Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Applying New Learnings on Human Milk Composition to Clinical Practice in the NICU

Transcript

Editor's Note: This is a transcript of a live in-person presentation on April 30, 2023. It has been edited for clarity.

Fernando Moya, MD: Brian and I are really honored to be able to stand in front of you. Many of you have contributed data to what we're going to present, so we hope we'll do justice to that as well.

I want to start by saying that I think this is a very important step, what we're all trying to do, in understanding how to better nourish our children. We're taking care of these infants in the NICU, and those of us who have been neonatologists for over 3 decades have realized that many of the future improvements in neonates' outcomes will derive from understanding better how to nourish them when they're with us in the NICU and beyond.

Throughout the presentation, Brian and I have made an effort to derive as much information from randomized clinical trials as possible, and we're going to highlight how the trials were conducted because I think it also impacts how we view and interpret that data.

You'll need to look at my profile, and you'll know that I've been a neonatologist since 1984. I'm presently part of the faculty at the University of North Carolina.

It's important to recognize that we are at a time when, fortunately, there have been a lot of advancements in understanding the field of nutrition and human milk and fortification. So, it's continuously evolving, and what we're going to try to do is give you some updates on a lot of data and some studies that have influenced the way we nourish our infants, with a focus, of course, on fortification.

Nutritional Needs of Preterm Infants

Now, why is this important? Well, many organizations, in this case, for us, the American Academy of Pediatrics, have recommended that we should provide nutrients to approximate the rate of growth and composition of weight gain as it is found in the normal fetus. So, with that in mind, we know by now, due to extensive work by many investigators, that this improves short- and long-term neurological outcomes. Also, these improvements are seen way past the neonatal and early childhood periods, impacting school performance, reducing difficulties there and also improving short- and long-term impact on body composition.

We've also recognized that not growing well in the NICU carries a substantially increased risk for some of the common morbidities we are dealing with among these infants, and some of those you can see there. It's not only a suboptimal impact in neurodevelopment—mid- and long-term—but also a higher risk for some of these morbidities.

Some of the cumulative evidence has suggested that actually if we pay attention from the word "go," you can see that from 1 week of age to term, for every improvement we make in z-scores in either weight gain, body mass index (BMI) or head growth, there's going to be improvements in the Mental Development Index (MDI) and Physical Development Index (PDI) that are substantial; therefore, our aim should be to try to avoid that weight loss and try to prevent excessive drops in z-scores. Now, the impact of this goes beyond the usual follow-up period of neurodevelopment at about 2 years. The impact can be seen through childhood and, of course, early adulthood.

Related to this, there are several organizations—we're just going to focus on 2—that have tried to put together and update guidelines for nutrition, which are invaluable resources. We've listed here the latest guidelines found in the Koletzko book (*Nutritional Care of Preterm Infants*). It's a big effort; some of you in the audience participated in that. We coupled that on the slide with the most recent European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommendations. What we can see here is there's been some changes. The Koletzko guidelines and the ESPGHAN guidelines, as you can see for fluid and energy, are fairly close, with some

subtle differences. But, very importantly, they have been modified since their previous editions. I think we're going to highlight some of those and the importance as it relates to human milk composition and what we need to be thinking in the clinic, of following and potentially supplementing and adding.

More specifically, the latest changes in the ESPGHAN guidelines from 2010 to 2022, over 12 years, are a tighter recommended range for fluid intake. Do note that the upper end is up to 180 mL/kg/d, and even today, in many neonatal intensive care units (NICUs), there's an adversity to go past the 150 or 160 mL/kg/d. And whereas perhaps there may have been—I don't want to say necessarily more appropriate—but relevant when you were feeding primarily formula, with the advent of increased use of human milk, either mother's own or donor, providing an adequate volume, usually a higher volume, becomes of paramount importance.

Now, you will also note that the changes include—and here there's a slight difference between the Koletzko and ESPGHAN guidelines—that the upper boundary for the recommended intake of protein has been made a little tighter with a ceiling of 4 g/kg/d in the ESPGHAN recommendations. There's a little change in fat and carbohydrate and there's also been some important changes in the micronutrients that are listed here. Those have come, once again, think of 2010 and before, at a time when we did not use a lot of mother's own and donor milk. So, the new chapter of learning more what's in it has prompted changes in these guidelines.

In the Koletzko guidelines—found again in that book—you can see that the changes are a little wider range of fat so as to provide a little higher level of energy intake, a little tighter range in carbohydrates—but not very different. Notably, there's been some changes and I want you to pay attention to zinc, and Dr. Stansfield will spend a little time on that, and that's also something we've learned. We are going to have to take our monitoring and understanding of what we do not only beyond calories, fluid, and protein, but also focus more on micronutrients as well.

Human Milk and Preterm Infant Feeding

Brian Stansfield, MD: Let me just start by thanking you. I know that Fernando had an opportunity to thank you for being here this morning. I want to likewise do the same. We're delighted to share with you. A lot of what I'm going to present are data that we generated in our laboratory and in our NICU, and hopefully it'll complement and provide some information to you moving forward. But let's start with a couple of, I think, very clear paradigms: nearly every stakeholder in child and maternal health has said that human milk feedings are the preferred diet for infants under 6 months. Some of those have expanded those guidelines out to 2 years, but we know that given that our preterm infants fall within that 6-month timeline, that we strive to provide a human milk–based diet. Ideally, this would be derived from mother's own milk.

I think there are compelling reasons for this recommendation. I'm going to just provide what to me is the one that is maybe the most compelling, which is the prevention of necrotizing enterocolitis (NEC). These retrospective data (now 15 years old) looked at the composite outcome of death or NEC. On the Y axis is NEC-free survival, and on the X axis, you can see days of life. And so, whether you look at the amount of mother's own milk provided in the first 14 days as an absolute value in volume on the left, or as a percentage of total intake on the right, you see that there's a very clear dose–response in NEC-free survival as it relates to mother's own milk. So, I think it's very well described and accepted that mother's own milk is quite protective against NEC and this is just 1 example. I think Fernando's done a good job of highlighting some of the early and later outcomes of a human milk diet and its influence over short- and long-term outcomes.

There are some struggles, as we all know, when we try to provide a human milk–based diet, and this is just a highlight of a handful of those struggles. So, the first being we know that the last trimester represents a period of rapid growth for the fetus and trying to match that rapid growth in the steep incline of accretion is just extremely difficult. Preterm infants have a very high metabolic rate, particularly in comparison to their term counterparts. We know that if we do see suboptimal

growth, we end up with nutrient stores that are much lower than necessary. And the missing piece of this is that a lot of this should've occurred naturally from the mother to the infant, and so our focus throughout pregnancy is supporting maternal health, and maternal health begets fetal health in many respects. Here, we've been removed of the primary source of that transfer of nutrients and nutrition in the preterm infant.

The other major obstacle for us is that weight-appropriate human milk volumes just simply cannot meet the nutritional needs of preterm infants. If we are trying to meet these guidelines or this overarching theme of matching fetal growth in these preterm infants, we're going to really struggle to do that if we use human milk by itself.

And then, what I'm going to highlight a bit later on in this talk, is that human milk is quite variable. The composition—what's in it—changes both with lactation stage and with preterm and term infants.

What are the factors that influence maternal milk composition? We've tried to place these into 3 buckets for consideration. While there are others, these are the main categories that I think about. With maternal effects, we know that particularly demographic data like age, race, parity, and we suspect that maybe geographic location (not just country-specific but maybe region-specific) might influence the composition. We certainly know that diet and maternal BMI play a big part, as well as genetics. There are perinatal factors, like lactation stage, which have been well described in term milk, the volume of milk, and the mode of delivery. And then there are environmental factors. So, for those of you that use pooled donor milk, the pasteurization process (the heat treatment) has some effect on the contents of that milk. How you store milk. So even if you're talking about maternal milk directly, how do you store that? Do you use fresh? Do you use frozen? What sort of thawing practices you might undertake. Do you pool milk in 24-hour aliquots, or do you use it directly? I think all of these practices influence, in some regard, what you're actually giving a preterm infant.

Let me just highlight a couple of things here, looking at lactation stage and gestational age. So, a couple of things that we do know is that, in some respects, we can provide mothers with some additional supplements and drive the expression of those supplements into maternal milk. A good example is docosahexaenoic acid (DHA). So, if we can give a DHA supplement to mothers, we can provide additional DHA to the milk and subsequently to the infant. Similarly, vitamin B can be increased in human milk with supplementation to the mother. Other things are a little harder to take on that, so choline can certainly be supplemented. Some of the vitamins, there's some variable expression. So, some studies suggest that giving additional vitamin A and D can actually increase the content in human milk, while others really struggle to see, particularly with vitamin D, any real significant movement of vitamin D content. And then zinc and iron supplementation really, for the mom, don't provide any real substantive increase in those contents within the milk itself. And so we really have to understand where we can focus on the mom in providing additional nutritional support to her that then ends up in our patients. And then, where do we have to be more direct and actually provide the supplements directly to the infant.

We tried to summarize the data just a couple of years ago in 2021, looking backwards at what do we know about preterm human milk and the composition therein. Surprisingly: not a lot. This is unfortunate, and part of why we're here today. So, we identified, over the span of about 40, almost 50, years, only 27 articles that really met rigorous criteria for inclusion in a narrative review. Interestingly, for those of us that are in the United States (and I recognize that many of us practice outside of that) only 7 of these 27 studies were published in the United States, and all of them were prior to 1990.

A couple of things that you might just infer from this dot plot of when these studies were published is that there's a significant underrepresentation of the population that we care for today which is, in large part, less than 28 weeks. I mean, this is the population that is a real struggle for us. Studies in the early 1980s and 1990s really didn't have a lot of patients who were born and survived at less than 28 weeks. So, studying the mothers and their milk composition was a real struggle. And then there's just a tremendous underrepresentation of minority populations. So, I think we're all aware that African American mothers in the United States are much more likely to deliver preterm and then have adverse outcomes related to

that. Breastfeeding rates among minority populations can vary pretty tremendously, and so I think it's important to understand how these different populations might have different milk.

The summary of this study was I think to say that there's a couple of things. Caloric density seems to increase rapidly over the couple of weeks immediately after preterm birth. There is an increase in fat content and a simultaneous diminishment in protein content over time. Carbohydrates (the primary one is lactose) is really stable throughout gestation and lactational age. And then there are declining levels of sodium, particularly in the first 30 days. So, this is the summary data of those 27 articles and, again, with the caveats that they really don't represent the population that we're most concerned about today.

Along with Amy Gates, who was getting her PhD, we undertook a study of nearly 40 women, to provide a little bit more information in this regard. We took serial milk samples at 7, 14, 21, and 28 days. These are 24-hour pools of milk. We took a 20-mL aliquot, and we assessed macro- and micronutrients. A couple of things to highlight here in our demographic data were that the mean gestational age for this population was 28 weeks, the range being 23 to 33 weeks, and importantly, for what I was trying to point out, was that nearly half of our population were born at less than 28 weeks. And then simultaneously, I'd just point out that two-thirds were African American or Black. So, really a different population than was previously studied.

What we found I think was quite interesting. If you look at these graphs, all of them are going to look very similar. So, you can see on the X-axis, the day at which the sample was collected and then the Y-axis, all are in per deciliter (so per hundred milliliters). You can see that—counter to some of the other studies—energy content is relatively flat across the first month in preterm infants, somewhere between 65 and 70 kcal/dL. And while fat does increase over time, we do see a leveling-off effect and, overall, very little change in fat content. Carbohydrates, similarly, are relatively stable. But we did see an overall decline in protein content. I think what was most striking was that the value that is used often for preterm milk is 1.6 g/dL, and what we, in fact, found was that this number is not achieved until 28 days. So not only is early milk protein-dense, but in fact preterm early milk is quite dense in protein, upwards of 2.2 g/dL, particularly in that first week to 2 weeks of life. And so, thinking in a nuanced fashion around protein delivery—which is a target for many of us in the room—that early preterm milk is providing quite a bit of protein, and it's not until that mature preterm milk sets in that we're getting to that 1.5 to 1.6 g/dL number.

We also had the opportunity to look at the influence of various covariates in this content. Let me just highlight here, for example, protein content by race. White or Caucasian women had a dramatic decline in protein content over that first 28 days. Somewhat surprisingly to us, it was influenced by race. African American mothers had a persistence of higher levels of protein in that milk, and I want to provide some context for that here. Protein content is highly dependent on the volume of milk. So, when we actually look at mothers who are high milk-volume producers of that 300 mL/d, you can see that the protein content there is generally less than the mothers who produce lower volumes, or 65 mL/d. So, protein content's really dependent on milk. So, not surprisingly, when you look at the volume of milk produced over this first month of life, you see that African American women have lower volumes, typically, but also have pretty stable production, at least in this population of 40 women.

Conversely, White women tended to produce a lot more human milk in that 14 to 21 days. Again, everything merges at the end, but I think it helps us to understand. The way I interpret this is that African American women, and maybe other minorities, may be producing low volumes of milk, but that milk may be very enriched for certain nutrients like protein.

Similarly, we had the opportunity to look at gestational age. We divided these into less than 28 weeks and over 28 weeks because, the lack of data was below that threshold. The population that's less than 28 weeks had higher and more stable carbohydrate content in the milk than those that were born at a later gestational age. The reverse was observed when we looked at sodium content, which I think is striking, given the emerging prevalence of sodium supplementation for many infants is taking off. So, our youngest population really not only produces very low sodium, but that content does not change very much over time (20 mg/dL in that first week or 2 and then

some emergence of higher content in the older infants as milk matures).

In returning to our comparative studies, we have a lot of information on term milk. I think that the chart towards the right is highly reliable, and I think we're starting to find some better data on the middle column. We would suggest that protein content is a little bit variable in preterm milk, and it may be as much as 2-fold higher than term milk. Similarly, sodium seems to be concentrated in preterm milk, and there's higher content of zinc; although, I didn't show those data.

A couple of key takeaways from our studies and from our review of the literature is that preterm human milk is quite dynamic over that first month of lactation. There are some components that are stable and reliable (fat and energy). We can give energy and calories and carbohydrates without too much trouble. There is a diminishment of protein over time. Sodium fluctuates quite a bit and seems to be volume-dependent, along with protein. And then zinc diminishes over time as well. And I just would provide this little takeaway or hint: if you take care of minority populations, which I think we all do, to really think about race and protein content in particular in Black and African American populations in this group.

Donor Milk Overview

Fernando Moya, MD: Now my job is to give you a little bit of an overview of what we're using incrementally. If one had asked a question of how many people use donor milk 10 years ago, it would be a minority in the audience. So, I'm going to ask all of you, can you please raise your hand if you use donor milk in your NICUs. Alright, so it's the overwhelming majority. And we know that, and that has been well reported and substantiated.

You all know this, so it's recommended to give—if there's not enough or no mother's own milk—to give donor milk, especially early on. But we also need to think of the characteristics, and sometimes this is lost in translation. It's primarily coming from mothers of term infants. Some milk banks now have mothers of preterm infants, and that will be an advantage—we need to learn and study that more. Generally, excess milk is collected in the later stages of gestation (excess supply); therefore, it's being stored for a while, or it just reflects, as Dr. Stansfield has noted, changes in the milk composition.

Most of the time, donor milk is pooled into vials or bottles that can be measured more accurately—some of the macronutrients—and, of course, it undergoes a process of pasteurization. So, that process itself, while it accomplishes the goal of getting rid of microbes, it also accomplishes the goal of getting rid of other things. Very importantly, some of the enzymes present in milk associated with lipid absorption are either decreased or completely not found. Of course, the very precious neutrophils and stem cells are affected as well. And some things like lysozyme and lactoferrin, which we increasingly recognize are important, are also affected. Long-chain polyunsaturated fatty acids will go down, and there will be impact on other micronutrients. Of note, although there's variable evidence about this, I think vitamin A, which is not all that abundant to begin with, may also decrease.

Most of the time, especially at milk banks, what they do is undergo a process of target pooling. That is combining milk from many donors and multiple expressions and come up with a larger pool of milk where they can measure some of the macronutrients and, most of the time—not necessarily all the time—it may be sufficient or close to being sufficient in terms of the energy content, but it falls short in terms of the protein content. And most of the time—not all necessarily—the milk banks will have a label and what they provide to you, the protein concentration will be around 1 g/dL or slightly shy of that.

There have been some data and tests shown there on the slide, on the bottom of the slide, that are using target-pooled donor milk still had worse outcomes in terms of growth. So, we're starting to see some data showing that the impact was truly beneficial in some morbidities, mainly NEC. It may come with an additional burden, which is perhaps that growth is not as good as we would like it to be. Now, I find this study fascinating because this is something we do in the NICU, and sometimes we're truly not aware of the impact in what we're providing. This was done by a group in Brazil, which, by the way, trivia, has the most milk banks in the world. And they studied donor milk and what happened during the actual process of taking the raw

milk, pasteurization, freeze, and thaw. Then they studied when they gave it in different ways to the infant.

Let's follow the top line of fat. If you go from raw to pasteurized to thawed, there is about a 10% loss. That's a 10% loss of energy. But then, think of what you're doing in the NICU. You're ordinarily feeding by bolus. You have an additional loss. But should you say, okay, tolerance is not good, the abdomen is distended, there may be residuals if you're measuring, and you prolong the administration, you make it either 2 hours on, 1 hour off, or continuous feed, there's a dramatic additional loss of fat. And that's important because you may be losing close to 50% of the fat energy there, depending on how you're actually giving it to the infant.

We're showing some impact on protein, at least in this study, the impact is a lot less, yet significant. You start with not a lot and you reduce it through all the different steps.

Now we're going to have a true comparison of a lot of the contents and pass the baton back to Dr. Stansfield.

Donor Milk vs Preterm Milk

Brian Stansfield, MD: Donor milk is, I think, because of its emerging nature, we're now very familiar with its usage. I think a lot of us fall back to donor milk when mother's milk is not available, and many stakeholders recommend the use of donor milk as an alternative. I think that, while we have a label for donor milk, I think there's still a poor understanding of the analysis that follows. So, we have undertaken to provide some data here. These data were presented at the Pediatric Academic Societies (PAS) meeting on Friday, and so these are very fresh data.

What we have done is taken our early preterm milk at day 7 (in blue) and our late preterm milk at day 28 (in red), and we've made direct comparisons for each of the components in donor human milk (labeled DHM, in green). On your left, the calorie content—while a bit more spread out for early preterm milk and day-28 milk—there's really no difference in the calorie content for donor human milk as it compares to preterm milk. That should infer and reassure you is that you can treat donor human milk and preterm milk, from a calorie standpoint, identically. Similarly, carbohydrate content is largely the same between them and does not move very much. I think, as we all know and has been established in the literature, that donor human milk has a lower quantity of protein, around 0.9 to 1 g/dL. But in comparison to that early, immature preterm milk, you can see that there are differences in the protein content in that milk. Similarly, fat is relatively stable and then, ash and moisture are terms that we don't use, but let me just clarify that a bit. Ash is the mineral content (the things that are in milk) and then moisture represents the water or humidity in the milk. As you might infer from this, one struggle that we have with donor human milk is that it has a lot of water and a lower quantity of minerals overall in comparison to preterm milk.

When we look at the minerals (like sodium, which is of interest to us), while there's low sodium in preterm human milk, there's much lower sodium in donor human milk. The mean value for sodium across all donor human milk that we measured was about 11 mg/dL. That is anywhere from half to one-third of the value in preterm milk. Chloride matches that value quite similarly, and I'll just draw your attention to zinc. There's a lot of interest in zinc moving forward. Zinc is deficient in all human milk, but there are much higher supplies in preterm milk than there are in donor human milk.

These data were presented yesterday in a separate abstract, looking at what we consider to be the bone minerals (calcium, phosphorus, calcium/phosphorus ratio, magnesium, and vitamin D). There's really no differences. The supply of calcium, the supply of phosphorus and magnesium are largely similar between preterm milk and donor human milk. All low, so they're not to any great advantage, but there are similar quantities. And then I'll just highlight that while vitamin D is similar across all human milk and is really poorly expressed, there are some women who tend to produce more vitamin D in their milk. So if you are doing vitamin D supplementation and you have these few infants that really have high levels of vitamin D (if you measure those), these may be women that are producing sufficient or higher quantities in their milk than others. And I know that vitamin D measurements in milk are not a routine part of our care.

Applying New Learnings on Human Milk Composition to Clinical Practice in the NICU

Goals of Fortification and Fortification Strategies

Fernando Moya, MD: We're going to be talking a lot about and showing some of the evidence from the trials of fortification. We mustn't forget that we need to pay a lot of attention during transition and this is 1 of several studies that quantify what happens in administering protein and energy during transition from parenteral to enteral nutrition. This data, by Miller et al, was from Maimonides in New York, in which, in the top panel, they looked at total protein intake and on the bottom panel is energy intake, depending on the volume of enteral feeds. As you can see, with common practice, as you reduce the level of parenteral intake, the amount of protein you're providing goes down significantly. And, as you go up in the volume of enteral feeds, overwhelmingly we are providing either mother's own or donor milk with a lower protein content than what you were giving in mL per mL on your parenteral nutrition. The biggest drop is a significant decrease in the overall protein intake as you transition. The impact is a little less in terms of energy because the carbohydrate amount is not as impacted from the transition from parenteral to enteral nutrition.

Now, other studies have been more successful in trying to reach targets. This is data from the ImNuT randomized controlled trial. This is a subset of data. This was published recently in which, with a standardized feeding protocol—again, protein on the top and energy on the bottom, and in the shaded area, the target ranges—what they did is pay attention as they went up on the enteral intake, they sustained energy and particularly protein intake a little bit longer. And I think we can do that. It's not that hard, but we need to be aware and paying attention.

They advanced what we now would consider a little bit conservative (the volume of feeds on a daily basis), and they started fortifying at about 100+ mL/kg/d. And that has been an area in which we'll show a little bit of data as to whether we should modify that.

We know that just providing term infant formula, which is obviously targeted to term infants, and unfortified human milk, we do not meet the needs of the growing preterm infants, and we don't need to belabor this. There are an abundance of data. In this case, we're showing a meta-analysis showing that, with fortification, there's substantial growth benefits to be observed in weight gain, body length (a surrogate for fat-free mass), and head circumference, probably impactful in neurodevelopment.

But the goals of human milk fortification are to augment what's in it, not necessarily to replace what's in the breast milk. Moreover, I think we need to be—depending on what we choose to use—increasingly aware of the displacement of the very critical components of mother's own milk (albeit less so in donor milk). But when you add—especially now with the advent and wide use of liquid fortifiers—it is essentially displacing the valuable components that are already there. And we need to meet the estimated protein and micronutrient needs, and Dr. Stansfield will show you that this is of paramount importance. Not only are we falling short in calcium/phosphorus (we knew that), but also in sodium, potassium, and zinc. We haven't thought about zinc a lot in depth.

I love this article. Dr. Amy Hair summarized this really nicely in a review published recently. This is taking it back to the clinic and the paradigm that we face when we're making decisions about how to feed this baby. So, do you do mother's own vs donor? Ideally, you will have mother's own, but milk production in moms is very little over the first several days. You need to be aware of the differences in protein content, but also what the process of pasteurization and the differences in some of the good stuff, so to speak, that's in mother's own vs donor. And now, Dr. Stansfield and others have added an additional consideration, which is we need to be mindful of not only lactational stage, but perhaps the racial background of the mom and the volume being produced. Your additional decision is what fortifier type you use, and we will go, albeit rapidly, through some of the controlled trials comparing fortifiers. But we have options, which is very important. We just need to know those options and what's in it (or what's not) and also hopefully see where the improvement will come in terms of additional things.

I think we've answered the question of liquid vs powder. We'll show a little bit of data and their associated cost differences. And sometimes, at least in the US, some of these decisions are being made by administrators based on cost, and not necessarily on scientific data. A very important question is,

when do we start a fortifier? Is it relatively early vs relatively late? The overwhelming majority of the controlled trials of fortification have included fortifying at about 80 to 100 mL/kg of milk per day of enteral intake or above. So, we'll show a little bit of data of some trials that asked that question. And, of course, there's the remaining issue of how long should you fortify, and what options are there?

We don't need to belabor this a lot more, but the variability and the different gaps that exist when you compare the content of preterm and term milk and, just for illustration purposes, the last column on the right is the recommended intake. And you can do the math and you know you're going to be falling short in protein, sodium, potassium, calcium, phosphorus, iron, and zinc without the option of intervening in some of them of adding supplements to the mom and being able to modify this.

What about when to start? To date, there have been 2 randomized, controlled trials that have asked the question, should we fortify early vs delayed (or what I would call, as what most of us have done, as standard)? The table on the left side for you comes from the study, the original study of human milk–based fortifier conducted by Dr. Sandra Sullivan and collaborators, in which they had 3 groups, 1 randomized to start human milk–derived fortification at 40 mL/kg, a second group that was fortified with the human-derived fortifier at 100 mL/kg, and there was a third group that was a combination of a bovine-derived fortifier and the use of formula. For the purpose of the question here for us is "when do we start?" We're comparing the first 2 groups. In other words, fortification at about 40 vs about 100 mL/kg. You can see that the rate of NEC was not different, nor was the late-onset sepsis or any other thing they looked at. The rate of weight gain though was a little bit less than what we would desire, but no difference between the groups.

The table on the right hand of the slide is a study by Shah et al conducted in Tennessee. These investigators used only a bovine milk–based fortifier, and they compared starting when the babies got to an intake of above 20 mL/kg vs over 100 mL/kg. This study was a blinded study and about 50% of the infants were less than 1000 g, so the population of interest. You can also see that the rate of NEC—something we all fear—was very low. Now remember, they're getting only human milk fortified (in this case) with a bovine-based fortifier. The episodes of feeding intolerance were no different, and the cumulative protein intake was more in the group fortified early. However, both these studies did not achieve targets for either energy or protein, so not surprisingly, when they looked at growth—did the kids grow better when we were supplementing early—they failed to achieve that, and this was highlighted in the meta-analysis of only these 2 trials, as shown on the bottom of the slide. So, if we're going to move based on good tolerance, no higher risk of NEC, or other morbidities, fortifying early, we need to try to achieve targets of energy and protein.

Methods of Fortification

Brian Stansfield, MD: I think Fernando's done a good job of establishing the need for additional fortification of human milk. One thing I'd like to highlight is all human milk can largely meet the caloric needs of a preterm infant, and I think so often in rounds, my experience is that we report quite a bit on the caloric density of the milk that we're providing and there is a lot of focus on calorie delivery. But by and large, at 150 mL/kg or slightly higher volumes, which are now within the guidelines of both Koletzko and ESPGHAN, we can meet the caloric needs of preterm infants with unfortified milk. So, I would like to just suggest that caloric density should not be driving decision-making for us on rounds, but rather thinking holistically that fortification really exists beyond caloric density. It exists in providing additional minerals and protein and other nutrients.

How do we think about this? Well, again, I like categories. I think that this slide does a good job of helping us to understand what are the various approaches available to us. I think the most common is just standard fortification. The manufacturer produces a fortifier with some instructions and guidance to how to add that fortifier, and I think that the vast majority of units use that methodology: a fixed amount of fortifier per volume of milk, depending on what fortifying agent you're using, and that tends to work quite well for a great number of babies. And typically, we know that this assumes a couple of things about the milk that you're fortifying and 1 of those being that it is essentially 20 kcal/oz. We know that not necessarily to be true always and that it's about 1.5 g/dL of protein, which I've provided data to suggest that that's not always true as well.

The second and I think one that is the middle ground here is adjustable fortification. It is a little bit more labor-intensive but is not to the point of this precision fortification that I'll talk about in just a minute. But it's really about the middle ground of targeting specific nutrients like protein. One measure might be serial blood urea nitrogen (BUN) measures, and if you have a low persistent BUN, you might infer that you have lower delivery of protein overall and that providing additional protein supplementation could be helpful to drive that BUN modestly higher, above 10 mg/dL.

And then the last is the most precise and it's also the most intensive. It requires personnel; it requires equipment and space. This is what we have referred to as targeted fortification, where we are actually analyzing the human milk, deciding what content's actually in the milk we're fortifying at that time and then using very specific supplements or fortifying strategies to increase that to the recommended content that we've stated several times now.

A couple of comparative studies and, Niels—always a little odd to present data for someone that's in the room—is a leader in the thinking around targeted fortification. In his study of about 50 preterm infants per group, they were measuring the content of human milk 3 times a week, so that gives you some sense of the labor-intensive nature of targeted fortification. But then, once they had the analytes, they were adding additional protein and other nutrients to raise that content to the recommended values based on the 2010 ESPGHAN guidelines. And their primary outcome was 21-day growth velocity, and the group that was targeted fortification had about a 3 g/kg/d increase in growth velocity at 21 days and, while they were very similarly matched at birth, you can see quite clearly that the group in the targeted fortification had a 250-g difference at 36 weeks. So, there is a good suggestion that targeted fortification does improve growth and maturation.

If we think about adjustable fortification, which is that middle ground vs targeted fortification, so if we're specifically just targeting protein, in this study, Bulut et al really highlights how that approach can be efficacious as well. In this group, the standard fortification was adjusted so that we could deliver a protein target of about 4 g/kg/d, which is slightly above the new recommendations. And then, with the targeted fortification, they were trying to provide even higher numbers at 4.5 g/kg/d. And what they showed was that protein does help to provide some additional growth velocity later in life—about a 4 or 5 g/kg/d increase—so that these strategies that are really either making clear measurements of the milk or, as I'll show you in a minute, makes some assumptions about milk. If we pay just a little bit more attention to the content of milk and fortify it with some nuance, I think we can achieve better growth.

This is an observational study by Cardoso, and they had a group where they assumed the content of human milk based on the recommendations or the guidelines, and then a second group where they actually measured the content. And so, really in a practical way they did the study that many of us struggle with: how, if we make certain assumptions about what's in the content of milk and we fortify based on those assumptions vs if we measure and actually do more precise addition of macronutrients. As you can see, body weight z-scores were modestly, but not significantly, better in the group where they actually measured and added content specifically. Length was significantly better, as was head circumference, which is an important marker of future neurodevelopmental outcomes.

I think the overarching theme is whether you want to continue using standard fortification or you want to start emerging into this adjustable or targeted fortification, a major point or takeaway would be if you pay attention and if you consider that not all milk is created equal and that some appreciation for that variation really may have a significant impact on your growth outcomes.

Clinical Trials Comparing Fortifiers

Fernando Moya, MD: Now we're going to show you some of the data derived from clinical trials of fortifiers, asking a variety of different questions as we go. You may recall (this is about 10 years old) that there was interest in modifying the way we provided fortifiers from powder to liquid, and there were also some infectious concerns at the time. So, we're showing an example: the 2 randomized, controlled trials that were done. On the left, the one conducted with the bovine-derived acidified liquid fortifier, comparing that with the powder fortifier, and on the right-hand is the bovine-derived hydrolyzed protein liquid vs the powder. And in both of these studies, about 140 patients

were randomized and enrolled. One study was blinded; the other one was not. And what the studies measured was, with a little bit more protein and given liquid form, did babies grow better or not? And the answers at the end of the study period of 4 weeks was that infants grew better. Those who follow the recommended guidelines with the liquid fortifier do better. And since these studies, we're primarily using liquid fortifiers.

Parallel to that, the studies with human milk–derived fortifier were conducted. This is going back to the original trial by Dr. Sandra Sullivan et al, in which now we've added, on the far right, the comparison group that received primarily a bovine fortifier and also formula. And that fortification process was started when they hit 100 mL/kg/d or more. Weight gain was not different—slightly but not significantly better in the latter group fortified with the combination of either those patients receiving a bovine fortifier or some formula. Linear growth and head growth were a little bit below what we would want, and personally, I particularly worry about the reported head growth that was below what one would expect. The primary outcome of this study was median time on parenteral nutrition as a surrogate of feeding tolerance, and it was not different. And there were no differences in some of the other outcomes. In this study, they reported a difference in NEC between group 3 (the one that received a combination of bovine fortifier and formula) compared to the groups that received the human milk–based fortifier.

Now, having mentioned that perhaps growth might be a little bit less, there was an additional effort, a trial conducted by Dr. Amy Hair and collaborators, was assigned as a noninferiority randomized, controlled trial in a specific focus group of infants. And what was compared was the standard fortification using the human milk–based fortifier vs an addition of cream (in other words, a concentrated fat) to provide additional energy. Indeed, by providing that, they were able to show a higher weigh velocity (as shown on the top of the table). But do note that the standard fortification with the human milk fortifier, without the addition, resulted in no significantly lower rates of growth and growth velocity. Not surprisingly, there was no NEC and no difference in other morbidities or death.

What about other studies? This is a study conducted by Dr. Debbie O'Connor and collaborators in which they compared a completely human milk–based diet (in other words, milk or donor milk with a human milk–based fortifier) with another group that also received human milk but utilizing a bovine milk–based fortifier (in this case, a hydrolyzed protein liquid fortifier). And they were looking primarily at evidence of feeding tolerance and other morbidities. There were 232 patients eligible, and they randomized 127 infants; they were all less than 1,250 g. The comparison revealed almost no significant difference. Tolerance was fairly similar, and what they call a mortality and morbidity index—the reason why these investigators group this is because of the relatively low occurrence of some of the major morbidities we see in preterm infants—and no differences in NEC. Notice how uncommon it was, but keep in mind that all the babies in the study received human milk, either mother's own or donor. And there was, interestingly enough, a substantial drop in severe retinopathy of prematurity. This study also had a follow-up component.

There was also a comparison by Dr. Richard Schanler and collaborators. A randomized, controlled trial, unblinded, comparing the previous acidified human milk fortifier vs the nonacidified liquid human milk fortifier, both of which are bovine-derived. The primary outcome of that study was the rate of weight gain, and there was no significant difference, nor were there in length or head circumference. There were some minor differences in tolerance that were reported, and about 10% of infants in the acidified liquid fortifier group received therapy for what they describe as metabolic acidosis, as defined by either a clinician diagnosing it or Bayley-III score below -6.

There have been other trials of importance. I presume most of you are very familiar with this other trial by Dr. O'Connor's group. This was a larger, multicenter, blinded trial in which the question was: we know we can get a large proportion of the baby's feeding to come from mother's own milk, but what should we do for the remainder? So, about half or a little more, close to 60%, of feeds in both groups were mother's own milk, but then they were randomized to donor milk for the difference. In that case, knowing this lower amount of protein, they added a fortifier with protein and protein supplement. The other group randomized received close to a little over half of mother's own milk but was supplemented with formula.

That study had, as a primary outcome, neurodevelopment at 18 months, and I'll show that a little bit later. But they did report short-term outcomes, and this also somewhat convincingly showed that when the addition to mother's own milk was donor milk, the occurrence of NEC was significantly less than when they took this other group that received a little over half of mother's own milk and gave formula in addition. You can see this is proven NEC, not suspected or stage 1. This is all confirmed NEC, stage 2 or more. They also looked at other outcomes (death, the morbidity and mortality index, etc), and there were no differences in those short-term outcomes.

Based on this, donor milk has been recommended primarily—and I think it's a strong recommendation—for reduced risk of NEC. But more recent data have also called attention to the fact that perhaps there's some impact on growth, which may be less, and will be important to be more aware of. And we'll get an opportunity to show you a little bit of the impact, if any, on long-term outcomes.

We're not going to have time, but these are some of the options that we all do from a practical point of view for the duration of fortification, and if you choose to fortify past discharge from the NICU, you either have the option of using formula to supplement, powder, supplementing what we often do and that is well studied, having the mom feed breast milk and then give a couple of feeds of transitional formula for the baby. And depending on resources and availability, if they're in your region, you can continue to fortify, watching once again the fact that the needs for energy, and particularly protein, decrease further on.

Long-term Outcomes From Trials of Fortification

Fernando Moya, MD: What about long-term outcomes? And here again, we have picked showing you data from long-term outcomes of randomized, controlled trials. This is from the original study done by Dr. O'Connor, published in *JAMA* in 2016. The primary outcome was neurodevelopment at 18 months. This is a really well-conducted study with a large sample size of babies less than 1,500 g. And, as you can see, whereas the short-term outcome, particularly NEC, was different, there was no impact on whether you added donor milk fortified, vs formula, to mother's own milk in terms of the 3 long-term components in follow-up.

Of note—and again if you look at a lot of variables and you may get 1 that is significant—but of note for us in neonatology, we not only want to look at what the average is, but we want to look at the proportion of babies at much higher risk. And we have ascribed that to those that have neuro-impairment scores less than 85. And, at least in the cognitive score, the proportion of those infants that had a lower score was significantly higher with the supplementation of mother's own with donor milk as opposed to formula. Again, this is something that would need to be confirmed and explored further.

Of that original study comparing babies, there was more long-term follow-up now published more recently. This is at 5½ years. And the bottom line is, whereas there were some perceived differences in growth earlier on, they were no longer present in that or other measures looking more into the impact on long-term health in these infants (for instance blood pressure). So, the changes that were observed early on may not have lasted up to the point of 5½ years.

We're indebted to Dr. Tarah Colaizy. We're really happy that she agreed to let us share with you the slides of her study called the MILK study that was presented at Hot Topics. And this study, conducted by the Neonatal Research Network, was a triple-blinded, randomized, controlled trial for moms who could not provide their own milk. Here, the mother's own milk intake was very little or nothing at all, and they were randomized to receive donor milk fortified with a liquid fortifier vs preterm formula. So here we have donor vs formula.

The study was for infants who were admitted to any one of the Neonatal Research Network's centers by 7 days and they could be randomized up to 21 days. The primary outcome of the study was neurodevelopment at about 2 years' corrected age. Here is some demographic information. The trial was designed to have a larger sample size than this, but due to a variety of things, including slow enrollment, it was stopped here, with actually a quite significant number of infants. On the far right of the slide, you see the behavior of some of these demographics for the Neonatal Research Network at large. And I want to call attention to just a couple of things. The proportion of maternal education—this can impact follow-up data—of less than high school, was higher than what the Neonatal Research Network

at-large saw, albeit not different between the study groups. That was also reflected in the proportion using public insurance. There was no significant difference in the proportion of antenatal steroids.

Okay, so here's what we wanted to see. Here's donor milk vs preterm formula, and these are the means for the Bayley-III scores conducted at 22 to 26 months (in other words, about 2 years corrected age). As you can see, this is a high-risk group of infants, extremely low birth weight (less than 1,000 g) and less than 29 weeks. The numbers were not all that good, but there was absolutely no difference between the groups. When they looked at what I showed you before, the neuro-impairment score less than 85, there was also no difference between them (in very high-risk infants).

What about other outcomes? There was no difference in death before discharge. There was a significant difference, not surprisingly, in NEC. The group fed with formula had about a 9% (again single digit, but relatively high) vs a drop to less than half in the group that was fed donor milk, as there was no mother's milk. No significant difference in late-onset sepsis, but they call attention to the fact that the z-scores (growth) were clearly—at least in weight—not as good in the group that was fed donor milk, albeit fortified, compared to preterm formula.

Now hopefully to wrap it up, we will hear some additional ongoing research and unanswered questions.

Unanswered Questions and Ongoing Research

Brian Stansfield, MD: Alright, so we've laid the groundwork for why fortification is necessary for human milk, but we have not come close to answering all of your questions. So, let me just dive into a couple of thoughts.

Osmolality is gaining a lot of attention around feeding. So, one of my fellows undertook this study to understand the effects of various fortifiers on osmolality at caloric densities that we commonly use. As you can see, it's color-coded by caloric density, and the key is up on the right. As you can see, we have all of the liquid human milk fortifiers that are commercially available in the United States: 2 Similac products, 2 Enfamil products, and the variety of Prolacta products available. The American Academy of Pediatrics recommends an osmolality threshold of 450 mOsm/kg of water. That's represented by the red line. All enteral nutrition, supplements, etc, are meant to be below this number. There are some data to suggest that high-osmolality feeds may beget feeding intolerance, slow gastric emptying time, and are generally recognized to be safe at around 500 mOsm/kg and below.

As you can see here, there are clear differences in osmolality. As you increase caloric density, you also increase osmolality. With some fortifying agents, that increase is lower than others. The Similac product actually recommends that you provide a protein additive in order to meet a targeted protein value that is similar to the other fortifiers, and so when you add that fortifier or that protein supplement onto the fortifiers at 22 and 24 kcal/oz, you can see the results and the resulting osmolality.

Another consideration is displacement. So, displacement is the idea that when you mix fortifier with human milk, the residual volume is some less percentage of human milk. If you are taking 50 mL of human milk, 50 mL of a fortifying agent, then that subsequent 100 mL that you're providing—only half of that is mother's milk. I think displacement is something to consider in your fortifying selection. The caloric densities of the 5 available liquid milk fortifiers provide less human milk as you increase the caloric density of the overall net fortifying agent. What was somewhat striking to us was that there was a modest difference between the human milk–derived fortifier displacing more mother's own milk than any of the bovine liquid fortifiers. And let me provide that information to you in a slightly different way.

If you look at the 3 brands of liquid milk fortifiers and, on the Y-axis, we have displacement (how much mother's own milk is replaced by the fortifier as a percentage). And then on the X-axis, we have the additional protein that that fortifying agent is providing to the mixture. And so, at 24 kcal/oz, the 4 bovine liquid fortifiers (in green and blue) provide more protein at a similar displacement to the plus-4 that is the human milk–derived fortifier. So, at the same caloric density, you're able to provide more protein at a similar displacement of milk. But in order to match the amount of protein delivery, the human milk–derived fortifier requires more displacement of mother's milk. So, if we believe—and I think if we surveyed the room there'd

be a large percentage that do—mother's own milk provides some additional benefits over other sources of milk, that providing as much of that mother's own milk as possible is really ideal.

A couple of things just to consider. There are wide reference ranges for the micronutrients that exist in milk, particularly preterm milk, but there's really limited high-quality evidence for what the intake level should be and how to optimize those. And we also know that there's variable absorption of these minerals and nutrients and that things that we do in the NICU, like diuretic use, certainly change the needs and the absorption. So, high-quality randomized controlled trials are necessary to really understand micronutrient supplementation.

A couple of thoughts. There's really nice emerging data on zinc supplementation. There are now 8 randomized, controlled trials of almost 750 preterm infants that show that zinc supplementation increases weight; it's particularly beneficial to length gains, and there are higher motor development scores in those kids. It seems to be rather safe. There's no additional morbidity or mortality associated with zinc supplementation.

Iron supplementation, in a meta-analysis of over 1,000 infants, showed that there was improved linear growth, lower rates of anemia, and minimal effect on NEC. And more recently, a post-hoc analysis of the PENUT study suggested that potentially even higher doses than we typically use might improve cognitive outcomes at 2 years of age.

And then, finally, I'd like to just show that there's a very nice study published just a couple of years ago that strongly suggested that the fortifier type or the origin of the fortifier, being from the bovine or from the human milk, really had no impact on gut microbiome diversity or weight gain. And this is really important because we're starting to really understand the symbiotic nature of humans—that the gut microbiome influences so much of both immediate health and future health. What was more striking was that the source of the human milk itself (whether it was from mother or it was pasteurized and pooled donor milk) really did have a significant influence on the microbiome. So, if you're interested in that, I would just point you to this study to really highlight that mother's own milk, again, provides a very different source of nutrition and subsequent microbiome in the gut.

Key Takeaways

Brian Stansfield, MD: Just some final key takeaways. When we talk about optimizing human milk, I think we have to understand that preterm mother's milk is really dynamic. It's very protein-rich early on. Some of the nutrients diminish over time. So, consider sequential feedings. Whatever your practice is, providing that early milk as some of your first milk is probably optimal. There's higher protein and some of the minerals in preterm milk than in donor milk, but consider sodium supplementation after the first week. And I think that's becoming more widespread. And we are particularly prone to do this in infants who are entirely or mostly donor milk–fed.

Recognize that gestational age and race may influence the composition of mother's own milk and that pooling of 24-hour samples may diminish some of the hour-to-hour variability that exists in mother's milk.

I think 1 key takeaway is that preterm mother's milk is not synonymous with donor milk. Certainly, donor milk is beneficial in some regard and has its place in our nutritional arsenal, but I think, when we look at studies, when we look at outcomes, we really have to hone in on the differences between preterm mother's milk and donor human milk and not conflate the 2. And I think that's particularly important just given some of the differences that we've demonstrated here that pasteurized and pooled donor milk is lower in some of the key nutrients. I really invite you to reach out to your milk supplier and to understand how they're processing, pooling, and recording analytes. Additional protein is probably necessary for donor milk, along with sodium and some other supplements.

I think fortification strategies should change based on the type of milk, the base milk that you're using. You should really consider displacement as an important objective to avoid when you're using mother's own milk primarily. So, I think that if you have a mother who's producing sufficient volumes and you're looking for a fortifier, displacement is probably the key element there, at least in my opinion. Osmolality may be something to consider if you feel like feeding intolerance is an important

outcome you're interested in. And that nearly all milk is going to require additional protein, but it's definitely going to be different amounts based on the base milk that you're using, donor milk vs preterm. And then, recognizing again human milk can meet our caloric needs, but not our mineral and macronutrient needs.

Applying New Learnings on Human Milk Composition to Clinical Practice in the NICU

Impacts for an Interprofessional Team

Michaela Berroya, RNC, MSN Ed: I thought that this presentation was excellent. For myself, especially being a NICU nurse for a long time already, but only recently, in the last 2½ or 3 years, have we started a milk bank in our NICU, and so donor milk has become standard of care now for our NICU, but I don't think I ever thought about or thought in depth about the components of that donor milk and where that donor milk is coming from, and I thought it was very helpful to learn this. And it makes complete sense when you actually think about it, that donor milk often comes from moms that have excess milk—that are later on and their baby is older—that milk is extra for them and what the components mean for that milk that we're now giving to our very premature babies and how different that would be and what it is composed of. So, for me, that was a huge takeaway and really important to our practice and something that I'm sharing now with my nursing colleagues: just to think about this and where we can go from here.

Jennifer Fowler, MS, RDN, LDN: I agree wholeheartedly. I think that presentation was fantastic. I think we really need to understand that not all milk is the same. I think a lot of times we do focus on just calories. We want the baby to grow, we need to give it more calories, but there are so many other things that we need to think about with what might be missing in this milk or what might be low in this milk or what might be higher in this milk. So, I think it's really, really important that we focus on not just the calories, but the protein, the sodium—even the zinc and fat is a big component as well.

Just with that 1 slide that shows the difference between continuous feeds with human milk and then bolus feeds and how different it is with the loss of fat through those continuous feeds. So, I think this was an amazing presentation and it really showed how different milk is and how we need to treat the babies by not so much calories but the components of the breast milk they might be getting. And of course, the fortifier that we need to add. We certainly need to think more about how we can do better, making sure that we're targeting exactly what these babies need.

Multidisciplinary Care in the NICU

Fernando Moya, MD: I think that essentially every issue or care in the NICU should be multidisciplinary. In the case of nutritional support, indeed the providers—that is neonatologists, nurse practitioners or physician assistants, if they're in the practice—along with the NICU nurses and especially NICU dietitians, they all need to be involved. Why is it so important? Because NICUs are busy places, and yet we're feeding 100% of the babies. Whether we're doing a combination of enteral, parenteral going to enteral and using a variety of approaches, we still need to feed them all. And during rounding, in particular, when the decision is being made, it is really important to have input from all those professionals so that we do not leave important details aside. For instance, neonatologists are often used to rounding and being mindful about volume, total mL/kg/d, and calories (total kCal/kg/d).

And I think we need to be more cognizant of other components of nutrition, such as the amount of protein that the baby is getting from whatever the sources are and be also aware of the different components that may be deficient, so we supplement appropriately at different times. This becomes particularly challenging when we're transitioning from parenteral to enteral nutrition, in which if we're not paying attention (as it has been well shown in the literature), we may provide less energy, but particularly less protein in this transition, thereby short-changing the potential for growth of the baby. So, it needs to be an active process. It's useful to have guidelines; perhaps we can expand that, but guidelines need to be adjusted to the baby, and those adjustments are best done when it is a team approach with the key members that we just mentioned.

Berroya: Yes, and I agree with you, Dr. Moya, and I think the NICU nurse also comes with some more information that maybe the provider team might not be aware of because they're often spending a lot of time with the moms. As moms are pumping, they're in their room, the NICU nurse might be receiving that milk and they can already alert the team like, "This mom is having some issues with her milk supply." They can get lactation consultants involved, or other avenues that we can go down.

Because I agree that it's completely multidisciplinary, and we have a different approach that we can take and get lactation involved early so that they can start increasing their supply

quickly if supply is an issue. And I think sometimes, even just with experience, some milk that you receive from a mom, you look at it and of course it's really just what you see, but you can see some milk looks thinner than other milk that you receive. Some milk looks fattier. We don't analyze our milk at this time, but just by your naked eye you're like, "Oh, I wonder if this is why we're having some issues with growth and things like that."

Fowler: Yeah, I absolutely agree with both of you. I was actually going to say how important lactation consultants are. Because if you get a first-time mom, they have no idea what they're doing. So, they're key because the nurse should focus on the baby, and therefore, we have that lactation consultant that can focus just on the mom. I think that's really important that they're involved right away because their milk is so much more beneficial for the baby.

Also, I don't want to leave out those milk techs, so if you're lucky enough to have a milk lab or a milk room (nutrition, whatever you want to call it), they're really wonderful. And I think they help out the nurses a lot with that meticulous amount of time that they spend making sure that they're getting the exact amount of milk and the right amount of fortifier and that sort of thing. They're really key for making sure those babies get fed. I can't say enough, the multidisciplinary team is just key for everybody to be involved.

There're so many benefits, but I think it's really important that we involve parents right away. I think they're just so confused, and they don't know what to think and what to do. I think it's really important to include them on daily rounds, make sure that they're a part of it so they can feel a part of the team. A lot of times, they're the ones that are there all the time, so they might know things a little bit more because nurses switch; neonatologists switch; nurse practitioners switch—but those parents are the ones that are always there and so they always know what's going on with their babies. So, I think it's really important that we include the parents on rounds or make sure they're somehow involved in the decisions or included in the decision making. I think parents are definitely, definitely important to be a part of the team.

Berroya: Yeah, I was going to say, I think there are so many benefits for the multidisciplinary approach. As Dr. Moya had just said, it should be in all of our care of our babies because there are so many different ways to look at things, and it's so important in taking care of the baby as a whole, not just with nutrition, but with everything that we do with our babies. Everybody wants our babies to get home and get home in the best condition that they can to grow and lead great lives. And that's what everybody's goal is that is in the NICU. And I think parents do see that when they see that everybody is working as a team for their baby—for the best outcomes for them. And I think we do see the best outcomes in those units that work with a multidisciplinary approach.

Moya: If I may add the other things that both of you have commented, which is really important, is how accurate and updated is the information. For instance, the nursing staff can tell you about the timing of the feeds, the tolerance of the feeds, which sometimes the provider is unaware of, but really good to write orders. But that doesn't mean that in translation those orders will be carried out exactly or not. And there's sometimes things that need to be amended to make it more tolerable for the patient as well.

Moreover, having the multidisciplinary involvement allows reinforcement of the parents and their critical role, again, not only in nutrition but in all care of their baby. And also support more to those moms; often, when we're feeding premature babies, the level of stress is such that their milk production may not be as good. Therefore, we can highlight at those moments the critical importance of any milk, and, if not, make them well aware that the option of donor milk is a good one, but it has some limitations as well. And those are best addressed in a more casual conversation that hopefully you can establish during multidisciplinary rounding.

Berroya: We do have multidisciplinary rounding. So, every morning when our babies are rounded on, we have our medical team, our nursing team, as well as our nutritionists that are part of our rounds. Social work and care management is in and out there as well. So, nutrition is always a part of what we're talking about every day with every baby. We follow growth charts as well. Like Ms. Fowler was saying earlier about looking at calories and not just looking at calories, but obviously weight is something that's very important for our babies. How much weight did we gain? How much did we lose?

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We do have some feeding protocols, but again, every baby is different. So, we follow some protocols, but as Dr. Moya said, the nurse can mention like, "Hey, this is what we're doing so far, but it's really not working for this baby and this is what we're seeing. They're having increased vomiting, increased gas"—whatever that issue is. And in terms of our discharge planning for our babies, our nutritionists will meet with our parents a few days before discharge to discuss what the feeding plan is for the baby when they go home (eg, if they are still on higher-calorie formula or breast milk, how to make that milk). We have recipes that we give them and show them and teach them how to do that so that they feel confident when they go home that they can follow the plan.

Fowler: Yes, absolutely. We as well have that multidisciplinary rounding. It includes the nurse, the neonatologist, residents and fellows, dietitians. So yeah, it's really important that we're all involved on the rounds. Hopefully, parents can be involved as well. We do have a feeding protocol that we have put together, so there's very specific steps that they take within the first week of their total parenteral nutrition (TPN) and their feeds: what they're supposed to do as far as going up and then going down on the TPN. So, we have that pretty well laid out.

And as far as when the babies go home, I will speak to them if they're on any sort of complicated mixing recipe. So, like for a discharge formula that's higher calories, we'll talk about how to mix it. But for the most part, the nurses go ahead and teach them whatever they need before discharge.

Moya: I think that we have evolved in neonatal intensive care to having a bit more guidelines to decrease variability. They're not meant to be strict rules, but there's abundant evidence that care is improved when people adhere (when possible) in adjusting for changes in the baby to some general guidelines. They also need to be updated periodically as more knowledge comes on board. Because when we come up with these guidelines and get people framed, if we do a Plan-Do-Study-Act (PDSA) cycle or a quality initiative or just discussions amongst the team members, by the time you get everybody on board, it's very likely that new knowledge has emerged. So, they need to be constantly being updated. I also want to highlight that since we mentioned transition to discharge, that perhaps something that we need to invest more time in is the communication with the provider after discharge from the NICU.

Because we often discharge babies with very well-laid plans, but we miss that communication to alert the pediatrician or family practice physician following the high-risk baby of the importance of continuing with the regimen as prescribed and for how long, and the involved case managers that can tell you about the availability of some of the resources in the outside world. For instance, if we're going to fortify, what's available to fortify past the time of discharge? So, I think that by just providing more emphasis and communication—the continuum of care from NICU to post-discharge—the more involvement, the more knowledge we impart and discuss, the better off that child is going to be.

Berroya: I totally agree with Dr. Moya with what he says about the postdischarge follow-up because we'll teach parents that this is how you have to make the formula; this is what you're going to go home on. And then we say, "And the pediatrician will follow up with you and let you know when to stop," because that's a big question: "Oh, when can I start going to feeding every 4 hours," or whatever it is. "When do I have to stop this fortification?" And I think that pediatricians probably do need some more guidelines on when they should stop and more communication with that NICU team on, “This is what we're sending them home on. This is how often we want them to feed. This is how many calories we're giving them.” And so on, so that they have a better plan because our general answer is, "Oh, the pediatrician will work that out with you when you go home." And that is probably an area that we do need to improve on.

I will say, for our discharge instructions, it’s really important to start that just before discharge. It shouldn't be something that we throw at parents the day that they're going home or even the day before because questions do arise. Especially now with all of the supply chain issues, formula issues, fortification issues, are they even going to be able to get what they need in the outside world? So, helping them with resources and areas that they can potentially look to find these products that we're saying, "You should use this when you're at home." We know in the last few years it's very challenging for families and an added stress when they're already anxious and worried about taking their baby home after all that they've been through.

Moya: I do think that those are areas that we can improve on. And personally, we do discharge phone calls a few days after our babies go home, but again, it's just a few days later. They often are very overwhelmed with just being home for the first few days, so they don't often have very many questions yet, and they're like, "Oh, okay, everything's fine. The baby's not sleeping." And so, specifics they don't really have, so maybe some follow-up even further out from discharge would be helpful.

Fowler: Yeah, Michaela, absolutely agree with you. I think there's a lot of work that we need to do as far as discharge plans and working with a pediatrician. Because I think that's exactly what we do. We're like, "Oh, well, they're preterm, and you're on this formula, but your pediatrician will talk to you about it more." So, I think we definitely need to have maybe a better checklist of like, "Okay, well this baby was high risk, and these things need to happen on your follow-up," and, "This baby was moderate risk, and I think these things need to happen on follow-up."

We do have a program now that if a baby has a gastrostomy tube or G-tube, then they get close follow-up afterwards: the NICU follow-up clinic will follow up with them, and an infant feeding clinic will follow up with them. Because a lot of times we'd be like, "Okay, your pediatrician will tell you how much more to feed every week," and then a lot of times they don't always follow up with their pediatrician for whatever reason. So, now we have a system in place to make sure that we're getting those kids that have got the G-tube.

Moya: Clearly, over the years we have assigned a surrogate role to our high-risk follow-up clinics to do some of this, but that's not necessarily an all-inclusive. And sometimes, most people that do high risk follow-up will have categories, such as below a certain weight (eg, 1000, 1250, 1500 g) or babies with additional problems: a feeding team for those with short guts, G-tubes like Jen mentioned, etc. But there's also a wide gap between those babies we follow and those babies that truly need more supervision and ascertainment of how they're feeling, how they're growing. Let's also not forget that even though we're a busy NICU, it does not compare at all with how busy pediatricians are who generally get 15 or 20 minutes at best for a family and a child. And here we are sending them a high-risk or potentially high-risk patient. Just going through the discharge summary sometimes—it just takes the whole time.

I think that's an area where we need to understand better how to communicate it, how to manage it, how to make them grow appropriately. Because we often end up with excess growth or not enough growth. It's very common for us to see that. And now there's abundant literature to suggest that that may impact their health in the long run as well. So, probably, it all revolves around the fact that now we're valuing more nutrition and nutrition knowledge than we ever did before. And for the NICU, it's become particularly important because not only have we realized that we feed them all, but perhaps there are not many areas where we can improve what we do that will have such long-term impacts such as nutrition and developmental care. So, we need to learn more, coordinate more, and make sure we are the beginning of a continuum, maximizing the optimum nutrition for this infant.

Mother's Own Milk & Donor Milk Feeding in the NICU

Fowler: In our hospital, we have to get consent for donor milk. We don't need to have them sign anything, but we have to get verbal consent. So, I feel like this is a golden opportunity to make sure that moms understand that we just want to use this donor milk as a bridge until their milk comes in.

Berroya: I agree. Definitely a good place to start with education. I think one of the things that may be not be as strong, at least in my NICU, is the mental health portion of it. These moms are so stressed and anxious about everything that just happened. Many of them feel very guilty that there was something that they did wrong for their baby to be here so early. And getting them early to start talking to somebody about everything that's going on may help alleviate their stress and then may help them increase their milk production because we know that the stress leads to lower milk production. And so, getting them in with social work early or getting them in with a psychiatrist if we think that that's what they need, to educate on taking care of themselves as well.

I think also making things as easy as possible for them. Early and frequent education on how often they need to pump, how

it actually works, and that it is normal, when you're first pumping, that you're probably not going to get much (if any) milk during those first pumps, but please don't be discouraged and please keep going and how beneficial this will be to your baby going forward. And so, it is really taking another multidisciplinary approach because this comes from all of us. This comes from lactation. This comes from nursing, nutritionists—all our medical providers—and helping to support them as much as possible.

Moya: Indeed, those are all very valuable things. But being the pragmatic person I am, the reality is that at best, two-thirds to three-quarters of moms of preterm infants can provide their own milk, and even a lesser percentage provides milk for an extended period of time. So, the reality is that in most NICUs, we have evolved to use, as either a bridge or in a more sustained basis, donor milk. So, we need to educate more about that, but we need to start by educating ourselves. Part of the message that Dr. Stansfield and I tried to provide in that talk is that there's a heck of a lot to learn about how to manage. This is not a standardized medication where every time you give, it contains the same amount of whatever component it is it seeks to calculate. It is quite variable day to day or even more often, and we need to be constantly thinking of what needs to be added or not added or for how long, etc.

The other thing I wanted to touch upon is that I never tell parents I understand because I have never been the parent of a premature baby. We need to navigate the waters of encouraging them to provide breast milk without adding to the already overloaded burden of guilt they carry. And I think that sometimes the rhetoric and the semantics can be unequal and can be very gung-ho, and sometimes even adding a bit of guilt from a lactation team, etc. We need to be mindful that we want the parents to try their best, but their best may be different. Moreover, personnel communicate very differently with parents, and this is where the multidisciplinary team needs to be more where the most effective communication occurs and alleviate doubts that may have arisen from somebody else communicating things perhaps slightly different and bringing up more questions or doubts on the parents.

I think that generally NICUs are the largest intensive care units in any hospital. They have the largest number of sick patients, and they have the largest number of babies or patients at high nutritional risk. That alone should justify having dedicated dietitians there, obviously depending on the size of the NICU. But in addition, at least in our hospital and in all the hospitals where I have practiced, the NICU writes the largest number of TPNs on a daily basis compared to any other area of the hospital. And that in and of itself is already fairly complicated at times, even though we all have vanilla solutions to try to standardize that. So, I think it behooves us to advocate for the appropriate level of support in terms of not only nursing care, but NICU dietitians to go along with us, ideally every day.

This is a process that doesn't stop during weekends and sometimes especially with long weekends or long times when there's no NICU dietitian, it may hinder what we're trying to accomplish. Moreover, how often standards of practice improved in neonatology for such a long time that future improvements and the outcomes of our infants are not going to derive from new ventilators or new isolettes or new ways to monitor. They're not going to come from new medications (we haven't had really new impactful medications for a long time). They're going to come from doing better what we currently do, perhaps a few new discoveries and clearly from feeding them better. Learning how to nourish them appropriately using primarily human milk, ideally mother's own. Knowing the pluses or minuses of donor milk and enhancing that. And then we mentioned the continuity after NICU care. If we're able to do that, we will have a far more impactful NICU stay than what we currently do.

And for me, having been in charge of groups for many years, I think that the rounding time is critical, but it's fast and it's often needs to be efficient, especially in large NICUs. The 3 of us practice in relatively large NICUs, and therefore, you cannot afford to have half an hour or an hour conversation per patient with parents. Therefore, let's not forget that the provider needs to establish the plan for the day, looking at the whole variety of parameters. And it's there where having the specialized help from a NICU dietitian and the input from nursing care allows you to provide an overall far more well-rounded plan of care for that day. And of course, that should occur every single day for all those babies under our care.

Applying New Learnings on Human Milk Composition to Clinical Practice in the NICU

I think that in areas and NICUs that are lacking the staff, I think that with the staff that is there (nursing, any medical professionals, fellows, nurse practitioners, residents), coming up with feeding guidelines for your patients as best as you can is a place that you can start. While you're advocating for more resources to hire those dietitians, hire those other people that you need to be for sure part of your team, you can start somewhere while those are happening side by side.

Berroya: I think, as in the presentation, it was very clear that there's so much still to be learned and there's so much that we are lacking in nutrition for our babies that it is really important to remember that we need to keep looking at the research we need to keep up to date with anything new that has come out and advocating for our babies. Because I agree with Dr. Moya when he says that there haven't been a lot of new things in other areas for our patients, and we just try to do better with what we have—but this is an area where we really could make great improvements.

Fowler: I'm a big proponent of standardizing feeding practices. I published a study, *Improved Use of Human Milk, Growth, and Central Line Utilization With Standard Feeding Roadmap in an Academic NICU*. (Kohler JA Sr, Fowler JO, Moore RT, Higginson JD. *Nutr Clin Pract.* 2020;35(4):703-707. doi:10.1002/ncp.10441) It showed how, previous to any sort of feeding roadmap or protocol, and then afterwards, and we showed a decrease in utilization of our central lines. We showed an increase in utilization of human milk. We showed actually a decrease in days to full of feeds.

So, if you don't have a dietitian, you really need to come up with a feeding protocol, and it really doesn't so much matter what it is, as long as you have one. But like I said, the article that a neonatologist and I published actually tells you exactly what we did with our feedings. If you have a protocol on antibiotic use, if you have a protocol when you give blood transfusions or when you give iron or these kinds of things, I think is vital to make sure that you're decreasing those variables. But obviously I think you can't substitute a nutritionist of course.

⊙ *To complete this course and claim credit, click here, or go to: https://pnce.org/NICU-Milk-Composition*

Abbreviations

BMI	body mass index	**MDI**	Mental Development Index
BUN	blood urea nitrogen	**NICU**	neonatal intensive care unit
DHA	docosahexaenoic acid	**PAS**	Pediatric Academic Societies
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition	**PDI**	Physical Development Index
		PDSA	Plan-Do-Study-Act
		TPN	total parenteral nutrition

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