nutritional care because we know that markedly affects outcome.



So, this was the key motivator for us to invest time and work into developing these new global recommendations that appeared at the end of last year, compiled by leading experts from around the world.[3] We really tried to give this a global perspective because there are challenges in every country. We are focusing today more on the topics that are primarily relevant for practice in high-income countries, but we have a lot of reference in the book to restricted resource environments

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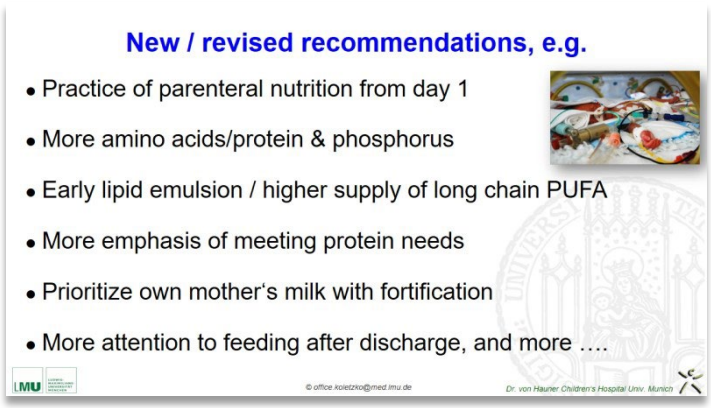
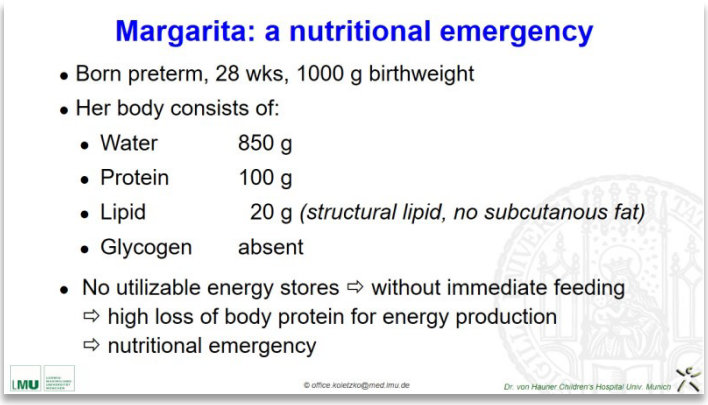
because we believe that also in other parts of the world, we need to have practical approaches.

We were quite thorough. We identified experts in the field who drafted a chapter, which was critically peer-reviewed by 2 external reviewers and 2 editors, and then often completely revised. This was followed by a formal consensus process, with 3 consensus recommendations, until we resolved all issues and had consensus on the recommendations.

So, what has changed? A number of things have changed. We have put more emphasis on parenteral nutrition from the first day of life, increased needs of amino acids and protein along with phosphorus. Brenda will focus on that. The use of lipid emulsions early on and the higher supply of long-chain PUFA [polyunsaturated fatty acids], more emphasis on meeting protein needs, prioritize own mother's milk with fortification, and more attention to feeding after discharge, among other topics.



Let's start with a case. This is Margarita, born at 28 weeks with about 1,000 g of birth weight. If you look at what she is, she is 85% water; she is 10% protein; very little fat, 20 g of fat, very tiny little bit, and all of that fat is not subcutaneous fat, which is exchangeable, but it's primarily structural fat. And basically, no glycogen. So, what does it mean? She does not have any energy stores that she can use, no subcutaneous fat, no liver glycogen. But if you don't feed her, she will have to burn her protein for energy production to meet her energy needs. That's why we call this a nutritional emergency.



What does this mean? If she were to have been in the uterus for another week, she would have accreted about 2 g/kg a day more of protein. If she is in your NICU and is given a glucose infusion only, then within 1 week, she would have lost, relatively speaking, 22% of her protein.[4,5] In other words, she would have eaten almost a quarter of her body, a quarter of her muscles, liver, brain tissue, all of that. That is something that certainly cannot be considered as an appropriate way to go.

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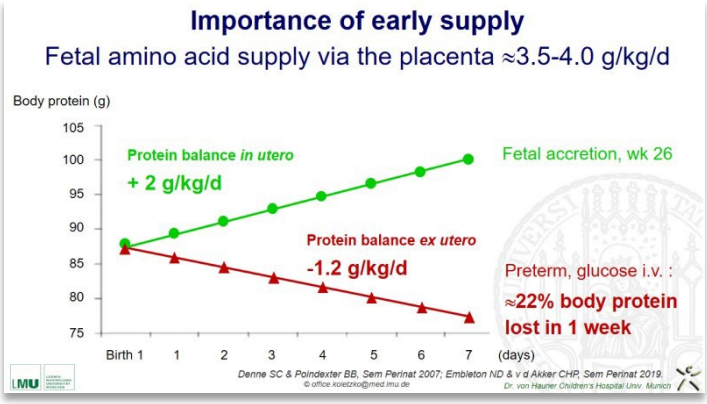
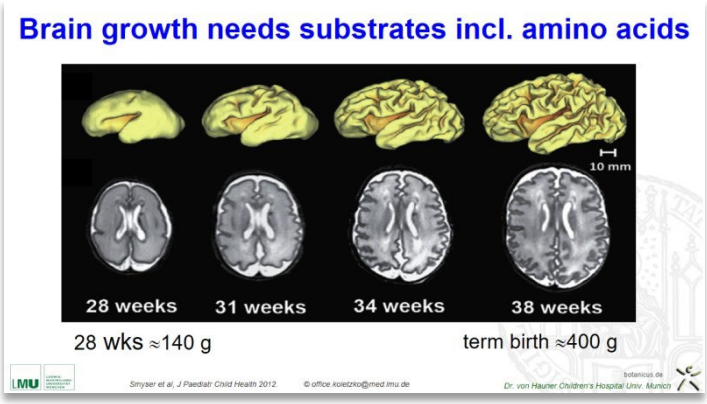
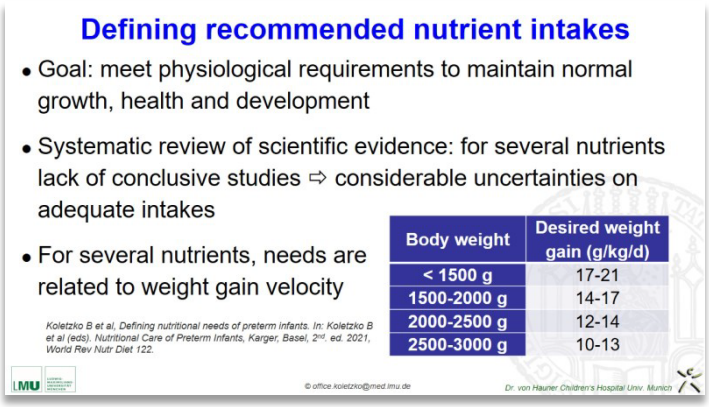


We're particularly concerned about this organ, which you all know well, grows extremely rapidly at the end of pregnancy and during the first postnatal weeks and months. So, if you think of Margarita, she has a brain of about 140 g, and by the time of term birth, it has grown to about 400 g. Huge increase in brain size, and, at the same time, the structure of the brain changes dramatically. At the time of Margarita's birth, it looks like a coffee bean. At term birth, it should look like a walnut. All this needs a lot of energy and substrates.



We all know from many studies, if you don't feed babies, if you malnourish them, then the brain suffers. There's a very impressive paper just published very recently by Katherine Bell from Boston who looked at what predicts brain growth, and she showed that **lean body mass of the baby, of very preterm babies, predicted brain volume**, **white matter volume and white matter macrostructure**, but body fat did not at all.[6,7] So, it is the lean body mass that we need to push. It comes back to the topic of protein supply that Brenda is going to address.

We tried to define the recommended nutrient intakes as those amounts that maintain normal growth, health, and development without inducing adverse metabolic stress. We built this on a systematic review of the scientific evidence. The limitation, of course, is for the different groups of preterm infants. We have limited evidence for a number of nutrients, and therefore we have considerable uncertainties on what is adequate intake. For most nutrients, the needs are related to weight gain velocity, and so we define here in the table what we consider **desirable ranges of weight gain for different birth rate categories**,[8] but of course that is also based on some assumptions, because **we still don't know exactly what weight gain for which baby will lead to the best outcome**. We can't assume it is just the weight category at birth that will predict it, but we will assume there are other factors—another unresolved topic for future research.



So, this is the concept on which we built those recommendations. A cross distribution of nutrient requirements in the population with the lowest threshold intake below. Almost certainly there would be a deficiency occurring—an estimated average requirement, which is the recommended intake for energy, and the reference nutrient intake, defined as the average requirement plus 2 standard deviations, which would be the adequate minimum

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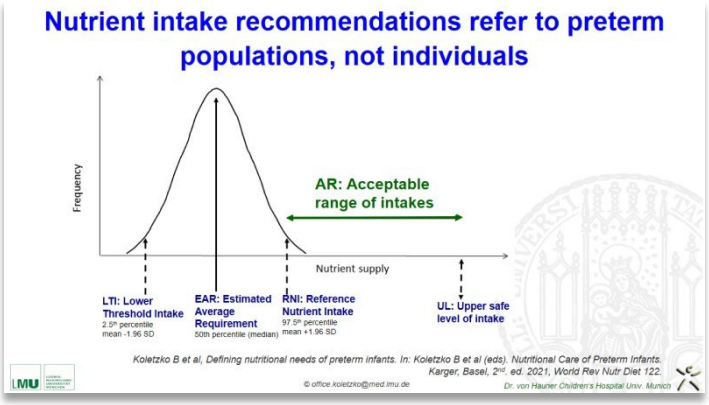
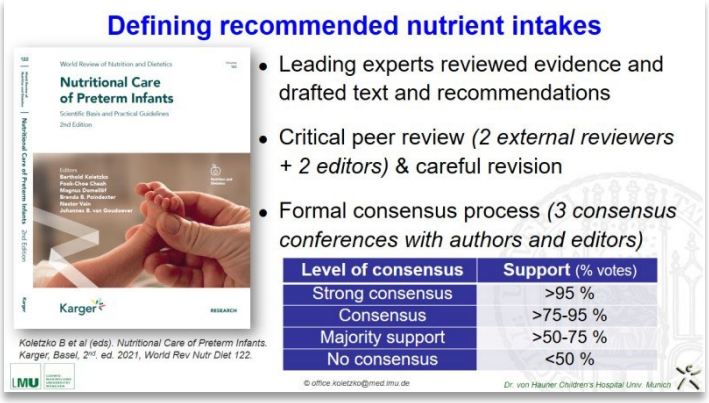
intake for almost all babies covering the needs of the population, basically, and then upper levels of safe intake. So, the acceptable range of intake is between the reference nutrient intake and the upper safe level.[8]

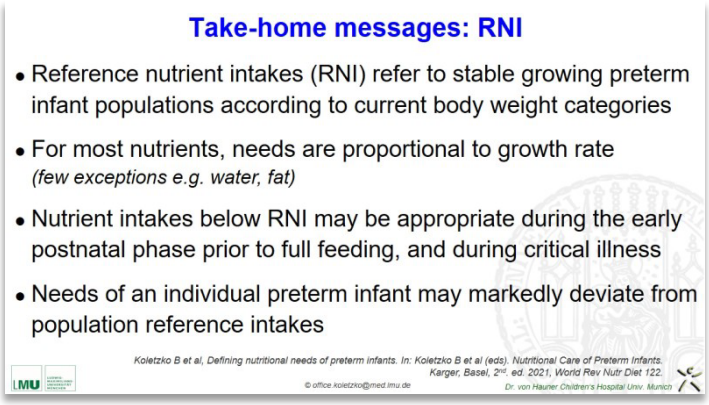


Now, this is a nice model, but it's not perfectly correct because we know, for some nutrients, the solution is not following a normal nascent curve, and we also have a lot of open questions. For example, defining the upper level of safe intake is not easy in preterm babies. So, we live with some assumptions. We live with some uncertainties in the way that we go forward.

Again, we had a very critical process, which I mentioned before. We defined the level of consensus that you will find in the book depending on the percentage of votes at the consensus meeting that was supporting the respective recommendations.[8]



Take-home messages: Reference nutrient intakes (and we state them in the book), refer to stable growing preterm infant populations, not individual infants, based according to body weight categories, most of them based on very low birth rate infant group. For most nutrients, needs are proportional to growth. Exceptions are, for example, water and fat. Nutrient intakes below these recommended values may be appropriate during the early postnatal phase prior to full feeding and during critical illness when the baby's metabolism cannot really use and utilize a full supply. And finally, the numbers in the book will not be appropriate to each and every individual intake: consider the child with cholestasis, with fat malabsorption, with a large cardiac shunt. There will be cases that have different needs, so you still need to look at patients individually.



We have enormous research opportunities, such as discussed by Dr. [Ariel A.] Salas, who has done great work in this area. We have technologies and methodologies today that allow us to explore nutrient needs without much burden on preterm infants, which will allow us to close the knowledge gap on nutrient needs in different subgroups of preterm infants. This will hopefully also relate the nutritional care and the details of that to outcomes, which I think is going to be a key question to guide our future practices.

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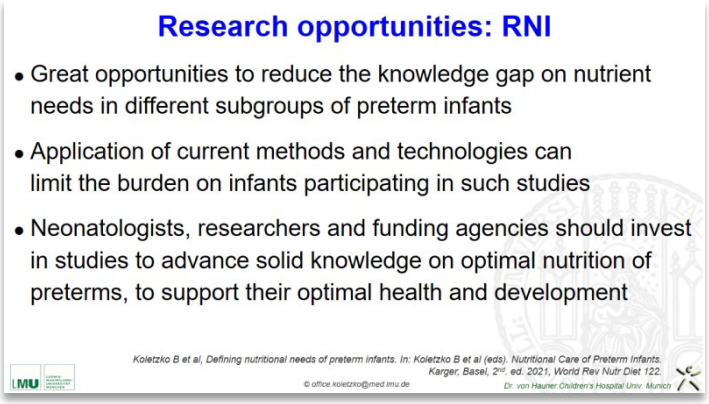

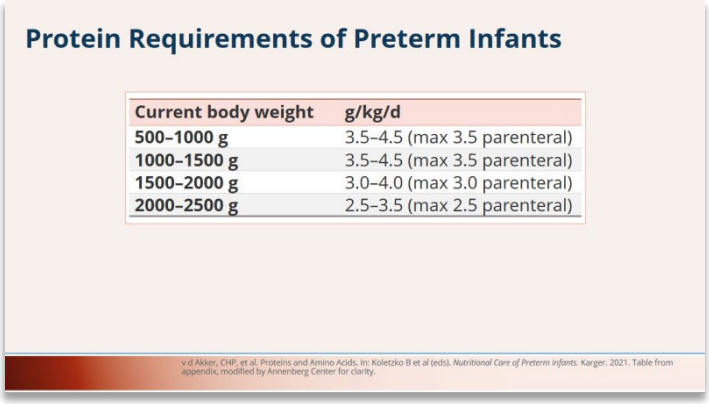

We have a great diverse group of people here—neonatologists, researchers, and funding agencies—help to invest in studies that advance our knowledge on optimal nutrition in preterms to support optimal health and development.

Protein Requirements of Preterm Infants

Brenda B. Poindexter, MD, MS: Participating as an editor in this book has really been one of the best parts of my career. I think the first edition, when we all were able to meet in Munich and reach consensus, was a little more fun than the Zoom meetings this time, but hopefully, for the third edition, we can go back to an in-person format.

I wanted to highlight some of the new recommendations for protein requirements of preterm infants. This is just a summary of the requirements where we landed for recommendations in the book.[9] They are based on current body weight, and this is probably well-known to most of you, but the protein requirements do change as gestation progresses. So, our tiniest, most immature infants have higher protein requirements than those who are approaching term.

The second point I want to make is that protein requirements are higher if the baby is being enterally fed. We really do not have good data to support going above 3.5 g if the baby is receiving parenteral nutrition.

We talk a lot about protein quantity, and I think that when we look at some of the studies that perhaps have not shown clear benefits to higher protein intake, one of the things I think a lot about is protein quality. It's really sad that in the past 30 years we have not had *any new products* developed for parenteral amino acids. I think this is a really important area of research. And just remembering that none of our currently available amino acid solutions were, in fact, designed for preterm babies and especially not extremely low-birth-weight infants.

The solutions we currently use were based to match plasma amino acid concentration of a term, breast-fed infant. There are several amino acids that are essential, or conditionally essential, for the preterm infant, or just not able to be stable in the solutions we currently have.

So, things like tyrosine, cysteine, to the extent that they're limited in the amino acid products, may be hindering our ability to promote protein accretion by their absence.[9] I think this is, in my mind, one of the most important future areas of research. And remembering that we've really never had any head-to-head comparisons of different amino acid

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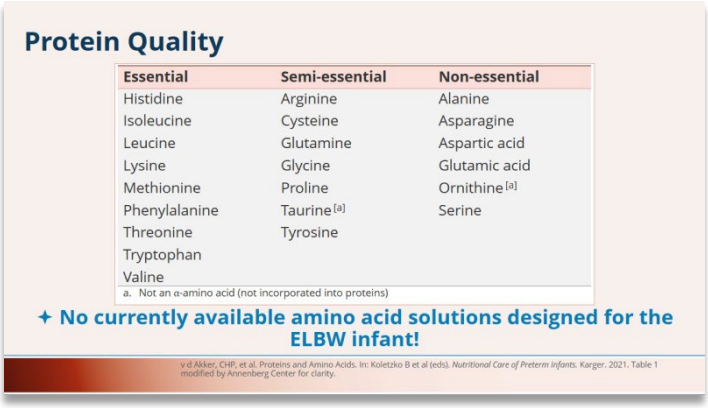
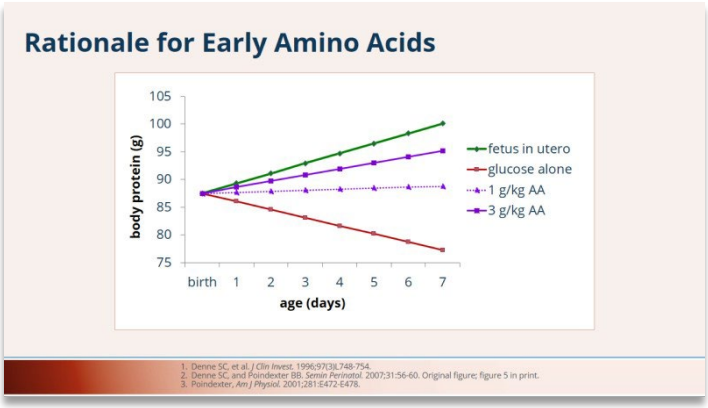
solutions to look at longer-term outcomes, such as neurodevelopment.

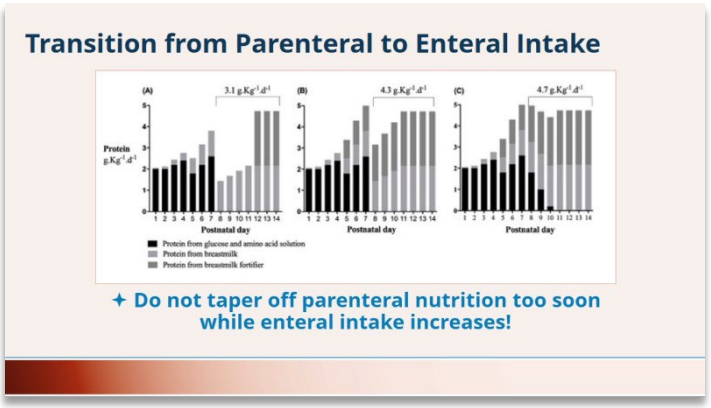


Early Fortification

Dr. Koletzko showed the slide earlier talking about the baby in the case, and what would happen if we did not give parenteral nutrition from the beginning. This slide adds in the anticipated rates of protein accretion in purple if you gave 1 or 3 g/kg/day. Just by starting some protein, we can limit catabolism. This really shows you the rationale for why we suggest starting approximately 3 g, as soon as possible after birth.[10,11] We can't quite meet the same rate of accretion that would have happened in utero, but we can come close, and we can hopefully prevent some of that deficit that can be really challenging to recoup.



One of the other concepts that has become increasingly important is **not thinking about parenteral intake in isolation from enteral**. For a lot of reasons—we'll talk about a little bit later—with the practice of enteral nutrition, it's important to think about giving both parenteral and enteral. What we've done on this slide is giving you 3 hypothetical differences in how you might approach parenteral nutrition, and then starting human milk, and fortification of human milk.



So, to orient you, the darkest bars are protein from parenteral nutrition. The medium ones are protein from human milk, and then the darker gray ones are protein from fortifier. In the first slide on the left, you're starting parenteral nutrition immediately; you're starting human milk on that first day but waiting to fortify until the second week of life. Then you contrast that with the graph on the far right, which is showing earlier fortification and continuing parenteral nutrition a little bit longer. You can see that over that week to 2 weeks, you're having a substantial difference in the amount of protein intake. In this example, it's up to 1.6 g/kg/day.

As you're thinking about starting early parenteral and enteral nutrition, a key takeaway is realizing that if you're not starting early fortification, and you're tapering parenteral nutrition early—and we all have to balance that risk of prolonged central lines and so forth—I think that's a really vulnerable period where you may, inadvertently, not give as much protein as you're intending.

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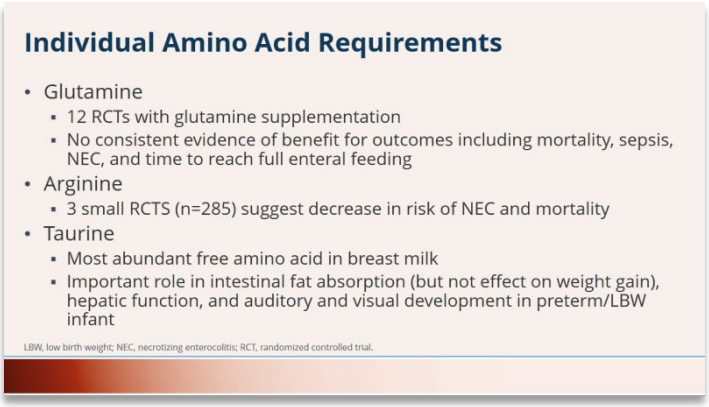
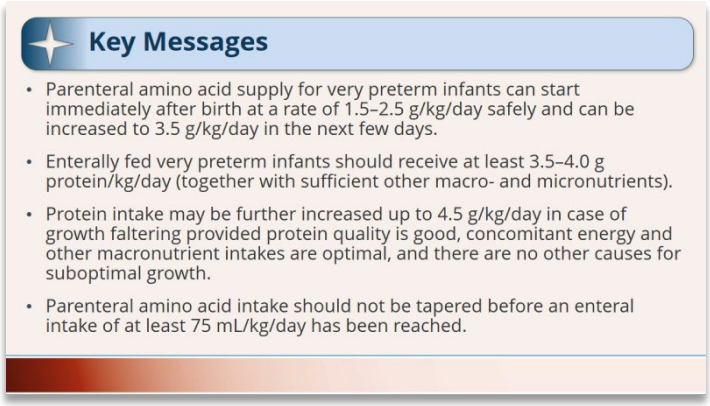
Amino Acid Requirements

We really don't know a lot about individual amino acid requirements. I wanted to highlight a few that may be of importance, especially for future studies. Glutamine is one of the most abundant amino acids in human milk. There have been 12 different randomized clinical trials looking at glutamine supplementation. Unfortunately, we have found no consistent evidence or benefit for outcomes, including mortality, sepsis, NEC, and time to reach full enteral feedings.

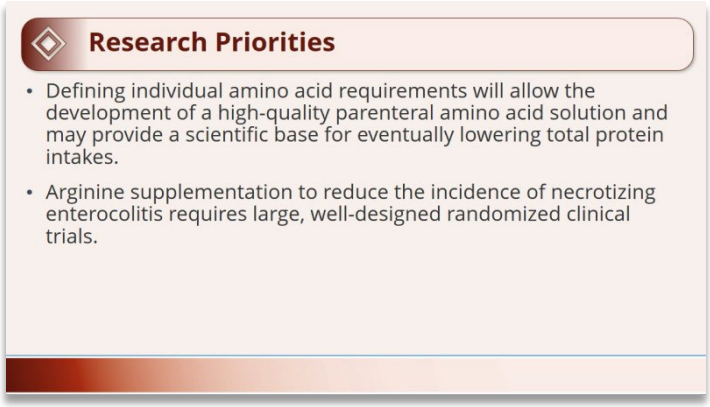


Arginine is one in which we have a few small randomized clinical trials that suggest a decrease in the risk of NEC and mortality. Taurine is the most abundant free amino acid in human milk and has an important role in intestinal fat absorption. But again, it has not been shown to have an effect on weight gain. It may be important for hepatic function, auditory and visual development in the preterm infant.

Some of the key messages from this section are that parenteral amino acid supply for very preterm infants can start immediately after birth. I would say a minimum of 1.5 g/kg/day and can be increased to the 3.5 g in the next few days. In thinking about enterally fed preterm infants, they should receive 3.5 to 4 g/kg/day. Again, this is contingent upon other macro and micronutrients being sufficient, and, as Bert said, this is a population recommendation. You may find individual babies who need a bit more than that. In the case of growth faltering, enteral protein intake can be further increased to 4.5 g/kg/day, but again looking at what are some of the other causes for suboptimal growth and addressing those. Then my personal recommendation is that we shouldn't be tapering parenteral amino acid intake until you're receiving at least 75 mL/kg of enteral.



Future research priorities in this area include defining individual amino acid requirements. This may allow the development of a high-quality parenteral amino acid solution and may then give us a scientific rationale to eventually lower total protein intakes. I think the opportunity to study arginine supplementation to reduce the incidence of NEC will require a large, well-designed, randomized trial. As we've heard in many situations at this meeting, sometimes when we have some prospect of benefit in smaller studies that are inadequately powered, it's an opportunity to finalize that question with a large RCT.



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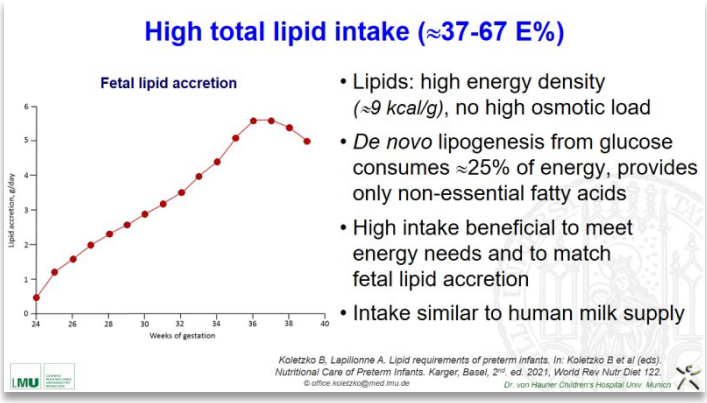
New Lipid Intake Recommendations for Preterm Infants

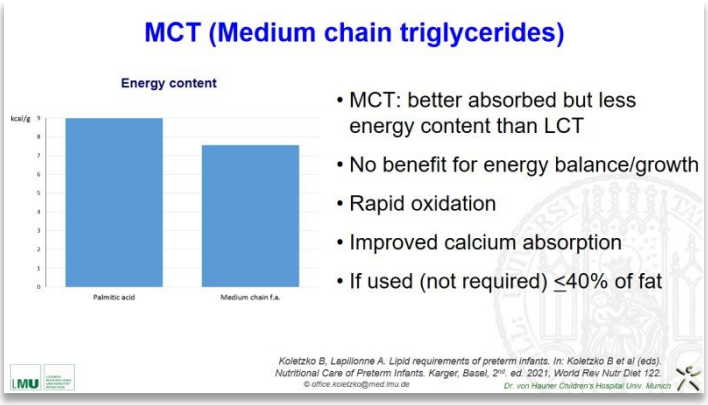
Berthold Koletzko, MD, PhD: Let's look at the fats. It's amazing how much lipid is deposited in the fetus during gestation. You see the increasing lipid accretion, 1 g/kg/day, going up to almost 6 g/kg/day at 36 weeks—a huge amount of lipids being deposited in the baby.[12]



We don't really have reason to define a strict upper and lower limit of lipid intake. Our guidance is based on the range we find typically in human milk, and we probably will learn more in the future. But clearly, there is a benefit of providing a high portion of the nonprotein energy as lipids, because it has a high density of energy without inducing a high osmotic load.

We know if we give more calories from carbohydrates, then we would need to produce lipids *de novo*, which is energetically ineffective. You lose 25% of the carbohydrate energy if you convert glucose into fatty acids, and you also provide a nondesirable fatty acid profile. So, we think it's advisable, for the time being, to go for a higher lipid intake similar to what you would provide with human milk.

Medium chain triglycerides [MCT] are better absorbed than natural fats, but they have less energy as the bar graph shows, about 16% less chemical energy per gram.[12] Therefore, many studies have shown if you add more MCT, you don't have a benefit in the population for energy balance and growth. You only have a benefit if you have severe fat malabsorption in cholestatic babies or in short-gut babies, or the like.



Other characteristics of MCT are that they are rapidly oxidized; they enhance calcium absorption. We think the use in enteral feeding is optional; it's not required, but if used, it should not exceed 40% of total fat intake.

Long-chain PUFAs

Now, the lipids topic that has received most attention is, of course, the long-chain polyunsaturated fatty acids. To wake you all up, we put in this very complicated question. Don't get frustrated if you feel this is too difficult. The options are A: High amounts of omega-3 DHA are deposited in the growing fetal brain, followed by modest amounts of omega-6 ARA [arachidonic acid]. Option B: Preterm infants provided with adequate amounts of linoleic and alpha-linoleic acids synthesize sufficient arachidonic acid and DHA [docosahexaenoic acid] to cover their needs. Option C: Human milk content of DHA is pretty stable, but ARA content in human milk varies markedly with maternal intake of vegetable oils. Option D: Preterm infants should receive about .2% to .3% of their fatty supplies as DHA. And option E: Preterm infants should receive ARA intakes 1 to 2 times the intakes of DHA. Very difficult, but make a choice, please. If

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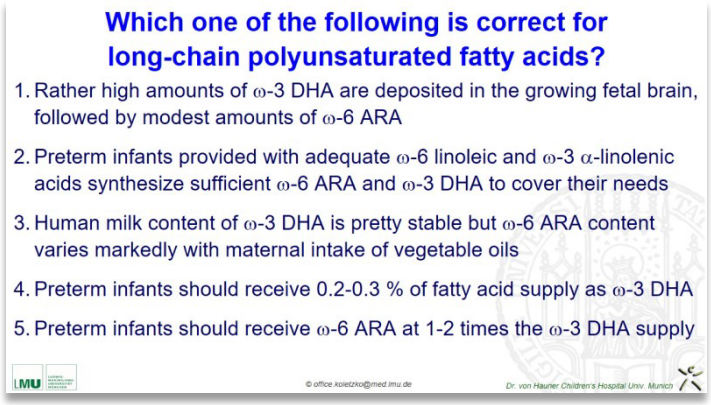
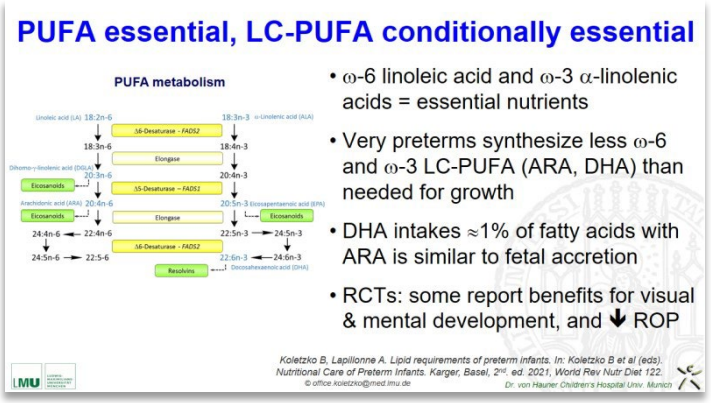
you don't know the answer, just take a random guess.



Wow! We have a great distribution. Every question had some attraction for someone. So, A, yes, high amounts of DHA are deposited, but the amounts of ARA that are deposited are even higher. B, we have a lot of evidence now that you provide enough linoleic acid, infants cannot maintain their levels of arachidonic acid and DHA because the rate of disappearance from the plasma is higher than the rate of synthesis. C, the human milk content of arachidonic acid is pretty stable and does not depend much on maternal diet, whereas DHA is more variable and depends on maternal DHA intake. D, we don't think .2% to .3% of fatty acids is sufficient for the preterm infant. We think preterm infants need something near 1% of DHA. And E, yes, we strongly advise that arachidonic acid intake should be at least as high as DHA—1 to 2 times the amount of DHA. I would go along with the majority that voted for E.

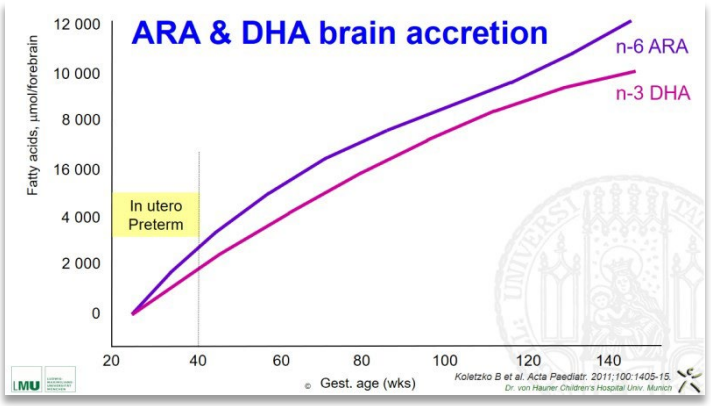
Polyunsaturated Fatty Acids

Let's have a quick look at the long-chain PUFA. You know that polyunsaturated fatty acids, omega-6, and omega-3 are essential substrates that we need to eat on a regular basis to maintain health and body function. Very preterms—which was 1 of the questions—synthesize less of the LC-PUFA of DHA and other than they need for growth. The rate of synthesis is much lower than the rate of disappearance from the plasma in a growing preterm baby. If you calculate the fetal deposition in the baby in utero, then you would require about 1% of fatty acids postnatal to match that accretion, along with arachidonic acid. RCTs all report safety when providing DHA and arachidonic acid. Some, but not all, report benefits from visual and mental development. And there's 1 exciting trial, recent trial, that reconfirms a previous observation that they are associated with less retinopathy.[12]



Brain Accretion

This is the brain accretion in utero and after birth of the term infant for the first 2 years when the brain grows rapidly.[13] You'll appreciate that the accretion of arachidonic acid is even higher than the accretion of DHA, although most of us are always hearing about DHA—arachidonic acid is the neglected sister, oftentimes, in the public discussion.



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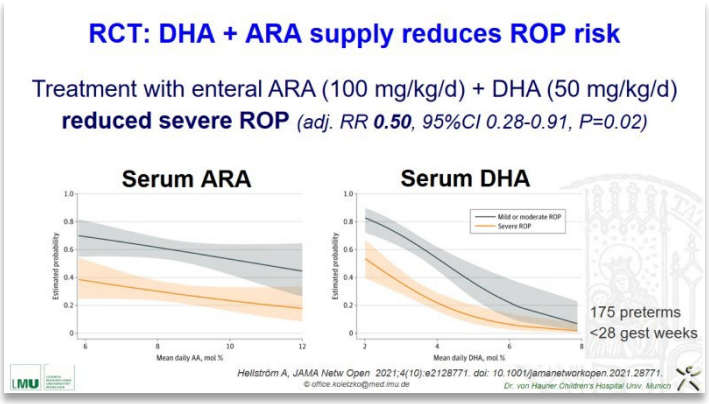
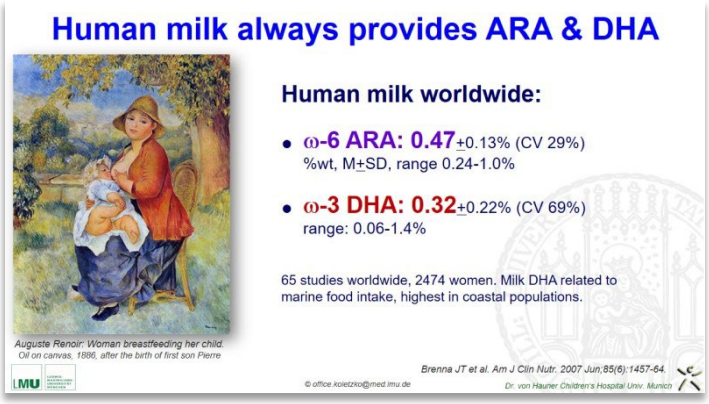
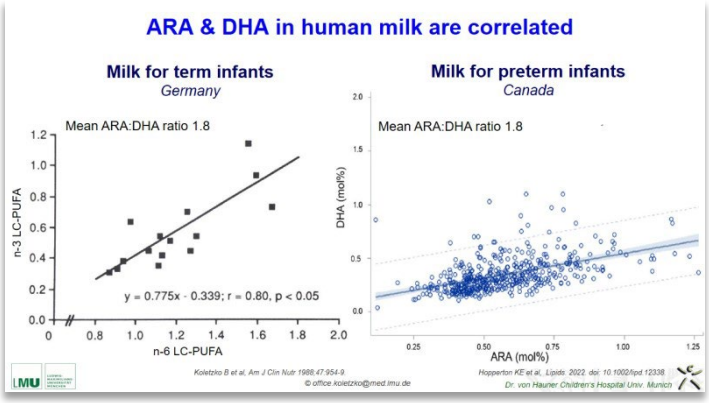
This impressive study by Hellström randomized preterm babies to standard feeding or an added arachidonic acid and DHA in a 2:1 ratio, 100 mg/kg/day of ARA and 50 of DHA.[14] She found this reduced severe retinopathy by one-half, [which is] an amazing benefit, and when you look at the data, it is both ARA and DHA levels in serum that predict the reduction of retinopathy.



Human milk always provides these fatty acids. If you look around the world, human milk on average provides .5% arachidonic acid and about .3% DHA.[15] If you look at CV, you see the variation of DHA is greater than that of ARA. Arachidonic acid in all populations around the world is stable, whether they have a high or low omega-6 intake, whether they have ARA found in their foods or whether they have a vegan diet, arachidonic acid changes very little. DHA, however, changes markedly with DHA intake from the mother. If she has a high fish consumption, then DHA goes up.



Interestingly enough, arachidonic acid and DHA are correlated with each other in milk. You see, on the left, an old study we did in term infants' milk in Germany;[16] on the right, a recent study from Canada in milk for preterm infants, and the ratio is actually exactly the same: 1.8 times the amount of arachidonic acid on average than the amount of DHA.[17]



Human milk provides LC-PUFA, but the amount is matching the needs of the term infant, not the needs of the preterm infants, which we believe would be matched by about 30 to 65 mg DHA per kilogram, and 50 to 130 mg arachidonic acid per kilogram a day. For mothers who provide breast milk for preterm infants, we advise to encourage them to eat oily fish regularly and to consider taking DHA supplements, about 1 g/day, which will enhance DHA levels in human milk to about 1%.

If you choose a preterm infant formula, look for whether you can find a formula that has .5% to 1% of DHA with at least as much arachidonic acid as

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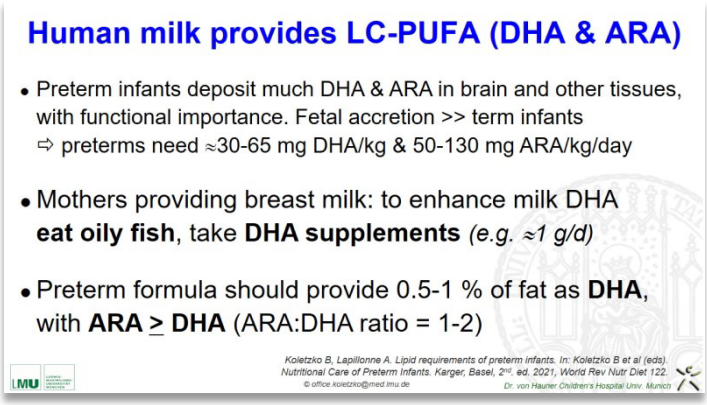
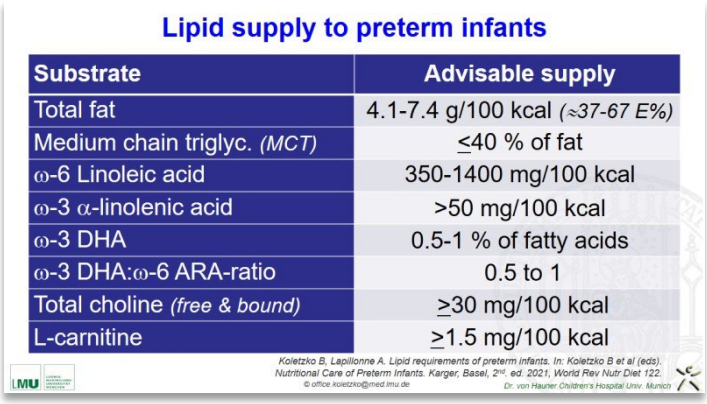
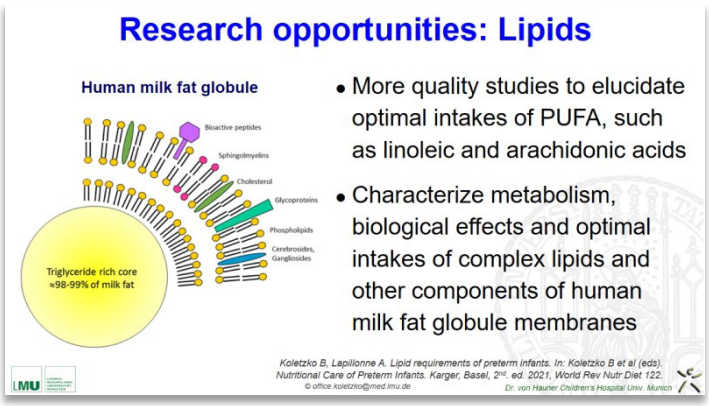
DHA, following the model of human milk composition.[12]



This is the summary. I won't go through it; we'll just say we also advise to provide preterm infants with choline and L-carnitine, but that is a given in human milk and also in modern preterm infant formula. You will find all the details in the book,[12] so I won't bore you with all the numbers in the table.

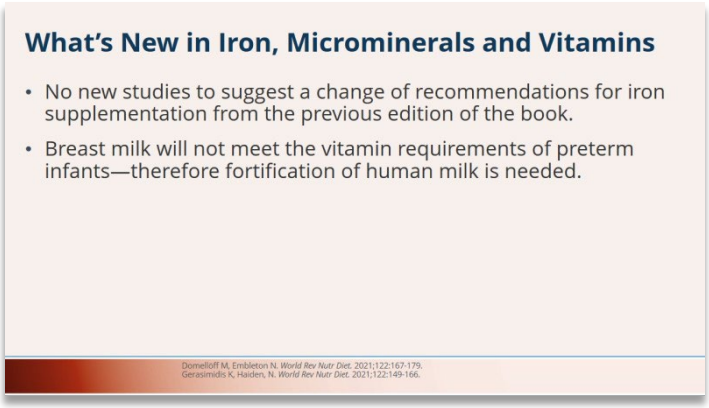


Research opportunities: I think we have great opportunities to try to understand better what the optimal intakes of polyunsaturated fatty acids are. We have questions regarding the right amounts of linoleic acid and arachidonic acid, which require further study. Also, we realize more and more that human milk lipids are very different from the lipids in traditional infant formula. If you look at the panel on the left, you see that human milk is rich in triglycerides and oils, but also has this amazing tri-layer of complex lipids around the milk fat globule, which contain a lot of bioactive substances. There are many indications now that these matter for outcome, for infection risk and for neurodevelopment. I think we need more studies to characterize the metabolism of biological effects and optimal intakes of these complex lipids and the other associated components of the milk fat globule membranes in human milk.



What's New In Iron and Vitamins

Brenda B. Poindexter, MD, MS: The unfortunate news is there is not a lot new in iron and vitamins. I think probably we've all encountered some of the various shortages, and some of the challenges are what to do when the hospital runs out of certain products. We unfortunately do not have new studies to suggest a change in recommendations for iron from the previous edition of the book.[18],[19] For some of the younger folks in the audience, this would be a great path of study.



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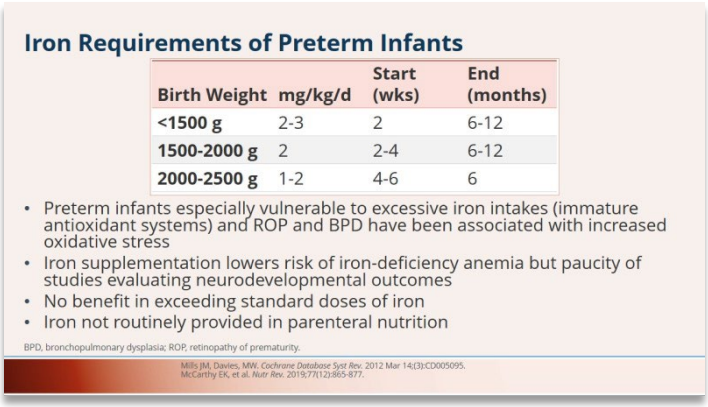
And important to point out that **human milk will not meet the vitamin requirements of preterm infants, and this is one of the important reasons that fortification is needed.**

This was the consensus agreement for iron requirements, again looking at by birth weight and thinking about the start and the duration of the supplementation.[20,21]



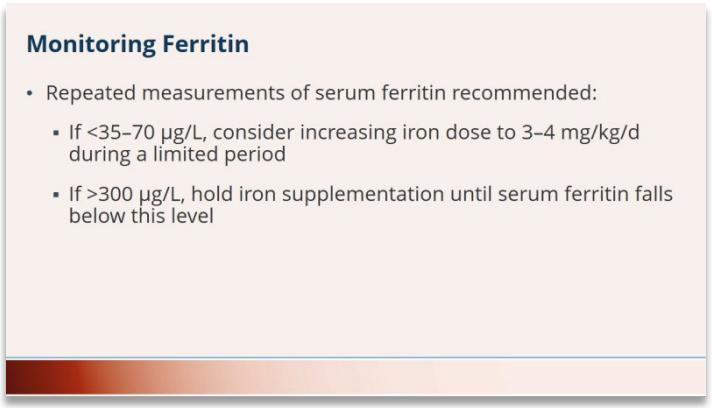
We know our preterm infants are especially vulnerable for iron deficiency and iron excess. We know they are born with lower stores at birth, they need iron for periods of rapid growth, and then most problematic is the amount of blood we insist upon taking from these infants for management.

Iron in excess due to immaturity of antioxidant systems has been associated with ROP [retinopathy of prematurity] and BPD [bronchopulmonary dysplasia]. Iron supplementation lowers the risk of iron deficiency anemia, but again we don't have a lot of studies evaluating neurodevelopmental outcome.

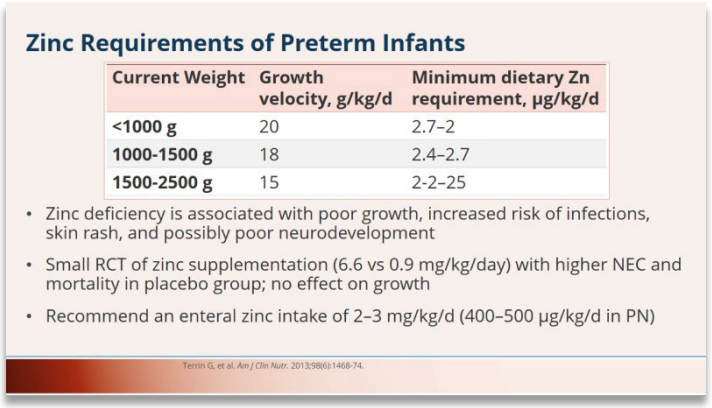
We do know that there is no benefit in exceeding standard doses of iron, and iron is not routinely provided in parenteral nutrition, although some centers that routinely use erythropoietin might have a different stance on that.

Monitoring Ferritin

One of the newer recommendations, though, is related to the monitoring of ferritin. The consensus was that repeated measurements of serum ferritin are recommended. If low, then you could consider increasing iron from 2 up to 3 to 4 mg/kg during a limited period. If the level is above 300, to hold your iron supplementation until the ferritin falls back below this level. In our unit, especially in babies who have had repeated red blood cell transfusions, we have seen some pretty high levels. I think this is something that, at least in our units, wasn't part of routine practice until very recently.



Zinc is another interesting topic for research. We know that deficiency of zinc can be associated with poor growth, infection, skin rash, and possibly poor neurodevelopment. Recently there have been a few trials that have looked at a higher level of zinc supplementation with the impact on growth and NEC.[22] I think this is an area where, perhaps with additional study, the recommendations may go up, but for right now targeting an enteral intake of 2 to 3 mg/kg, and then 400 to 500 µg/kg in parenteral nutrition.



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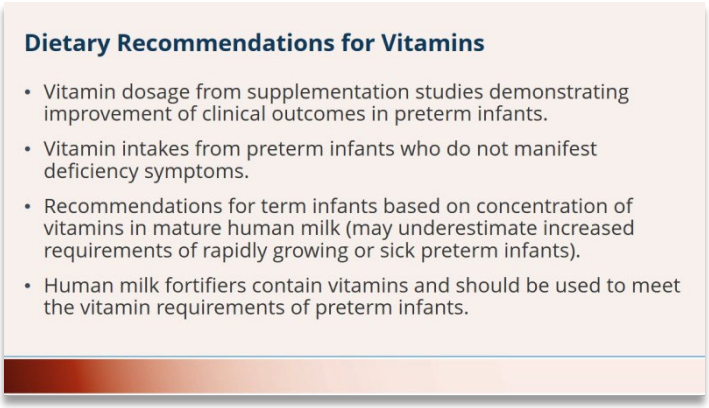
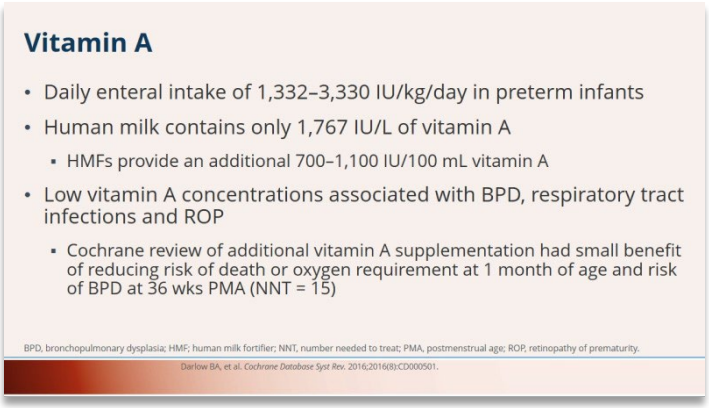
Vitamin dosage from supplementation studies have demonstrated improvement of clinical outcomes in preterm infants, vitamin intakes in preterm infants who do not manifest deficiency symptoms. The other way these recommendations come is, going

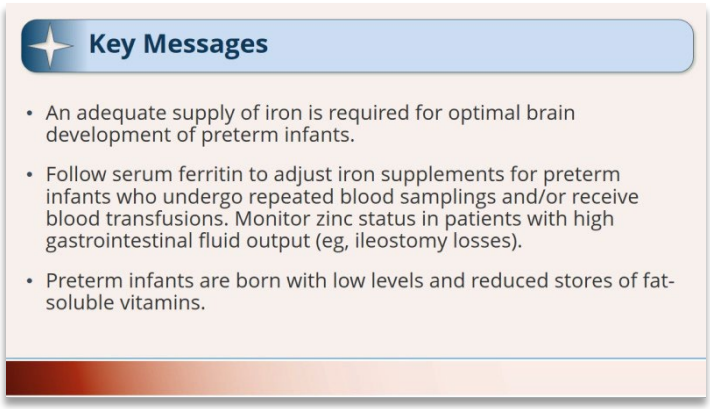


back to term infants and looking at the concentration of vitamins in mature human milk, which may not be relevant for our sick or rapidly growing preterm infants.

Human milk fortifiers do contain vitamins and are necessary to meet these requirements. When people ask, "Can we just add a single nutrient? Can we just add protein? Can we just add MCT to human milk?" I think this is an important part of making sure we're giving the vitamins and microminerals from fortifier.



Vitamin A is another topic that has been looked at in a number of trials. We recommend a daily enteral intake between 1300 and 3300 IU/kg/day. Again, human milk contains a lot, but not quite enough to meet that recommendation. Shown here is the amount that human milk fortifiers add. So, low vitamin A concentrations have been associated with BPD, respiratory infections, and ROP. The Cochrane review of looking at additional vitamin A supplementation has a small benefit on reducing the risk of death or oxygen requirement at 1 month of age and the risk of BPD with the number needed to treat of 15.[23] For a while, when we had the IM [intramuscular] preparations, a lot of units were using vitamin A as a prevention strategy for BPD. Then, with some of the shortages of the product, that went away, and some of the newer analyses are a little more mixed about the effect. There are new studies coming out looking at enteral supplementation, as well.



Key messages: an adequate supply of iron is required for optimal brain development, and, again, the recommendation to follow serum ferritin. Then looking at zinc status, especially in those babies who have had surgery, who have high gastrointestinal losses, such as through an ostomy. And then to remember preterm infants are born with low levels and reduced stores of fat-soluble vitamins.

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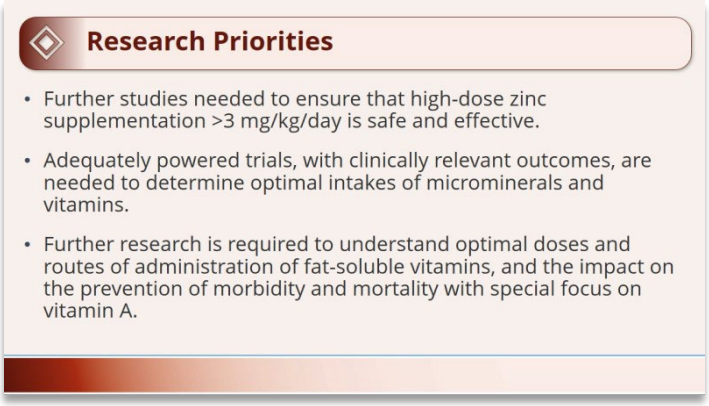
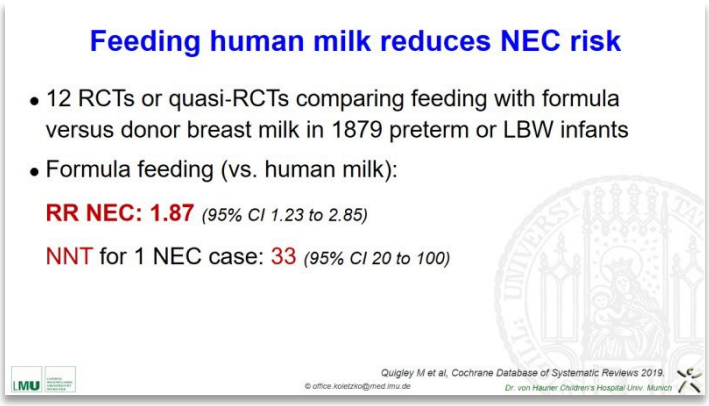


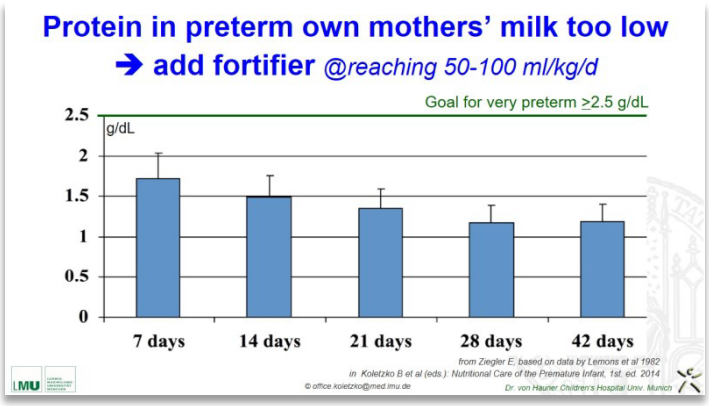
Research priorities, looking at the higher dose of zinc supplementation, looking at adequately powered trials with clinically relevant outcomes to further refine intakes of microminerals and vitamins. Further research to look at the optimal doses and routes of administration of fat-soluble vitamins, especially vitamin A with a focus on preventing morbidity and mortality.

Human Milk (Donor vs Mom's Own) and Fortifiers

Berthold Koletzko, MD, PhD: We're all aware human milk has benefits for the preterm infants. Probably the most important one is the risk reduction for necrotizing enterocolitis, as shown here in this Cochrane analysis where the relative risk to develop NEC was almost twice as high in preterm infants receiving bovine protein-based formula compared to human milk, with an NNT [number needed to treat] of 33.[24] The result has changed the practices in neonatal units all over the world where there's more and more emphasis everywhere to encourage mothers to provide human milk, and to support them.



Yes, that's great, but we also know human milk has limitations. It is designed by evolution for a healthy term baby, not for a preterm. We discussed that already with the long-chain PUFA content, and it's also true for the protein content. If we think of a goal for a preterm infant of having about 2.5 g/dL of milk of protein as the minimum to reach the amounts that Brenda has shared with you previously, we see that the typical amounts in human milk are lower, and they decline very rapidly with increasing lengths of lactation. So, in colostrum, the protein is higher, but then, in transitional milk and mature milk, it keeps falling. To match the needs of preterm babies, we really need to add human milk fortifier with protein and other nutrients that Brenda already alluded to.



We know protein fortification is beneficial. Another Cochrane review based on 6 RCTs, not a huge number, 200 preterms. You can see that the fortification of human milk improved weight gain by almost 4 g/kg/day.[25] More importantly, length and

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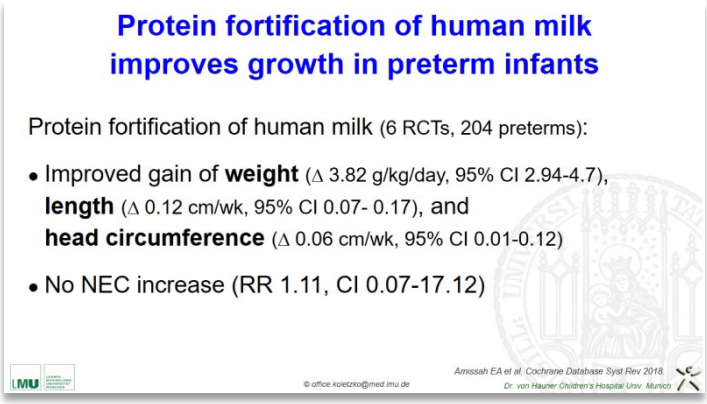
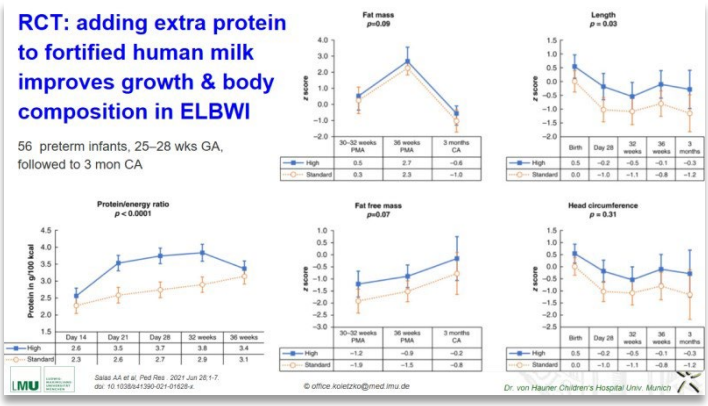
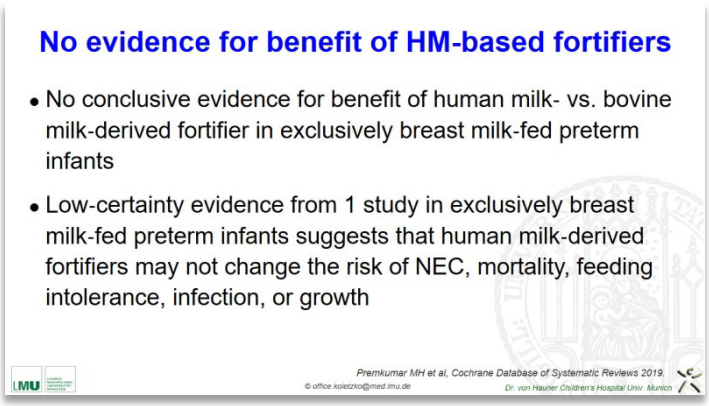
head circumference gain, which is really a measure directly of the lean body mass we would like to achieve. And, there's no adverse effect, no increase of necrotizing enterocolitis, no other adverse effects of adding fortifier to human milk—a topic that is raised again and again: Are we not harming the baby with the fortification? We have no evidence from available studies that this would be the case.



There is also an interesting study by Dr. Salas, here in the room, showing that adding extra protein—this was about 1 gram more per 100 kcal—had a benefit for growth, for enhancing lean body mass gain, fat-free mass, length, and head circumference gain without enhancing fat mass.[26] So, exactly what we would like to achieve. **Adding protein to human milk matters!**



We have concluded that there's no conclusive evidence for the benefit of human milk-based fortifiers.[27] There are a lot of claims made based on studies that have a study design that is not really clean, where there is an intervention group of babies fed human milk plus human milk fortifier, and a control group of babies fed human milk plus a bovine fortifier, *plus* bovine protein formula. You mix 2 interventions, not only the difference in the fortifier, you can't draw conclusions about what the effect of the fortifier is. There is only 1 clean study



I'm aware of, by Dr. O'Connor in Toronto, who has randomized human milk-fed babies to human milk or bovine fortifier. She finds absolutely no benefit of the human milk fortifier. Probably a question that needs to be followed up.

Fortification of human milk is required. We always advise to do this for preterms below 1800 grams. Start full-strength fortification between 50 and 100 mL/kg/day of enteral feeding.[28] That's a wide range, and we really couldn't agree on a narrower range because of lack of data. Some people do it regularly with 50cc and see this is going well, but there is a difference of opinion here. We recommend, as a standard, the bovine protein multicomponent fortifiers, because we see no evidence for a greater benefit of human milk-based fortifier, but of course [there is] a much higher cost. And again, **aim for protein intakes above 3 g/kg/day**. And the last line is really for research-restricted environments where people have no access to fortifier where formula powders have been used as a second-best choice to fortifier.

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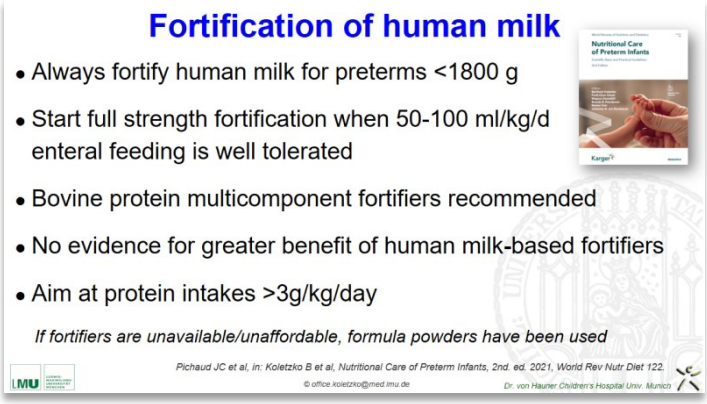
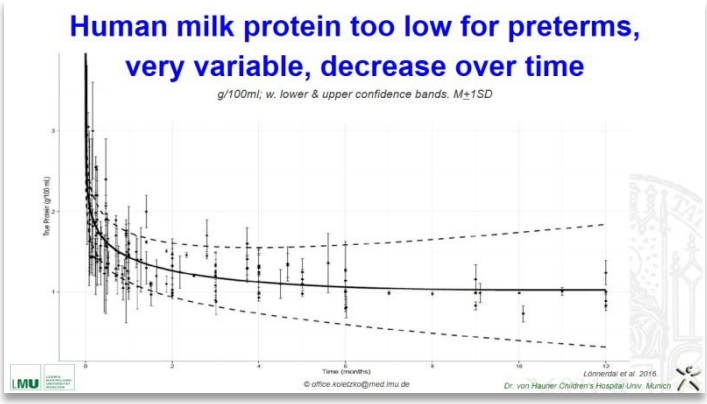
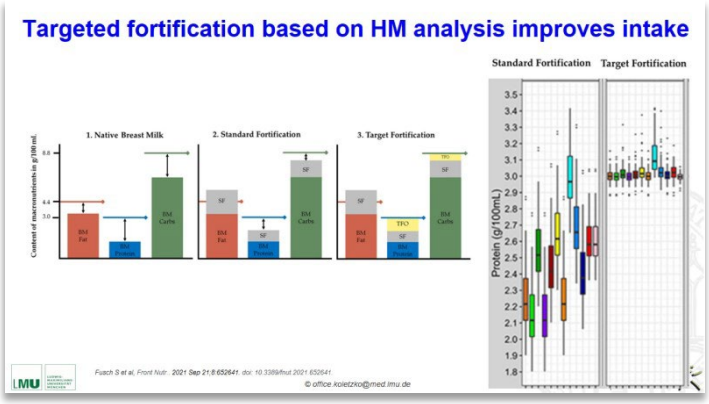


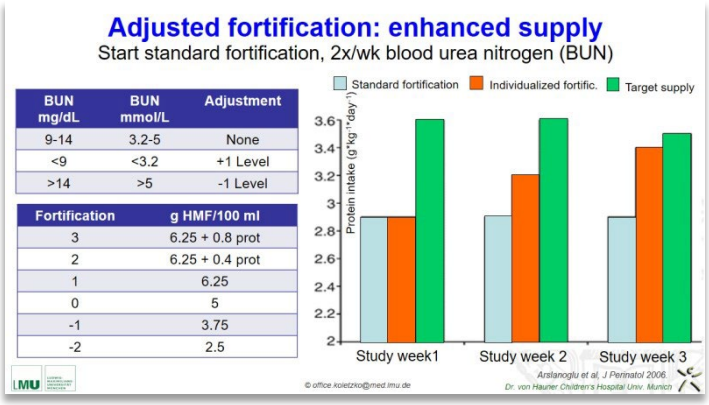
Now, the problem with fortification is that human milk is enormously variable in protein content. You see, again, what you've seen before, the decline of the protein content. It's high in colostrum and falls very rapidly with advancing duration of lactation, but at each and every point you find enormous variation between milk samples.[29] That limits the benefit of adding one of the same dose of fortifier to every human milk dose you have been provided by the mother.



So, what are the options? One way is to analyze human milk composition with infrared spectrometry. Then, based on the measured protein content of your milk, you add a dose that matches your goal. You see this study by the Fusch group who shows you on the left panel that standard fortification gives you a wide range of different protein amounts, and, with targeted fortification, you can achieve something very close to your goal.[30]



The other opportunity, if you don't want to invest in an expensive machine to measure the human milk composition, is to follow the concept of Dr. Arslanoglu and measure blood urea nitrogen in your baby,[31] which is a good measure of protein metabolism. Basically, her concept is to start with the standard fortification and then measure blood urea nitrogen twice a week and, depending on the categories of the blood urea nitrogen that you see in the panel, leave the fortification as it is or go up and down one step with the concentration of your fortifier.



You see that with individualized fortification, in orange, with closer to your target supply. It takes a bit longer than if you measure human milk composition, because then you can react more quickly, but you can get there. She shows there's a benefit for growth using that approach. There was a significant improvement of weight gain and head circumference gain and a trend to higher length gain as well with this adjusted fortification.

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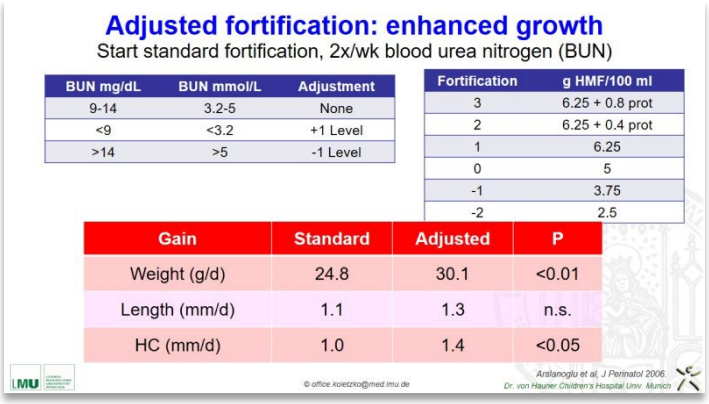
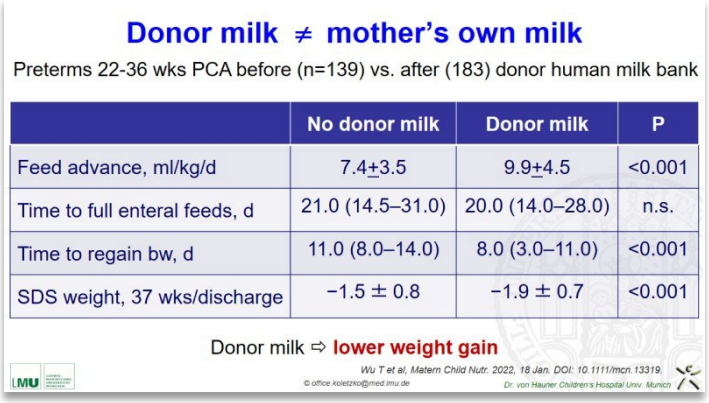


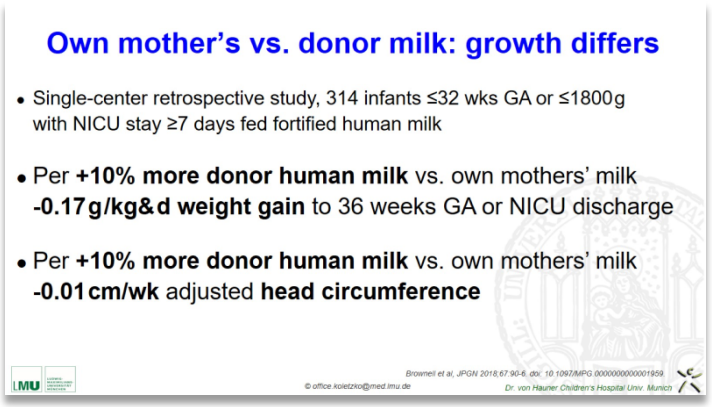
Donor Milk

Finally, donor milk is good. It also reduces necrotizing enterocolitis. [There are] good randomized trials that have compared donor milk with formula. It's effective, but still, it's not the same as mother's own milk. You can see here a study documenting in preterms between 20 to 36 weeks postconception age[32] that those given donor milk had a more rapid feed advance, but slower growth, lower standard deviation of weight at discharge.



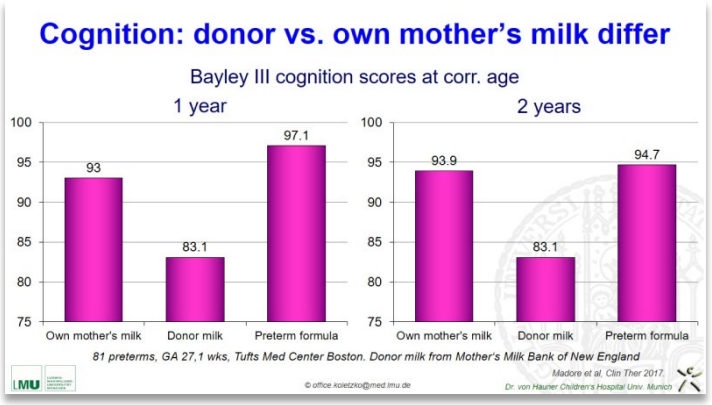
So, lower weight gain with donor milk. Why is that? It's probably because donor milk typically is collected at a later time point in lactation. It's more diluted; it has less protein; and also some other nutrients are lower than the mother's own milk that is collected typically at an earlier stage of lactation.

Another study that shows the same: single-center retrospective study in 300-plus infants below 32 weeks.[33] For each 10% more donor milk given compared to own mother's milk, there was .2 g/kg/day less weight gain and also significantly lower adjusted head circumference gain.



Donor milk is good, but it's not the same as mother's own milk. We really need to try everything we can to encourage and support mothers to provide their own milk. It's also saving us money compared to investing a lot of money in milk banks.

There is another interesting observation, which I think needs follow-up, but it raises questions from Boston [Madore et al], who compared the cognitive outcome at 1 and 2 years based on Bayley III.[34]



You see here that donor-milk-fed infants performed worse than infants given their own mother's milk. It is, of course, possible that there's other confounding factors, so I don't think we can call this a conclusive study, but if they grow less, we certainly have a plausible hypothesis that also could have other effects on mental development.

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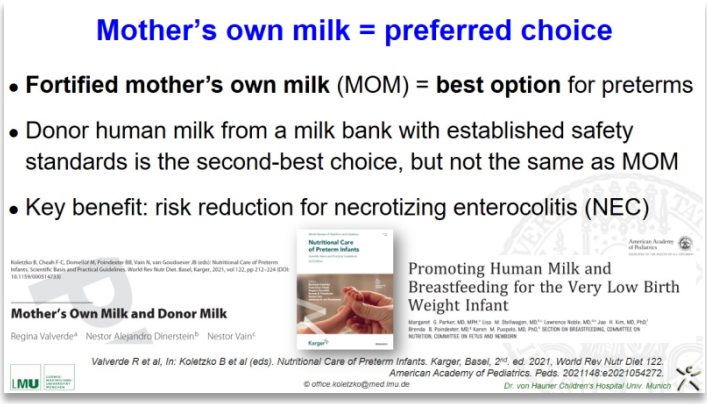
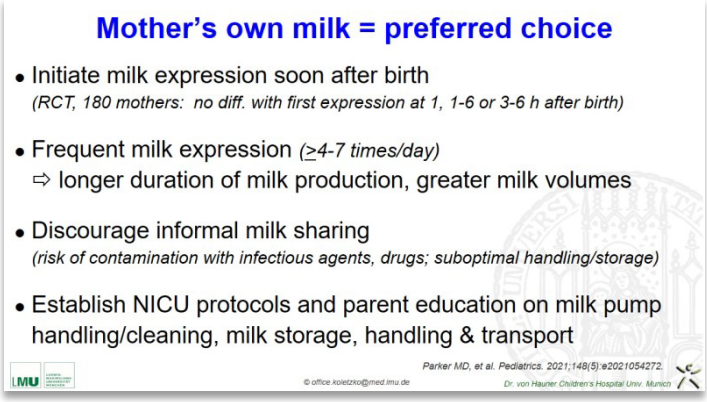
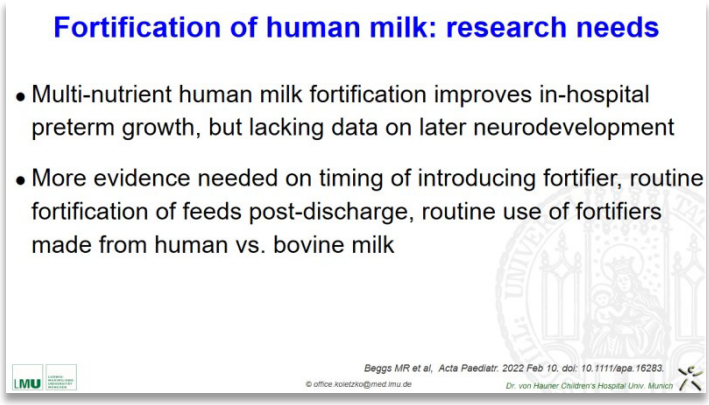
Clearly, **fortified mother's own milk is the best option for preterm infants.** Donor human milk from a milk bank, with established safety standards, is the second-best choice, but it is not the same as mother's own milk. The key benefit again, for both, is risk reduction of NEC.[35,36]



What do we want to do if we promote mother's own milk? We should encourage mothers to initiate milk expression soon after birth. There's an interesting RCT that shows it doesn't really matter whether this is happening within the first hour, within the first 6 hours, or between 3 and 6 hours after birth, so no stress. You can take it easy, but still try to do it in the first hours after birth.[36] Frequent milk expression at least 4, up to 7 times a day, was shown to be associated with longer duration of milk production and greater milk volumes. We clearly should discourage informal milk sharing for all the reasons known to you.



If you want to succeed, each and every unit needs to establish its own protocol involving all staff and engage in parent education on milk pumping, handling, cleaning, milk storage handling, and transport. Only if you have a written guideline and have everybody on board, and have the enthusiasm, will it actually work.



We have a lot of research needs in this area. We know that much nutrient fortification improves growth in the unit, but we have very little data on the long-term effects. Does it affect neurodevelopment, other long-term outcomes, and is there a difference in how we approach fortification? We need more evidence on the timing of introducing fortifier. Emphasize we have this wide range 50 to 100 because we don't have sufficient data. We have questions whether it is beneficial for infants postdischarge to use routine fortification and, if so, for whom and for how long. And then again, we have an open question regarding the choice of fortifiers, human milk, bovine milk, and other compositional aspects of the fortifiers.[37] So, we need to invest more work in this area.

ENTERL NUTRITION IN VERY LOW AND ESTREMELY LOW-BIRTH-WEIGHT INFANTS

Brenda B. Poindexter, MD, MS: I'm going to go over some of the recommendations for the practice of enteral nutrition, and then I'm going to highlight some of the new chapters in the book on involving parents, having

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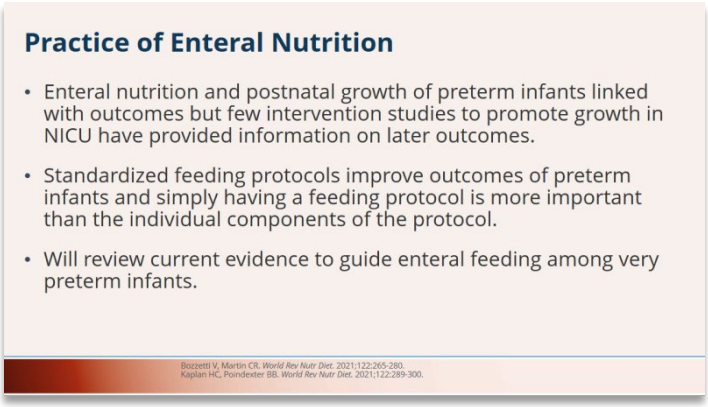
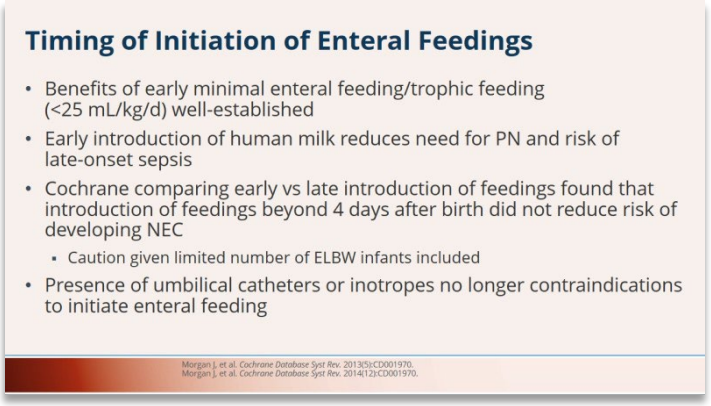
multidisciplinary teams, and standardized feeding protocols.

We know that enteral nutrition and postnatal growth of preterm infants are linked with outcomes, but few intervention studies to promote growth in the NICU have provided information on later outcomes. As I mentioned, we know that standardized feeding protocols do improve outcomes, and simply **having a feeding protocol is probably more important than the individual specifics of that protocol**.[38,39]

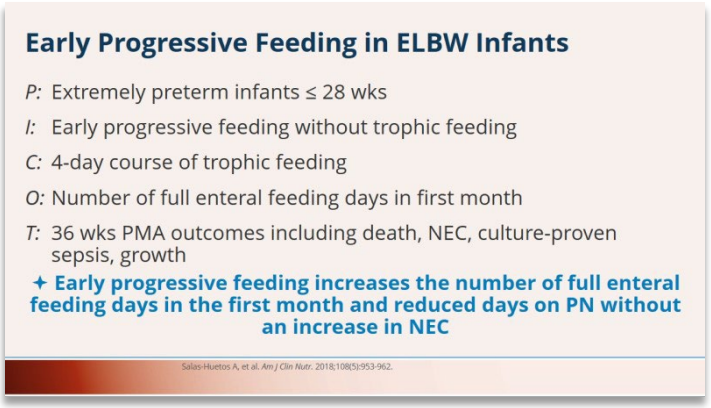


Evidence-based Guide to Enteral Feeding

We're going to review current evidence to guide enteral feeding among our preterm infants. The timing of initiation of enteral feedings, I think it's very clear that the benefits of early feeding are well established, and the early introduction of human milk reduces the need both for parenteral nutrition and the risk for late-onset sepsis. The Cochrane review that compares early vs late introduction of feedings found that waiting to introduce feedings did not reduce the risk of NEC.[40] As with many of these studies, the number of very, very tiny babies, immature babies, is small. I think that another previous-viewed contraindication to starting feedings is the presence of umbilical lines. I think we do have good evidence now to suggest that really is not a contraindication.



So again, Dr. Salas is in the audience and, in my mind, is really a rising star in nutritional research. He's contributed to so many of some of our newer studies, so we probably need to have him at the podium next time. He did a great study where they looked at extremely preterm infants, less than 28 weeks, and they randomized either to early progressive feeding without maintaining several days of trophics vs a more traditional 4-day course of trophics.[41] The primary outcome was the number of full enteral feeding days in the first month. They looked at 36-week outcomes, including death, NEC, culture-proven sepsis and growth, and found that early progressive feeding, again without continuing trophics, increases the number of full enteral feeding days in the first month, reduced the number of days on parenteral nutrition, and, importantly, without an increase in NEC.



We're going to talk a little bit about the SIFT trial [Speed of Increasing milk Feeds Trial], as well. I think one of the challenges with our standardized feeding

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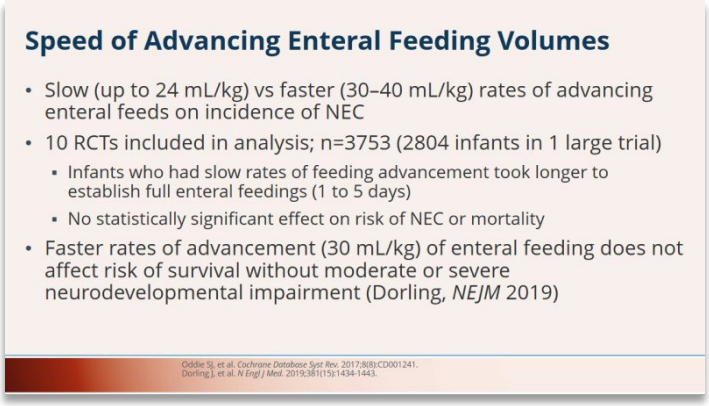
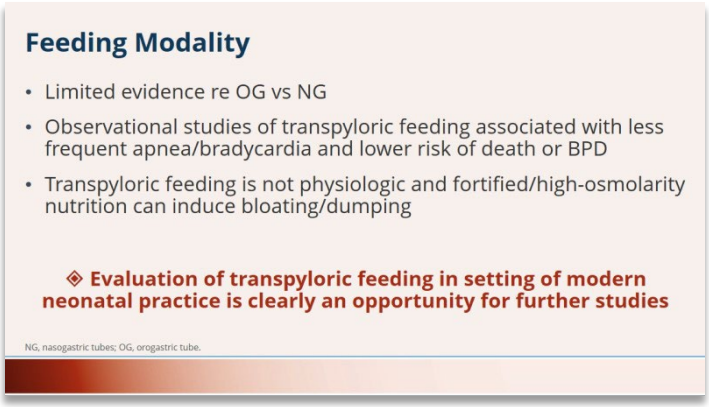
protocols is how do we continue to modify them and update them as new evidence emerges.

We've got an ARS question. I'm going to ask: You're developing a standardized feeding guideline for your unit for VLBW infants. What rate of enteral feeding advancement would you like to incorporate into your guideline? Ten, 20, 30 per kilo per day or something else? It looks like the overwhelming majority would like to do 20/kg/day.

Let's look at some of the evidence. There has been a Cochrane analysis comparing slow (which by their definition was up to 24 mL/kg) vs faster, 30 to 40, on the incidence of NEC.[42] This review was recently updated to include the results of the largest trial to date, which was the SIFT trial done in the UK with John Dorling's group.[43] There were almost 4,000 babies included in this analysis. Not surprisingly, the infants who had the slower rate of feeding advancement took longer to establish full enteral feedings, but no significant effect on the risk of NEC or mortality. The primary outcome of that SIFT trial was looking at survival without moderate or severe neurodevelopmental impairment. They found no difference with the faster rate of advancement of 30/kg.[43] I think it's interesting that we have this high-quality data, and there still are many units that are not routinely using 30/kg as their rate of advancement. I will say that I think that rate of advancement is probably one of the most difficult things to get consensus on. So, in setting up a feeding guideline, I always tell people, don't let perfection be the enemy of good. I'm happy if they're advancing by 20, but I think that that is an area where you could go back and do a PDSA cycle to try. Maybe you start in the bigger babies and implement the 30, and then work your way down. I think that's definitely an area where we could go back and change our guidelines.



There's very limited evidence on whether we should be starting with orogastric vs nasogastric. We have some observational studies of transpyloric feeding being associated with less frequent apnea and bradycardia and perhaps a lower risk of death or BPD.



I think we worry about aspiration, especially in our babies who are having evolving BPD. But keeping in mind that transpyloric feeding is not physiologic, and especially if you're giving fortified or higher-osmolarity feedings can cause issues with dumping. I see a lot of units across the world routinely doing transpyloric feedings, and I think that is an opportunity for more studies in the setting of modern neonatal practice.

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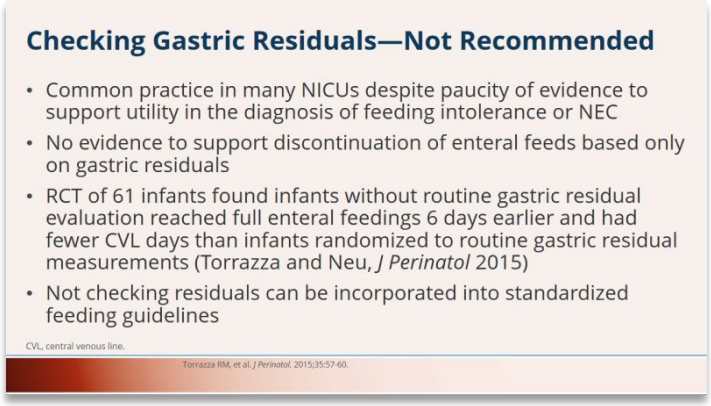
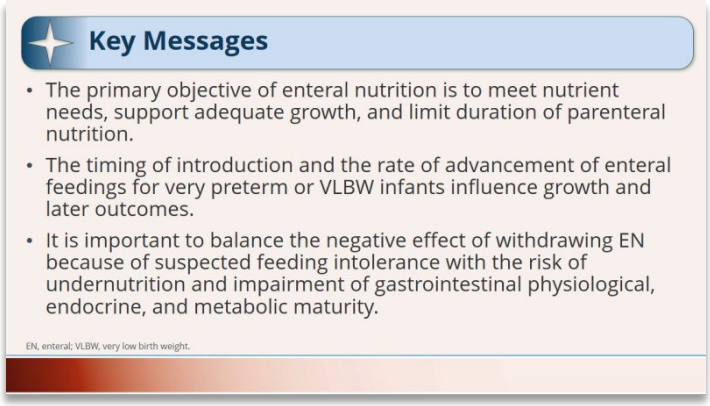


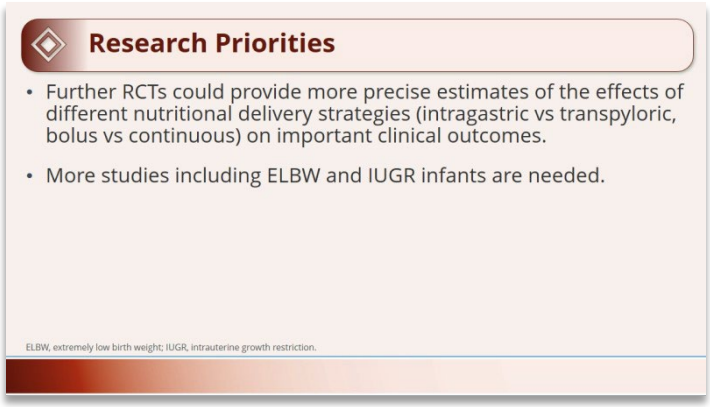


So, the dreaded gastric residuals. I think we can say equivocally that is not recommended in routine practice. There's really no evidence to support the utility in the diagnosis of NEC, and Joe Neu has done a small, randomized trial where they randomized for routine checking of gastric residuals vs no, and found that the infants who did not have routine gastric residuals measured reached full enteral feeding sooner and had fewer central line days.[44]

Again, I think that this is an aspect of our practice that can be incorporated into standardized feeding guidelines. It's probably one of the most difficult because the bedside providers have long relied on this and are very skeptical that they're not going to cause harm if they don't check it. You may want to start with a very small scale, even 1 nurse with 1 baby, and then expand it throughout your unit.

Key messages: The primary objective of enteral nutrition is to meet nutrient needs, support growth, and limit the duration of parenteral nutrition. The timing of introduction and the rate of advancement of feedings does influence growth and later outcomes. And then balancing advancement of feedings with the negative effect of withdrawing enteral nutrition because of suspected feeding intolerance and the resulting risk of undernutrition.

Some of the research priorities that we identified are that future randomized trials could provide more precise estimates of the effects of different nutritional strategies, such as intragastric vs transpyloric, bolus vs continuous. Then, like so many of our aspects of provision of nutritional support, we need more studies with the infants at the lowest gestational ages and birth weights and those with intrauterine growth restriction.



MULTIDISCIPLINARY APPROACH AND AUDIT NUTRITION IN PRETERMS

I am excited about the 3 new chapters we added to this edition of the book and want to talk a little bit about the multidisciplinary approach and auditing of nutrition.

The overall theme is that **nutrition is the cornerstone for improving neonatal outcomes**, and we need to have a multidisciplinary approach to focus not only on macro and micronutrient intake guidelines, but also on the technical aspects and

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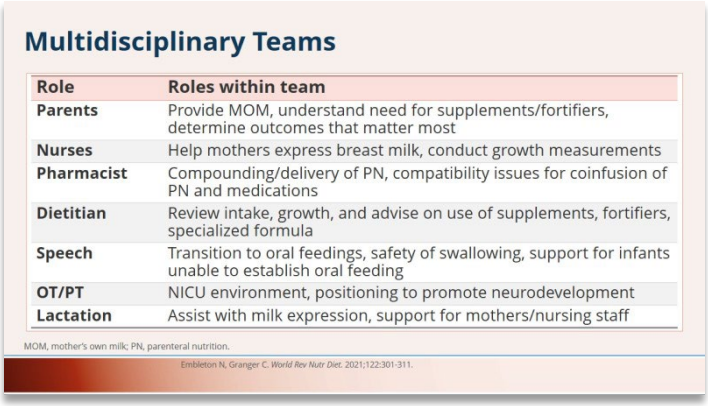
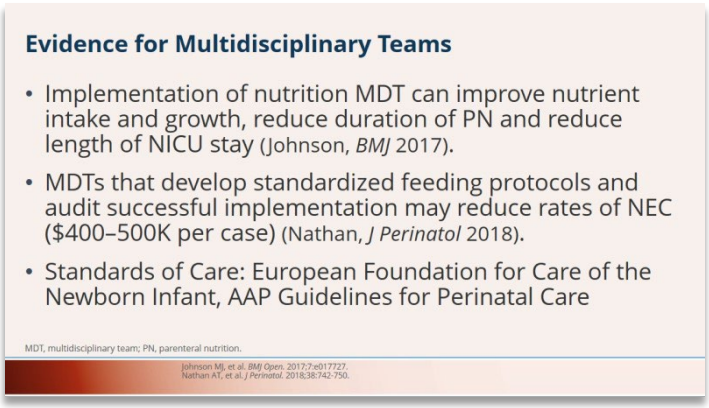
some of the behavioral aspects. NICUs must implement policies, procedures, and guidelines that help to ensure safe and effective nutrition and to conduct regular audits to ensure high-quality practice.

This is a table showing the different roles that multidisciplinary teams can have in your unit related to the provision of nutrition.[45] I think this can be one of the most difficult things to advocate for in the system and to help to get resources to support all of these various parts of the team.

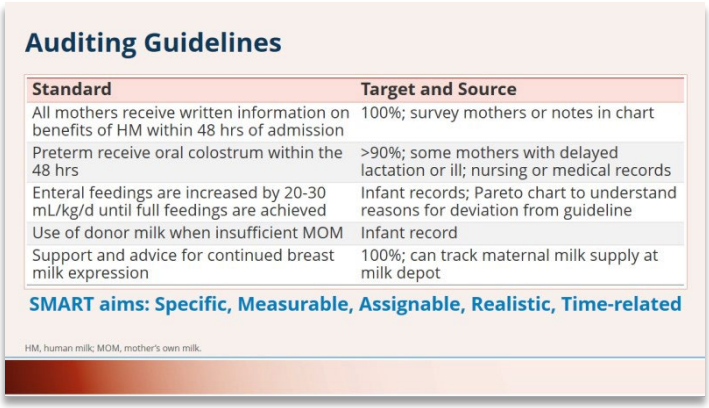


Some of the evidence for multidisciplinary teams: it's been shown to improve on the delivery of nutrients, improve growth, reduce duration of parenteral nutrition, and reduce the length of NICU stay. We know that multidisciplinary teams that develop standardized feeding protocols and then actually audit the successful implementation may reduce rates of NEC, which can be upwards of half a million dollars per case.[46,47]

Various bodies are great resources. The European Foundation for the Care of the Newborn Infant, AAP Guidelines for Perinatal Care,[48] these are all important resources you can take to your hospital administration to advocate for resources to give the people on these multidisciplinary teams the time and ability to perform this work.



Some of the auditing guidelines: it's really important, like with all quality improvement, to have specific, measurable, realistic, and time-related goals. These are just some of the examples given of things that you may want to consider. I would encourage you to go to that chapter in the book.[49] I think it has a lot of great ideas for how to get started.



Guidelines and Run Charts

We know that just simply having a guideline isn't enough. We can't improve what we don't measure, and so a lot of places will say, sure we have a guideline, I think it's in a binder somewhere in the

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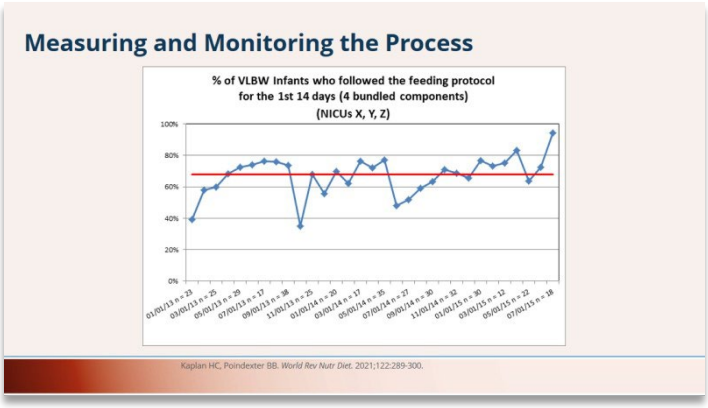
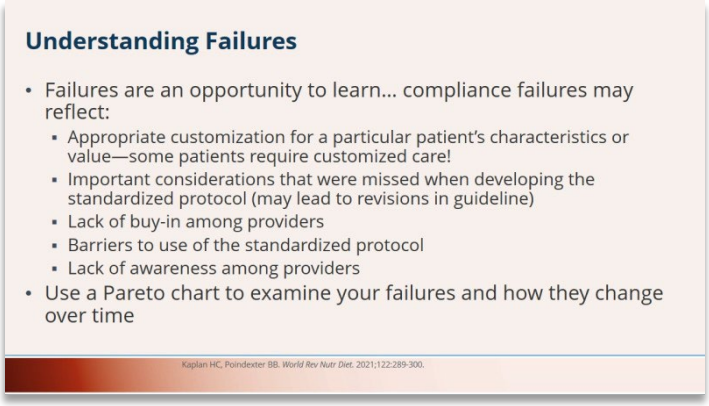
back closet. This is just an example of a run chart. This was from work that I did with Heather Kaplan when I was in Cincinnati, and just measuring what percent of the infants followed the various bundled components of the feeding protocol.[50] That can be important to learn, too, because if people aren't following the protocol, it's not always because they're just being noncompliant. Sometimes, there's learnings to be had there, and they may think of something, a concern, that maybe wasn't identified when the guideline was drafted.



Another important aspect of monitoring how you're doing with the feeding protocol is understanding failures, because compliance failures may reflect appropriate customization for a particular patient's characteristics. When we see someone not following the guideline, instead of scolding and saying why didn't you follow this guideline, it's more to say what was it about this patient in this circumstance that made you feel that a customized care was appropriate, because maybe that would be important to incorporate for other babies.



Again, we may have missed considerations when we developed the protocol, and this may lead to revisions in the guideline. Sometimes, we haven't had appropriate buy-in among the providers at the onset. I think that before you roll out a guideline, making sure that all the key stakeholders in your organization have had ample time to give buy-in and feedback. I would say also involving your biggest skeptic in the unit is important because if you can convince them, then they will be able to spread that throughout the unit.

Thinking about what those barriers are to using the protocol or simply a lack of awareness. One of the important ways to look at failures in a protocol is the Pareto chart. It is based on the principle that 80% of the output in a system is based on 20% of the input. You organize from left to right the factors that are most prevalent to least prevalent. In this situation, 32% of the reasons that people weren't following the protocol were related to feeding intolerance.[51] That is then the area you go focus on. If you were thinking, well, this is really an access issue, you might be focusing on something that's not going to result in as much improvement with trying to improve compliance of the protocol.

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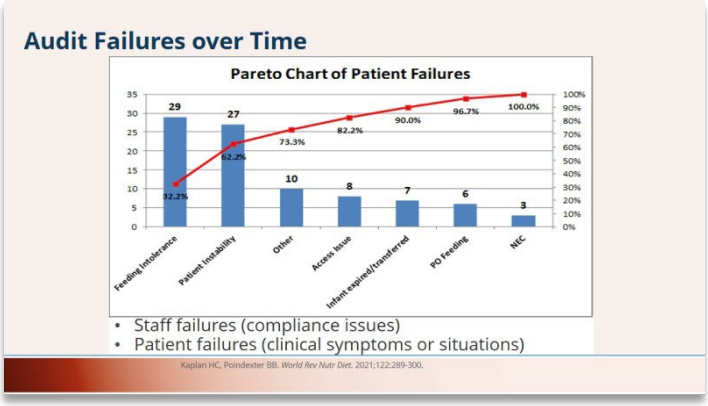
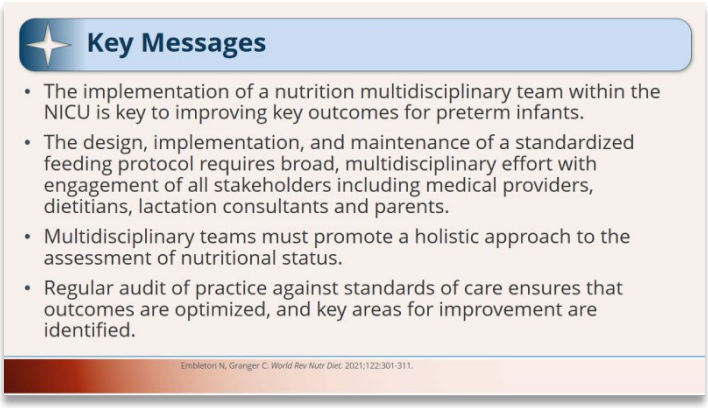
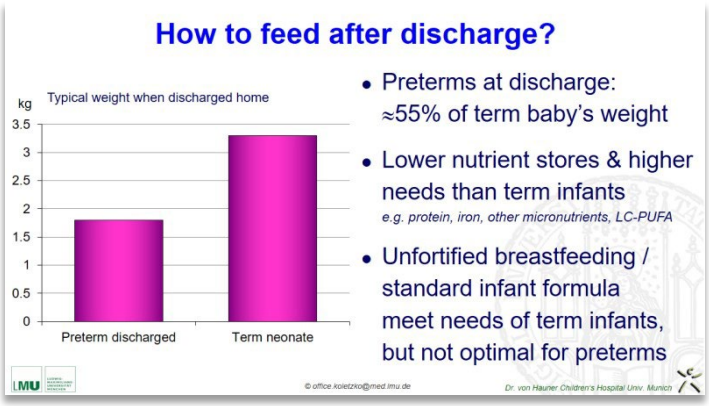


Some of the key messages: Implementation of a nutrition multidisciplinary team within the NICU is key to improving key outcomes for preterm infants. The design, implementation and maintenance of a standardized feeding protocol requires broad, multidisciplinary effort with engagement of all stakeholders, including medical providers, dieticians, lactation consultants, and parents.[49] These teams promote a holistic approach, and then regular audit of practice against standards of care ensures that outcomes are optimized and that key areas for improvement are identified.



Feeding After Discharge

Berthold Koletzko, MD, PhD: Think of Margarita. Finally, she's going home. She's fully breastfed at the breast, everybody is happy, mother is happy. She thinks now I have a baby that feels like a healthy baby. Everybody in the unit is happy, but are the problems solved? Let's remember, if she's going home, she just weighs a bit more than half of the weight of a term baby. She has much lower nutrient stores and higher needs than a term baby. Unfortified breast feeding and standard infant formula would not be ideal to meet her nutrient needs.



What we often see is something like this. A baby is going home on a reasonable percentile, but then if she's at home, the weight doesn't follow the percentiles as we would like.[51] So, what do we do? Encourage the mother to feed more often, more volume? Some say add calories, add carbohydrates and oil through the feed. Is that a good idea? Well, not really. If you add empty calories, if you add carbohydrates in food, we dilute the essential nutrients behind the kilocalories. These extra calories will only produce more fat deposition, but not lean body mass deposition. That's not really what we want because we don't want growth with excessive fat deposition.

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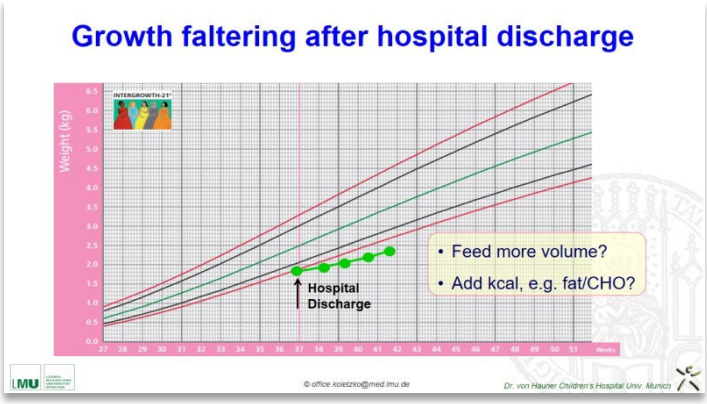
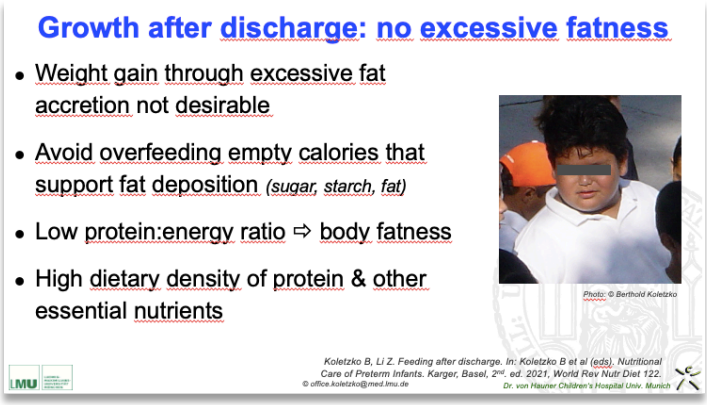
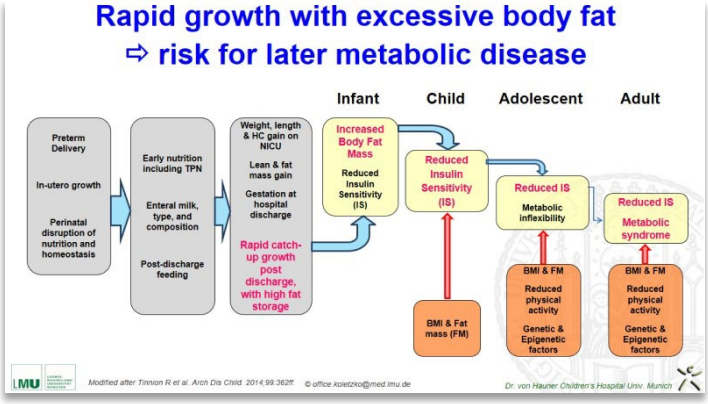


We know preterm infants at term, on average, are fatter than a healthy term baby. Some studies have even indicated they may be fatter in adulthood, although there is controversial data on that.

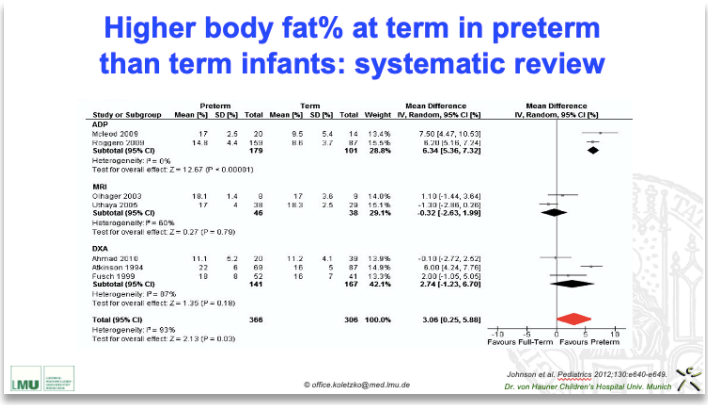
Now what happens if a baby has more body fat? It basically has a higher likelihood of insulin resistance and metabolic disorders, increased risk of noncommunicable diseases in later life.[52] We don't want this to happen.



The key predictor for body fat is a low protein to energy ratio. We want a higher density of protein and other essential nutrients in this baby. We don't want empty calories to be added.



We remember the calculations of Dr. Ziegler who showed us that a baby who goes home somewhere below 2,200 g of body weight will need about 3 g of protein per 100 kcal, and later on, between 2.2 and 3 kg, about 2.6 g of protein per 100 kcal.[53]



That's much, much more than human milk will provide or standard infant formula. In those babies who fail to thrive after going home, we are challenged with the question, should we add extra nutrients, particularly extra protein?

Protein & energy supply to match fetal growth

Weight (g)	500-1000	1000-1500	1500-2200	2200-3000
Fetal wt gain (g/kg/d)	19.0	17.4	16.4	13.4
Protein (g/kg/d)	**4.0**	**3.9**	**3.7**	**3.4**
Energy (kcal/kg/d)	106	115	123	130
Protein/100kcal (g/100 kcal)	**3.8**	**3.4**	**3.0**	**2.6**

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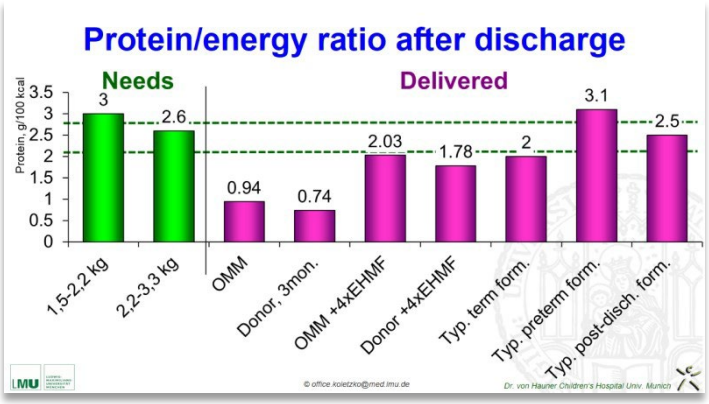
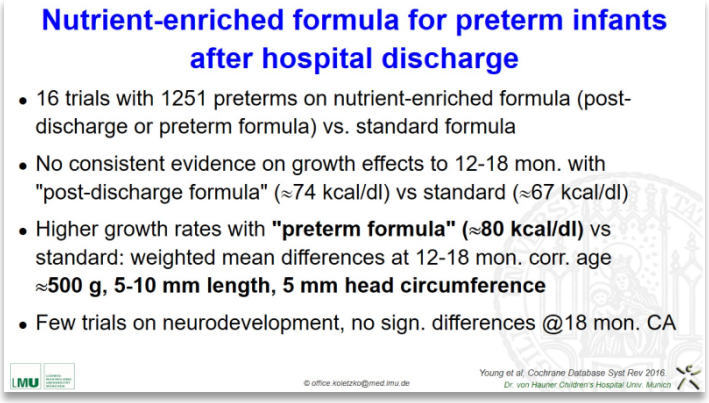
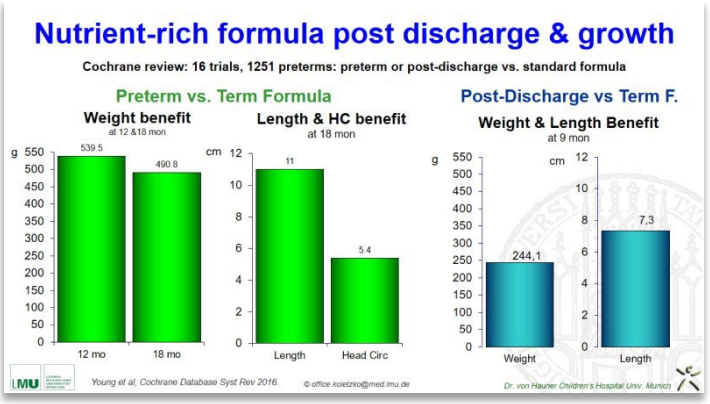
So, if you look at the needs in the smaller or the larger baby on the left compared to providing own mother's milk or donor milk, there's a big gap in the protein needs. If we were able to add fortifier, we would improve the situation, or if we replace standard-term formula by a preterm formula or a postdischarge formula, we also improve the nutrient composition provided to that baby.



Do we have evidence for that? This is a Cochrane review looking at 16 trials, 1,250 preterm infants.[54]

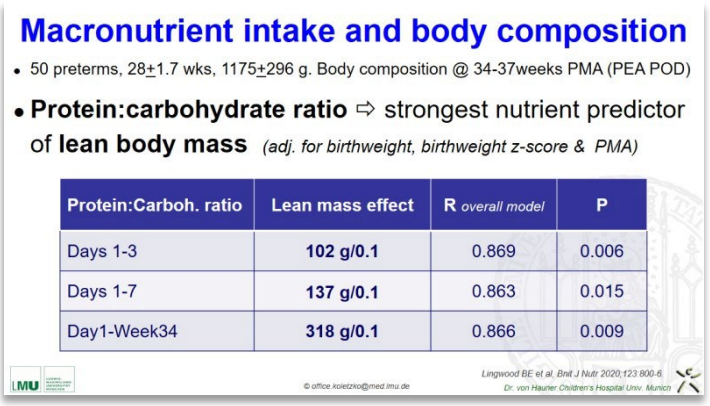


There is a higher growth with preterm formula given after discharge, 80 kcal/dl higher protein, with improvement not only of weight but also, importantly, of length and head circumference, but very little evidence on other outcomes, like neurodevelopment.



This is the summary of that Cochrane review.[54] If you provide, after discharge, preterm or term formula, you have a benefit for weight gain, length, and head circumference gain. If you use a postdischarge formula with a term formula, which has a slightly lower protein content than the preterm formula, you also have a benefit, but the benefit is quantitatively smaller than giving a preterm formula after discharge.

Importantly, **it is the protein to carbohydrate ratio—the proportion of protein you give is the strongest predictor of the lean body mass achieved.** So, the emphasis, like in the beginning in the unit, is on providing enough protein. You see here the effects on the lean body mass effect.[55]



The conclusion is after discharge, up to about 2 kg per body weight, we should aim to provide about 3 g of protein per 100 kcal. Between 2 to 2.5 kg per body weight, about 2.5 g of protein per 100 kcal.[51] This is particularly important in those infants who

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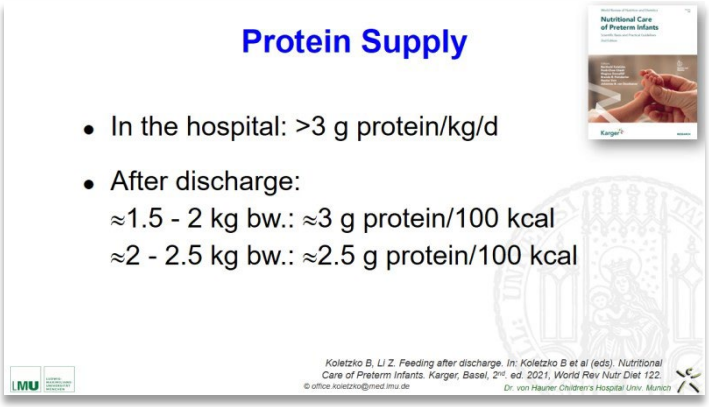
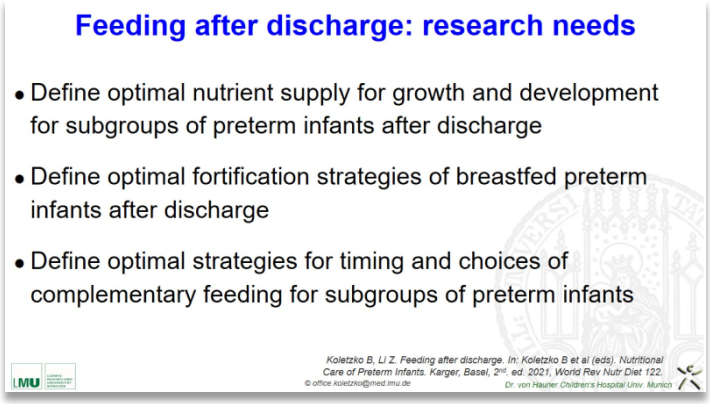
have a poor growth curve after discharge, and, ideally, we would measure in the follow-up not only weight, but we would aim to measure body composition as well, which would give us better guidance.



Research needs: We need to define optimal nutrient supply for growth and development because we don't have enough data on the effects on outcome. We need to think about subgroups of preterm infants. Not everybody's equal, particularly at discharge, if you have an AGA [appropriate for gestational age] or an SGA [small for gestational age] situation at discharge that would probably make a big difference, and also the preceding history. Define optimal fortification strategies for breastfed preterm infants after discharge. Some proposals have been made with finger feeding along with breastfeeding, which seems to work well. And define optimal strategies for timing and choices of complementary feeding, again for subgroups of preterm infants where at the moment we have very little evidence on what is appropriate.



Question & Answer

Editor's Note: This is a transcript of audience questions together with presenter responses from the April 24, 2022 symposium.

If the availability of human milk fortifier (HMF) was not a problem at discharge, would you recommend that people use formulas to fortify the breast milk? Or do you think the HMF can actually not be good for them, meaning that has more calcium phosphorus than the discharge infant needs?

Brenda B. Poindexter, MD, MS: I think that both approaches are valid. When I'm thinking about how to approach discharge nutrition, I try to look at where mom is in terms of making that transition to direct breastfeeding. If there are some direct breastfeeding attempts, then you have to think about whether they can fortify the remaining feeds and have successfully sent families home with the commercial HMF.

I think other groups have taken an approach where they are using preterm formula to fortify the milk. Even if the baby had been growing nicely on 22 or 24 cal feedings, if I know mom is actively working towards more attempts at the breast, I may go up in that situation to a 27 cal recipe because it's a relatively lower amount of volume to balance things out. But in a lot of places, sending families home with a commercial HMF isn't an option, but we have done that. I think it's individualizing that and making sure you have close follow-up. I think that's where

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communication with the pediatrician who is going to be following the baby is so key, because oftentimes they don't have as much of an understanding of how hard we've worked in the NICU to get the baby to finally grow, and it can sometimes discontinue some of the interventions we've started.

We are checking ferritin levels for babies that have over 3 transfusions as a guideline, and I find myself having to stop iron a lot and then wait weeks for the ferritin to come back down. When we looked at all the ferritin levels, they didn't correlate well with how many transfusions they received, especially after they received over 3. I'm worried about not providing enough iron to some of these babies, and if there isn't a true iron overload phenotype I need to be looking for and what the threshold in evidence is with the ferritin levels?

I feel like we're representing all of the authors. Honestly, I don't know the answer to that. I've seen that in some cases too where they're just sky high and 3, 4 weeks go by, and they really haven't come down. In that case, it may be more of an acute phase reactant. You brought up a great, I think, opportunity for additional studies. But to be very honest, I don't know the answer to that.

Congratulations to both of you and the enormous editorial effort on the book. I wanted to comment, there's good data from Brazil, which has an enormous number of human milk banks showing that if you slow down administration velocity of the feed, there's a dramatic loss of fat and about a 10% to 15% loss of protein, especially with donor milk. I think that's an area we need to study more because, in practice, when there's an issue of feeding tolerance in babies, we will slow down the feeds and, as you pointed out, the increasing use of either continuous feeds or transpyloric feeds, perhaps we need to focus in offsetting that potential loss of energy and protein.

I don't think we have gone back to some of the trials comparing supplementing donor milk or supplemented with formula. To my knowledge, the largest trial is Dev O'Connor's trial. I don't think we comment enough on the fact that the majority of the outcomes, and NEC was clearly favoring the utilization of donor milk, the primary outcomes of this study were neurodevelopment. Parts of the Bayley III favor and numerically, everything favored the groups supplemented with preterm formula, in spite of the fact they had more NEC. I think that we cannot blindly, without more data in neurodevelopment, favor necessarily donor milk as there may be some shortcomings. So, you trade perhaps less NEC for maybe a potential impact in neurodevelopment. If you were in a situation where your NICU has a very low rate of NEC to begin with, maybe food for thought? We need more information, clearly.

I will say the NICHD Neonatal Research Network has recently completed the donor milk study. We're hoping the results will be out before PAS next year. So, stay tuned on that, but I think you raise a really important point, Fernando. I will say related to the loss of fat in the tubing, I do think when the nurse comes to us and says, "Oh the baby's spitting, they're not tolerating the feeds, can I stretch it out?" I've started having that conversation of "Did you know that we may be losing some of the nutrition by going to continuous?" Nine times out of 10, they're like, "Oh, I didn't realize that." Let's give it more time, and I think by providing some of that conversation at the bedside, we can hopefully decrease the reflex behavior of, okay, let's just stretch it out over an hour or 2 to avoid some of those, maybe not that clinically significant symptoms.

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I have 2 questions from the overall presentation. Talking about early aggressive increase in feeding and more weight gain, which you showed in various studies and the Cochrane review, and the comment that there's no increase in NEC, but it depends on what your standards are for NEC. Sometimes I'm shocked to see rates of 6%, 8%, 10%, even 19% in some of the presentations here.

Our goal, in the place where I work, is to have a less than 1% NEC rate. We use a very slow feeding protocol. If you both can comment on that because it's very hard for us to accept NEC as a problem in the NICU. The second question is, yes, we see a weight gain. We are all happy. The baby's growing at the 50 percentile or more. What about the quality of weight gain? Why don't we think of doing whole-body plethysmography as a routine tool in all NICUs, which are especially level III or more, and use that as a guide to achieve a very high quality of growth instead of just growth?

Berthold Koletzko, MD, PhD: Two very important points. So, NEC, as we all have learned, is not something that just falls from heaven, but it depends on our strategies. We've known for a very long time that the occurrence of NEC, while fluctuating, can be very different in different units and has been associated with practices. So, while people have thought going for parenteral nutrition with NPO [nothing by mouth] for a long time would protect against NEC, we have learned it actually increases the risk for NEC, because, at least minimal enteral nutrition protects the gut physiology. We have also learned that, in units that use human milk predominantly, the NEC rate is lower than in those who don't. We have seen in previous years, at least, a much lower NEC rate in Europe than in North America for reasons that were difficult to understand, but one difference was that previously there was much more human milk used in Europe than in North America. I think it's changing now and is changing I would say for the better. But if you look at the evidence, while there is a number of variables that may influence NEC rate, feeding advancement appears not to be. We have good evidence for that. I know it's very difficult to change practice, because if you've done something for a long time, it's very difficult to change. We've always done it, why should we change? But the evidence is there, and we know if we advance slowly, we can induce harm. We adversely affect growth and potentially long-term outcome.

The second point was quality of growth. I couldn't agree more with you. I think, over time more, we need to move away from just looking at grams of weight gain because it's the quality of growth that matters. I think we will have much more opportunity for clever ways to noninvasively measure body composition. There's a lot of new strategies that are being looked at, and I think this is going to be the future because, as I said before, we can make every baby grow by just increasing body fat deposition, but we know that is not going to help the baby. We really need to look much more at the quality of growth. Brenda, what do you think?

Brenda B. Poindexter, MD, MS: Well, I also think that just having a peapod in every unit probably isn't going to be an effective use of resources. They're expensive and some of the babies I care about their body composition the most are those babies with significant lung disease and evolving BPD. I've not been able to figure out a way to put a baby on oxygen into the peapod. I think it might be a useful tool for some of the relatively healthier babies in the unit, but for it to be something that's routinely used when we can't effectively use it on the population that I'm most worried about, I don't think that that's a practical approach.

I have a question about the IUGR and SGA preterm infant, and perhaps also the term SGA, very low-birth-weight infant. Could you comment on the nutrition for those subgroups?

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Berthold Koletzko, MD, PhD: It's an important question. As we know, our patient population is very heterogenous, and those who are SGA at birth and SGA at discharge are probably the highest risk because they have more limited nutrient stores, and they will have, if supported well, a higher growth rate. So, yes, I think we need to look at that more closely. Some years ago, ESPGHAN [The European Society for Paediatric Gastroenterology Hepatology and Nutrition], for example, in their recommendation has emphasized that we should, after discharge, increase nutrient intakes, use more preterm and postdischarge formula, particularly in the SGA babies, but I think we have more open questions. We know they are different, but to define exactly what is best for whom, I think we need more work.

Thank you so much. Just a short question on fortification of breast milk. In our unit, we used to use quite a bit, the extra fortification 26 until we looked at the components and got concerned about the high delivery of vitamin A. So, we've dropped back to 24 and added some modular protein or carbs. What is your thought regarding that?

Brenda B. Poindexter, MD, MS: I think there's a lot of different approaches people take. I think, when we need to go above 24 cal—this would be off-label—but using more fortifier than is on the back of the package. I do think that adding the modular protein—I will sometimes do that if I'm seeing significant length faltering and have found that to be a good strategy. One of the things, and Bert emphasized this really well, is that the recipes we use for fortification, they're all based on some assumptions about the base diet that you're adding the fortifier to. So, even if you're using maternal milk, if the milk is now 6, 8 weeks into lactation, the protein content of that has already fallen off. That's where it makes sense to me that you might need to be compensating for that decline in protein and maybe keeping the vitamins and the other things relatively constant. But certainly, I think an area that is a great opportunity for additional studies. Thinking about should our fortification strategies be different for babies that are predominantly receiving donor milk vs maternal milk, I think is a really important area.

Abbreviations

AGA	Appropriate for gestational age	**NEC**	Necrotizing enterocolitis
ARA	Arachidonic acid	**NNT**	Number needed to treat
BPD	Bronchopulmonary dysplasia	**NPO**	Nothing by mouth (*nil per os*)
DHA	Docosahexaenoic acid	**PDSA**	Plan-Do-Study-Act
IM	Intramuscular	**ROP**	Retinopathy of prematurity
IUGR	Intrauterine growth restrictions	**SGA**	Small for gestational age
LC-PUFA	Long-chain polyunsaturated fatty acids	**SIFT**	Speed of Increasing milk Feeds Trial
MCT	Medium chain triglycerides	**VLBW**	Very low birth weight

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