Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

TRANSCRIPT

Emerging Developments in Human Milk Fortification: Problem Solving for Clinical Practice

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Importance and Challenges of Optimal Nutrition for Preterm Infants

Brian K. Stansfield, MD: I speak for both Ariel and I that we see a lot of passion in this community around infant nutrition, and we share that passion. We'd like to just provide some of our own thoughts and ideas around infant nutrition and try to really look at this as a pragmatic opportunity to both engage and hear from the audience that cares about this particular area of newborn medicine. And so, with that, we'll jump right in. We've framed this talk to really look at, what is the neonatologist nurse, emergency medicine clinicians, the support staff, the hospital administrators—what are they thinking about? What are they confronting when they're tasked with a very difficult job of growing and caring for preterm infants?

We're trying to frame this whole talk around the challenges of optimal nutrition for preterm infants. When we think about these challenges, we want to start with a framework and provide at least a little bit of context for how we encounter these challenges. The first and the obvious one is that preterm infants are born preterm, and so, with that, there's an entire developmental immaturity that we're confronted with, not the least of which is the gastrointestinal (GI) tract. And then you're cohorting an entire population of premature infants from, essentially, 36 weeks down to, now, 20, 21, 22 weeks, and we're calling them all by the same moniker, which is "preterm." And I think we all in this room recognize that they're entirely different populations that really require focused attention.

And then with that complication, you've got provider confidence issues. We now are seeing preterm infants at the margins—what we used to call the margins that are no longer margins—of viability. And we are trying to extrapolate information that is usually not focused on that particular population, with that particular event or complication, and then we've really done ourselves a disservice as a group to not standardize things across our entire population. We still have individual ways that we do things, and they're good. They all have their benefits, they all have their problems, but we've taken the goal of providing infant nutrition and said, "Within your cohort of patients, we want you to do it in a standardized method," but we've never really taken that to a larger audience and said, "Let's try to standardize across much larger swaths of the population."

So those are big-level issues, but then underneath all that is the complication of healthcare, right? Which is—you've got administrators, limited resources; you've got busy providers, both nurses, staff, physicians; and then you've got to incorporate all of this information, all this knowledge, and use it. And so there's just a lot to be said about how difficult it is to focus on preterm nutrition when you may have bronchopulmonary dysplasia as a major issue, or retinopathy, or other complicating factors.

But we know that in providing optimal feeding to preterm infants, there are some marked benefits. If we're able to match the intrauterine growth rate, that that's our goal. Then we can see benefits to comorbidities of premature birth; we can see better composition, for which we'll show some of that data. We know that neurodevelopmental outcomes are closely tied to good growth, so the better we grow infants, the better they're going to perform when they hit those school-age years.

And then, what are the guidelines that we're following? Well, we're fortunate today to have these guidelines updated. I know that Berthold Koletzko updated his in 2021, but we're going to use European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) as an example. How do we provide adequate nutrition to preterm infants? And fortunately, there is some guidance in this, and it's updated every 8 or 10 years. And so we've seen these—and I want to just draw some attention to some of the goals when it comes to fluid administration: how much sodium you should provide on a daily basis, zinc or calcium. But the recognition is that, as good as these recommendations are, they're based on limited evidence. We still are trying to understand: what is optimal nutrition. What are the macronutrients and micronutrients and minerals that we need to provide? And there's just so much to

be said about that, right? We're talking about the whole swath of nutrition, not just how much protein do we deliver, how much selenium do we deliver. And it requires a great deal of effort and cost to really define that across an entire population, and so it's just important to think about. We do have some guidelines, but just to recognize their own limitations.

And then within these guidelines, recognizing that there's not 1 thing to necessarily focus on. When we have a variety of different targets, we need to do so in a comprehensive and thoughtful manner. A couple of the guideline recommendations are, again, to start with small-volume feedings; I think that's a pretty common practice across neonatology. You can call these, “minimal enteral feedings” and to advance slowly as clinically tolerated. “Clinically tolerated” is often difficult to describe, but we know it when we see it. And then we want to increase those volumes by up to 30 mL/kg. I think one of the big recommendations that we continue to harp on is just standardized feeding protocols. Standardized feeding protocols. So while I say we still don't really understand best practices across the whole swath of neonatology—the United States, Canada, and Mexico, but also Europe and Asia, and those goals may be different in different populations. But recognizing that standardization within an institution has significant benefits for the infant, and that should be comprehensive.

Growth is whatever you think it is. And I say that in all honesty because we really struggle to define what growth is. Is this in the eye of the beholder, or is there a real true marker that begets some outcome that you're interested in? And so we've tried to define poor growth in a couple of different ways, and I think some of those have fallen out favor, like “extrauterine growth restriction,” which is now less commonly used. This idea that if you were growing below the 10th percentile for your gestational age, that you had some risk for late outcomes, and we've really seen that that wasn't a really good marker for us. So we're now using terms like “growth faltering” or “slow postnatal growth” to define those infants who are at risk. But recognizing—within that population—that you've got familial factors, constitutional factors. You've got an intrauterine growth environment, before you've seen the patient, in many respects. And then you've got comorbidities that have to be accounted for that may require more or less nutrition, based on how you perceive the literature.

We recognize, I think, across care for newborns, that we're going to experience some weight loss, and that should be appropriately managed, and that should reach its minimum within the first week of life, and then we start to see regain of birth weight. That occurs, usually hopefully, by the end of that second week. And then we expect infants to grow along their growth curve over the course of the next, hopefully, rest of their life, right? But at least it's, with our management, up to 36 weeks or 40 weeks corrected. And 1 thing that we're now becoming much more aware of is that we're not trying to pack in the growth, right? So when you identify an infant that seems to be growing a little bit slower, we don't have to rapidly shift that narrative, right? We can look at and make interval changes to try to improve linear weight growth, head circumference growth, but the goal should not be to move them immediately into a new lane, and so we call this “rapid infant weight gain.” And we know that, in key windows of life, if infants (or just humans in general) experience rapid weight gain, that we can set them up for later metabolic syndrome, obesity, hypertension, etc. And one of those key windows is certainly in the first year, and so when you hear something like "the first 1000 days" or "the first 300 days," these are the key windows where we want to be particularly precise about the things that we're doing and thoughtful.

ESPGHAN also had some comment about critically ill neonates. I think when you're talking about less than 30 weeks, you're almost talking about the whole population. So critically ill, again, is in the eye of the beholder, but there weren't any major changes to their recommendations. Again, I think that there is still a lot to be said about how do we feed critically ill infants, and particularly, acute critical illness. So that infant that has a sudden concern that arises, how quickly do we resume feedings after some sort of intolerance or low-stage necrotizing enterocolitis (NEC) (stage I or II)? And those questions still abound when we don't know. And so I think, as pediatricians, I'm not out of line in saying that, in many respects, feeding is the first thing to stop, right? Enteral nutrition is the first thing that stops, and it's often the last thing we resume—and maybe that's not best practice, right? Maybe the metabolism, the

recovery from illness, the inflammation that occurs would be better suited if we were able to continue even small-volume feeds to provide some nutrition, and I think that's an opportunity for research that I don't have an answer for today, unfortunately, but would love to see more advancement there. And I think they do speak to this in some respects when they say that, on that recovery phase (so once you've decided the acute illness is starting to resolve and the infant is starting to recover), that may be a time where maximizing nutrition might be necessary.

We're going to transition a few things and talk here about the role of nutrition in overcoming the developmental immaturity, and specifically talking about donor milk. And we'll talk about a lot of different nutritional elements, but I think donor milk is now prevalent in (the last I saw) about 85% to 87% of level III and IV neonatal intensive care units (NICUs) have access to donor milk, which means that it's everywhere. And I think there's still some difficulty in using it in that context that I described, where you've got developmental immaturity, provider confidence, and it's on the subtext of cost, right? Hospital administration running an efficient unit.

And one thing that we need to recognize is that preterm milk and donor milk have different compositions, and so some work that we've done to define this was, we took maternal samples of milk at day 7 (what we considered early) and then at the end of the first month (what we considered more mature preterm milk) and then compared the composition to commercial donor milk (so the things that you can buy right off the shelf). And essentially, from here, you can see that there's very little difference in some key nutrients: the calories in that milk are pretty similar; the carbohydrates are very similar. But as has been said over and over again, and I think we show it very clearly here, is that there are some key differences. So the protein content, which is really one of the key drivers of infant nutrition, is lower in donor human milk than it is in particularly early preterm milk. But if you look at things like what is the composition? What are the things that are in milk, which we would define as ash or the water content of milk? The moisture. You can see that preterm mother's own milk is enriched for just the nutrition and that it has less amount of water as a part of it than, say, donor human milk does. And that arises from very natural observations that the vast majority of our donor human milk is derived from term infants at later lactation stages. And therefore it is often targeted (or naturally has matured) to care for the needs of that term infant that's now 6 months old, and not necessarily for the brand new 22- or 24-week infant.

But there are other things to be aware of, as well, that I think are not often discussed, and that is the sodium content of donor human milk is also pretty low. And so, when we measure this, on average, we were somewhere in the 10 mg/dL range. Just in comparison to early preterm milk, you can have as much as 50 or even 75 or 100 mg/dL. You could be talking about the differences between mother's own preterm milk and donor human milk being 4-, 5-, 6-fold in sodium content. And I think we're learning more and more about how important sodium is in supporting later growth. We have lots of good initiation, and maybe as they're transitioning later on in the NICU stay and donor milk may be arising for those few mothers, you may need to think about that nutrition a little bit differently because of things like sodium content.

And then we're starting to understand a lot more about how do we make up the gaps? So, what are the optimal ways when mother's own milk can't be the sole nutrition? How do we think about that, and what are the optimal ways that we can make up those gaps? I think this study from Tarah Colaizy and the Neonatal Research Network was just really well done. The MILK randomized controlled trial (RCT), I'd encourage you to take a look, published just this year. But the essential goal here was to compare the neurodevelopmental outcomes in preterm infants fed fortified donor milk, to preterm infant formula in filling in that gap.

Across 14 centers, they randomized almost 500 preterm infants—all less than 29 weeks. And what was really nice about this study is they took a hands-off approach. They said, "Hey, we want to guide a few things, but we want to leave it open to your own feeding protocols. We don't want to tell you how to fortify. We want you just to do it on your own." I think that's what we all are recognizing that we all do this.

Their primary outcome was to look at Bayley Scales of neurodevelopment at 18 or 22 to 26 months. And so the primary outcome: there was no difference between the groups. And I think that when you look at Bayley scores less than 85—

these are kids who essentially have any neurodevelopmental impairment as they define it—you can see that, whether you're supplementing with fortified donor milk or you're supplementing with preterm formula, that you're having essentially nonstatistically significant differences in neurodevelopmental impairment. But there are opportunities apart from that, right? So they also identified about a 5% difference in the rate of NEC in those infants provided preterm formula. But on the same vein, they noticed that weight loss (or change in *z* score) was a bit better in the preterm infant formula.

So that, again, understanding the pros and cons of your choices I think is really critical. You can have some equipoise and say, "I'm choosing to do this because I really think that ultimately our weight gain is going to be important," or, "I'm going to choose to do donor milk because I do have some concern about the risk of NEC or some other outcome." In the same vein, thinking about, well, if we want to use donor milk as our primary supplement, is there some advantage to using preterm donor milk? All the arguments I made about term donor milk being made for term infants, what if we sort of remove that argument and just focused on preterm milk?

Well, there can be some advantages to that for sure, along with some actual costs. In this randomized clinical trial just published a year ago, they looked at supplementation with term vs preterm [donor milk], and their primary outcome was to look at protein intake over the first few weeks of life. This was a limited study where the supplementation was really occurring during this first 3 weeks of life, so I don't want to confuse and sound like they were continuing this supplementation out to 6 or 8 weeks, or even hospital discharge. But in those first 3 weeks of life, you can see in the middle column there that they were able to deliver roughly an extra 0.5 g/kg of protein, consistently, over those 3 weeks. We now know there's a tremendous body of evidence that protein delivery is a major driver of infant growth. And they were also able to see that the infants in the preterm donor milk group had higher *z* scores for weight, and head circumference, in particular, was benefited. Then the net weight or the mean weight for the group that got preterm donor milk was higher. Individually, there may be benefit—a little harder to say—but as a group, there was clear differences.

When we think about how do we look at these base diets, how do we think about the supplementation program if mother's own milk is not sufficient? I think there are some key takeaways that we can lean into, and that is that we now sort of have this target protein range of 3.5 to 4 g/kg. And with the few kids that you might have to go a little bit higher, that could be necessary. But we really need to think about that protein delivery in total. And so that's parenteral nutrition; that's the composition of donor milk, mom's own milk. Ultimately, we're going to talk about fortification here in a little bit. When we think about providing that protein, we need to think holistically about it. We also need to recognize that donor milk and mother's own milk are just different products, both in where they're derived from and their composition. Thinking about optimal sodium supplementation or zinc supplementation, something that our unit has taken on over the last handful of years, we do see improved growth with some of these supplements. But when to start them and how to start them, how to use them are still questions to be answered.

I think also having a really conservative view of optimal growth is important. Once you've optimized volume; you've fortified; you feel like you've added the right minerals; we need to monitor for a period of time and not feel this anticipatory surge to correct the things that often take weeks to correct. And then if you see growth faltering persist, particularly as you're outside of the first 28 days or 6 weeks, consider transitioning to preterm formula.

But one thing that is still to be said, and I think I've sort of highlighted this, is that we still have a number of unanswered questions, and I was just kind of commenting this morning that as a group, I think we're really good at the first 2 or 3 weeks of life, and we struggle with what do we do after that. And so, we really like to initiate, and we struggle to know when to take away. We have a lot of evidence for how we initiate feeds and not a lot for how we transition, and I think one of those key opportunities is donor milk. At some point, we have to transition off of donor milk, and whether that occurs at a particular gestational age, weight, after discharge, or at some point, we need to be thinking about other nutritional

opportunities, and we have no real guidance there. But it is important to recognize that, and I think in this room, it goes without saying, that we need to consider all of the risks. One of the major risks that we think about is NEC and recognizing that based on the gestational maturity, that that risk may dissipate as infants get older.

The Latest Evidence for the Role of Nutrition in Overcoming Developmental Immaturity

The Preterm Microbiome

Ariel A. Salas, MD, MSPH: Thank you, Brian. So now we're going to shift gears a bit, and we're going to start talking about the microbiome. And I know there are a lot of experts in nutrition here in this audience, so I'm not going to go into details about how they interact, but I think it's important to make sure that we're all on the same page in terms of how the microbiome could impact your nutrition and growth.

And I think this slide provides you a visual of the concept of building a community. I think to me, when I think about the microbiome, I like to think about communities in general and how those get established. Think about a new neighborhood in your city and how that needs to be developed—how that neighborhood needs utilities (that would be the nutrition component) but also needs a diversity. When I talk about diversity, I'm not talking about how they look, the people that live there, but the function. What they do, and how they can contribute to that community to grow? And how can they make that environment also more efficient in terms of utilizing all those resources? The development of the microbiome kind of follows that same pattern. You start with nothing—or at least that's what we thought, that your microbiome is established at the moment of birth. But in reality, as you can see here, there are some exposures to microbiome even in the amniotic fluid. Then, of course, the type of delivery is also going to establish the first colonization, and your diet most likely is also a way to introduce different types of bacteria. And then, in term infants in particular, there's more about how that transition to solid foods is going to, again, just reestablish this community, and then eventually, yes, the long-term diet after childhood. So pretty dynamic, and definitely not straightforward, particularly in preterm infants.

Now, in terms of the diet that infants receive and how that affects the microbiome, I think it's important to recognize that breast milk will have a lot of these different patterns of microbiome. As you can see, it's not the same throughout the lactation stages. Some infants—so the type of bacteria that you have soon after birth in your milk is probably going to change in the next few weeks. And that probably is going to determine how your growth and how your nutrition is going to go the next few weeks. So very important.

At this point, most of what microbiome research has done is to be descriptive. We can tell you proportions, we tell you there's a bit more of this, and that's that this relative abundance is a very common way to report proportions. But again, at this stage we're looking at the description, we're telling you what type of bacteria we see. We still don't know a whole lot about the function, how they work together. Do we need a little bit of some type of bacteria combined with the other one to be efficient in terms of nutrition, or it's just the amount? So, the more we have of this type of bacteria, the better the efficiency of how we absorb nutrients.

As you can see, there's a lot of variability and over time that changes when you compare the preterm infant microbiome and term microbiome in infants that receive human milk diets. There's definitely much more diversity in preterm infants. And that probably has to do with the supply. If the milk that they're receiving has more bacteria, more diversity, it is more likely they'll get colonized with it.

Now, I think to understand the challenges to establish a normal microbiome in a preterm infant, we need to use the term reference to understand that it is not a straightforward path. If you think about a term infant—so again, there's a bit of exposure to maternal microbiome through the amniotic fluid, then most infants are going to be born via vaginal delivery and then eventually have a normal diet, hopefully breast milk exclusively. It's expected that the microbiome development is going to be normal in that sense. But when we think about preterm infants now, it's not that straightforward. First of all, there is a reason why they're being born prematurely that could itself trigger a different type of development of that microbiome, different exposure to those maternal microbiota. Then there's definitely more cesarean delivery, one way to

affect that. Diet is unfortunately not very easy to establish. That's why we're here. We're talking about how important it is to establish that early colonization with feeding, and then they get complications along the way. We get worried about sepsis, we start antibiotics. As you can imagine, whenever you start antibiotics, especially broad-spectrum antibiotics like we do in the NICU, that community disappears and starts over again and there are multiple cycles of that. No wonder why the microbiome is so hard to establish just because there are all these events that change the course of normal development.

Now, the question is: how do we label that change—that abnormal microbiome development? I think right now, this is probably the best term to describe that: dysbiosis. Dysbiosis has been associated with a lot of neonatal complications, and those are listed here, particularly NEC and late-onset sepsis.

Now, as we try to put this together (so nutrition and microbiome), there are very interesting studies about looking at what you have, your diet in the microbiome. And this is a good example, where they randomized infants to 2 different types of fortifiers, and they collected stool samples to see what happens to that microbiome over time. As you can see here, in those that received the human milk–based fortifiers, there was a difference between the 2, and the pattern was slightly different. But again, this has to do with the type of bacteria, but we still don't know what function they have and whether they are important at different concentrations. So it is different, and maybe some of it has to do with the processing of those diets. A human-based fortifier will require pasteurization, and maybe that, in a way, is affecting this particular element of the diet.

Maybe it's not just the fortifier, maybe it's the type of diet, maybe it matters a lot whether you get a predominantly maternal-milk diet or a donor-milk diet. So, when you do that comparison—when you look at the proportion of maternal milk that is being provided vs the proportion of donor milk—so maybe in those situations we can have a better understanding of how those can influence the development of the microbiome. And here what we want to point out is that when you compare maternal-milk feeding with donor-milk feeding, you see important differences in bacteria that help a lot to become efficient with how you absorb nutrients, particularly *Veillonella* and *Propionibacterium*.

Now, there have been randomized trials specifically developed to see this effect of type of fortifier on the microbiome, and as you can imagine, it's really hard. Think about the amount of variability that exists in the microbiome data. We're talking about again, type, but then with such an abnormal course that we see in the NICU in preterm infants, it's really hard to create even patterns. So the trial didn't really find much differences in richness and diversity. The one thing that they reported was a decrease of *Lactobacillus* in this trial. But again, that's probably not the whole story. There's more that needs to be done to understand how diets influence the microbiome. And the one thing that can be concluded from this trial is that yes, the differences between groups, if there are any, are probably not mediated by the microbiome, and that's I think where we are right now.

Now, when you think about, what can we do about this? Right, because that's (I think) the obvious question of a clinician when you become aware of all this issues with the microbiome development and the assembly of all this bacteria. So far, what we have are probiotics. The way to provide some type of bacteria that we hope can minimize dysbiosis in a way, and then through that mechanism, prevent clinical adverse neonatal outcomes. Like everything else, this started with observational studies and then eventually transitioned to RCTs.

But if you look at observational studies where you just start supplementing with probiotics, there was already very consistent effect in decreasing NEC in particular. These are, if you combine all those large cohorts and observational studies—so we're talking about hundreds of infants that have been exposed—so plenty of data available to say that this effect seems to be consistent along and across studies. Now, again that was observational data. You can say that maybe there was some bias in how those infants were selected and all that, but for those reasons, many, many clinical trials have been done to look at that same difference between groups and see if offering probiotics could make a difference on outcomes. And again, you see that there are benefits on time-to-feeds, on reducing even the length of stay, and prevention of sepsis, and the effect size on NEC risk reduction, which was recently reported, again, in a meta-analysis in 2023. So very important outcomes. As providers, we do want to decrease NEC; we want to decrease

mortality, for sure. So the evidence so far seems to be consistent in favor of probiotics.

Now of course, the benefit is going to depend on the type of alterations in the microbiome that the patient has. And I think there's a lot that we need to think as clinicians, too. What are we doing to affect the microbiome? And to me, 1 of the common issues is just the constant use of antibiotics. It's been really hard for me to analyze microbiome data because, I just—we're seeing a pattern, and suddenly someone starts antibiotics for just a 48-hour rule-out just because they're not sure what's happening, and then the pattern just goes away, and then you try again. Remember that generating that evidence on the effect specifically on the microbiome is going to be hard, but not because we don't have the tools to analyze the microbiome, it's just the clinical pattern that we see in terms of our practices that are not very consistent. So that's how we started talking about the use of probiotics to see if that could have an impact on the development of the microbiome and the prevention of adverse outcomes.

And there are pretty specific—in terms of what strains might be more helpful—components that have *Lactobacillus* and *Bifidobacterium* seeming to be very consistent in being beneficial.

Now, as you are aware, everything changed last year in October when this notification was issued about the safety of probiotics, and that's what led to discontinuing the use pretty much across the United States. Now recently, I really recommend you go and look at this reference because the ESPGHAN group in Europe kind of issued a position about that statement from the US Food & Drug Administration (FDA), and they point out all the evidence that has been generated in favor of probiotics and that now, in a way, is being discarded.

Now, the current recommendation is not routinely used. Probiotics, that's an American Academy of Pediatrics (AAP) statement, and ESPGHAN has some recommendations about it, and they do think that it's necessary to have good manufacturing practices. It's true that there have been issues with contamination in some products; that it's sometimes hard to isolate the bacteria that you see in the label. There is evidence that those practices could be potentially harmful, but those are things that the industry needs to take care of. And then when that happens, right now, there's this issue that probably there are infants out there that are not getting the benefit of having restoration of the microbiome. For the reasons at this time, I think it's important to acknowledge that there is a risk, right? And RCTs have reported that risk, but it's not clinically significant because it was a very unusual event even in those RCTs.

So here are the recommendations for ESPGHAN that I think are very practical. Talk to parents as well, right, so just share that conversation. I think not discussing that there are studies how they're suggesting benefits and that it could be an individual decision, I think could improve outcomes.

In general, for microbiome, I feel like we could do our part. If we're not using probiotics, maybe we should start thinking about what can we do to prevent dysbiosis if we don't have a treatment for it, at least not at this time. I think the most effective way is, as I said, feeding, right? Because that's a way to establish your microbiome and maybe minimize the use of antibiotics. To me, NEC is a very interesting disease because we know that those 2 things—fasting and antibiotics—can increase your risk of NEC, but that's how we treat it. So, the treatment of NEC is fasting and antibiotics. I don't think there's any other disease out there that the factors that cause NEC are also the treatment of it. I think we can do our part. We can try to at least feed early and limit the use of antibiotics in them.

The Latest Evidence for Overcoming Provider Confidence Challenges

Enteral Nutrition & Fortification Practices

Okay, now I'm going to talk to you about something that I'm definitely more passionate about: enteral nutrition and how that can be influential on growth. And for that, I think, this is a great way to think about this problem. Because first you have to know what you have available. What kind of breast milk you have? Is it maternal? Is it donor? And then you want to decide on what you want to use as a criteria to start fortification. And then your options—so what's out there and what you have available. And then later on, like Brian pointed out, you have to start deciding when you're going to stop, because sometimes that's not discussed when you start, and that becomes a postponed decision I feel like.

What I want to talk to you about now is early fortification, because that has been not clearly defined. What people would say is that you want to start when volumes are around 80 to 100 mL/kg, but that could mean postnatal day 10, 14, depending how aggressive you are in terms of advancing feeds. So that adds a lot of variability. Now, when you look at postnatal age, that seems to be more consistent: you can say if you start within the first week, so maybe that could be considered early and everything else will be late.

For this trial, we chose this high-risk population because there's a lot about fortification in older infants and people that are concerned about fortification in NEC usually talk about that limitation—that not all infants were extremely preterm infants. That was the whole point of doing this trial with only babies 28 weeks or less. And the way we did it was just early fortification with a human milk–based fortifier for the first 2 weeks, and then transitioned to the bovine milk–based fortifier. And when we look at outcomes, yes, we didn't find any difference in fat-free mass because that was our main goal—trying to see if we could get a bit more lean mass as a result of getting more protein and early fortification. But the effect on length and head circumference was consistent in 2 analyses when we look at the entire group (the entire randomization group) but also when we look at a subgroup excluding small-for-gestational-age infants. We think the effect on those anthropometric measurements is real, and it's something that could makes us start thinking about how to start fortification.

Another trial that we conducted recently at my institution was early enteral nutrition. And this concept talks about the idea of starting, from day 1 or so, full-volume feeds. "Full volume" is being defined as a traditional total fluid intake target in the first 24 hours, which is usually between 60 and 80 mL/kg. That was our intervention group. And then we use a control group where we would do the traditional trophic volumes with 20 to 30 mL/kg and then allow people to stay on that, and clinicians to keep doing trophics for as long as they want. When we compare those 2 groups, we did see differences in full enteral feeding days. If you start early and advance fast, you're going to spend more time taking full feeds during those first 28 days. I want to explain that outcome a bit more because it's different than time to full feeds. Yes, you can expedite the process to get to full feeds, but then what if you developed intolerance because of it later on? So, time to full feeds is not going to reflect tolerance—if by going too fast, then you start having issues with intolerance in fasting. When you look at full enteral feeding days, we're telling you how many days of the first 28 days were on full feeds. And that's why we think just being aggressive with volumes didn't necessarily lead to more intolerance. And all the benefits—more fat-free mass accretion, a better length and reduction of healthcare costs.

One thing, and this is new information, this is something that I'm presenting for the second time. This hasn't been published yet. But the 1 question that came up when we did that first trial that I just saw is when to fortify. Because if you're on full feeds by day 2, is it too soon to start a fortifier? Maybe that could lead to complications. So, for that reason, we're designing this trial in which we randomize infants to get earlier or delayed fortification. "Early" in this group meant to be on a bovine fortifier before day 7, and "delayed"—which has been our traditional practice—more like on day 10 or 14. As you can see in the table here, the groups were pretty similar in terms of baseline characteristics, and there were no differences in fat-free mass. The effect that we see is probably the early feeding had a similar effect in both groups. And the fortification didn't make a big difference for fat-free mass discourse, but there was a difference in length. Just like in the trial with extremely preterm infants, early fortification here seems to be associated with better length. Again, more evidence that early fortification is a reasonable option that helps you stay on track with your growth, and no additional complications, which was the main concern in previous literature.

Stansfield: Thanks, Ariel. We have taken on some of these same opportunities about timing and fortification in our own RCTs. And this has just been accepted at the *Journal of Perinatology* just a week or so ago. What we did was to look at 52 preterm infants, and again, as I said at the outset, prematurity is a big population. And so here we were looking at the implementation of a bovine milk–based fortifier beginning with first feeds, but we selected a population that we considered relatively low risk, which is 1000 to 1500 g. And so, these are infants that definitively need supplementation of human milk but may not generate all of the risk profile that you

see with extremely preterm infants. 52 infants randomized to either receive bovine milk–based human milk fortifier on feeding day 1 vs feeding day 8, which is what we consider delayed.

And so, you can see here that there were really no statistical differences in growth, either head circumference, length, or weight, over the first 28 days, and similarly out to 36 weeks. The mean weight for those groups was identical. But I think, as important as the fact that there may have been no difference or significant benefit, was that there was no difference in tolerance either. We looked at this in a variety of different manners to really get a sense of it, and we all tracked this entirely prospectively. And we did this through looking at stool count, stool volume, emesis count, emesis volume, feeding-related nothing-by-mouth days. And across both groups, we saw really identical numbers. There were no major comorbidity differences like NEC, retinopathy of prematurity, late-onset sepsis, or acute kidney injury. We essentially walked away from this saying, at least in modestly low-risk—I use that term a little bit pejoratively because they're all high risk, but if we categorize modest high risk to really significant high risk. If you think about the population that maybe doesn't require all of the attention that maybe some of these practices like what Ariel is talking about with aggressive feeding volumes or early fortification, that if we could target say 28 to 36 weeks or 1000 to 1500 g or even 750 g and above, that we may be able to optimize nutrition for them a little bit faster and segregate out the truly high-risk population—these extremely, extremely preterm infants or very, very low-birth-weight infants—and really focus on them separately because their needs are going to be different.

I think just in consideration of some of the things that we're very interested in is that in the transition or the run-up with donor milk. And I think a real significant transition from the common use of preterm formula to really implementing maternal milk diets—maybe that occurred 15 or 20 years ago—we've taken a big step backwards in just thinking about some of the practices that we did for generations. And I think maybe the pendulum swung a little bit too far back, and we're challenging those notions by saying, “No, I think in some populations, you could be more aggressive with volume or early fortification and have the same safety profiles or side effects and risks”—whatever you're interested in. I think that those aggressive feeding advancements really are appropriate. And to Ariel's point, both about the microbiome and early feeding, you may reduce risks that are really important, like late-onset sepsis, which is closely connected to gut health and growth. And there may be good evidence that infants can experience growth benefits from early fortification, whether that's with a human milk–based fortifier, and potentially with bovine milk–based fortifier as well.

But there's still uncertainty and work to be done in all of these spheres. There's nothing definitive to be said, but I think that if you read the literature, particularly over the last 2 years, around early fortification or some of Ariel's really novel work looking at higher-volume feedings, I think you're going to find some confidence to challenge maybe these old notions that we need to start really small and advance up really slowly.

The Latest Evidence for Overcoming the Unknowns

Fortification Types & Strategies: Fortifiers

Let's look at transitioning to fortifiers themselves a little bit more and overcoming the unknowns, which remember, the whole idea or concept of human milk fortification is relatively new when you think about the whole field of neonatology. And I say that recognizing that my entry into the field of neonatology is relatively recent as well. But there is the idea of fortifying human milk is something that we've long known needs to be done, but I think we've paid a lot of attention to it over, say, the last decade and a half.

Again, returning to our decision tree, one of the concepts that we need to think about—and I think is both an economical, practical, storage comes into this—is what type of fortifier do we use? And the selection of a fortifier begets all kinds of choices downstream of that. Nurses become very attuned to changes in the NICU. If you decide, "Oh, we're going to transition," there's a feedback period (whether you want it or not), and you're going to have ways of doing things. We transitioned really away from powder into liquid-based fortifiers and formulas. There was a transition that occurred with that. Supplementation is becoming very popular. How do we think about that? And then the extent of research that supports those decisions.

I want to just share a little bit about the differences in fortifiers on clinically relevant outcomes. So, a couple of trials looking at bovine milk–based human milk fortifiers and then human milk–based. This was 1 of the trials that was published a handful of years ago that looked at feeding intolerance and neurodevelopment in 2 groups of about 60 infants. And you can see that, regardless of the fortifier that they were randomized to in this very low-birth-weight population, that essentially tolerance factors were statistically identical between the 2. And I would say feeding interruption, which is probably the best one—is the most clear, it requires an action by the nurse—was really about a third of infants. Regardless of the fortifier you use, about a third of infants are going to have some sort of feeding interruption. And I think if you can start from that baseline, then you start to say, "Okay, is this more or less than where the baseline really is?" And then, importantly, when you look at neurocognitive outcomes at 18 months or 2 years of life, they were essentially identical or nonstatistically significant in all 3 domains.

More recently, just published this year in one of the *Lancet* journals, an RCT that looked at severe morbidities. They had a composite outcome of culture-proven sepsis mortality index. These 3 are clearly linked to gut health, and they took a really high-risk population, of 22- to 28-week infants. About 229 were randomized to mother's own milk or donor milk. So, to no real regard for what the base diet was, but the randomization was around the type of fortifier. And as you can see here, the composite outcome was statistically identical. And then when they separated out those composites to look at NEC individually, death individually, or culture-proven sepsis, there was still no statistically significant differences between those groups.

I think this really provided some evidence to say you should have some equipoise in choosing a fortifier. There's probably someplace where the choice that you make can be supported by good data, and I think that probably reassured a lot of people, but also brought confidence into the conversation that, if you're concerned about NEC or late-onset sepsis or growth or whatever the chief driver of your decision tree is as a clinician or as a group of clinicians, that you can have some confidence that the fortifier is probably not a major driver of any differences in those groups.

And then when they look at exclusive human vs bovine-based fortifier… Here they were really doing something a little bit different in this population of 38 preterm infants. They were looking at moms who received human milk–derived preterm formula—so the ready-to-feed 26-kcal/oz human milk–based formula vs a cow's milk–based formula—and looking at supplementation within those groups in the first days of life. And again, no significant difference between the groups in either adipose tissue or free-fat mass.

We're talking about that, and I think we probably should have backed up and defined that we've long used—weight—as our own marker for growth, and it's just a terrible marker. It does nothing to talk about how appropriate growth length is critical to that assessment. And I think, in the past, resorted to some index—Ponderal Index or body mass index or whatever—to accounting for a weight-for-length ratio that also has problems because there are a variety of fluctuations in any of those indices. And so, we're trying to get at how do we grow infants well without making them obese? And that's probably not the right term, but just having an overrepresentation of fat. And so, fat-free mass, which Ariel's been really a leader in thinking through that, is really a nice marker for, are we growing infants to develop more adiposity, or are we developing lean preterm infants? So, just to give a little caveat there.

And then again, just pointing to Ariel's work just a couple of years ago that if we are going to use a human milk–based fortifier and adding a protein supplement on top of that, is that beneficial? And so, in this RCT of about 55 high-risk infants receiving either mother's own milk or donor milk, that hydrolyzed protein supplement had some modest benefits to weight *z* scores, and you can see graphed there on my right and I guess your right as well. And then again, fat-free mass, maybe have some benefit as well with adding that additional protein supplement on top of the human milk–based fortifier.

Some considerations for your practice when you're thinking about a fortifier is that they seem to be well tolerated. And I think both of our studies show that even the early introduction or early transition to a bovine milk–based fortifier from a human milk–based fortifier seems to be well tolerated. And I

think that's the question. I don't think a lot of people worry about transitioning from a cow's milk– to a human milk–based fortifier. That's probably not the question to be had, but there probably is some consideration about the inverse. And so they seem to both be well tolerated. They seem to both do the job of growing infants. As Ariel pointed out, neither seems to contribute in a significant way to the microbiome. And so you can make a selection, based on a lot of confidence, that whatever you choose is going to be well tolerated.

And maybe we should be thinking about other things like protein intake or some data I'll show you here in a minute, like displacement. If you're thinking about mother's milk being the primary driver, that's what we're trying to get. The more volume or more percent of mother's own milk that we can get into preterm infants, the better they're going to grow, the better tolerance factors we're going to experience.

If we look at displacement, there's a linear relationship between the amount of fortifier you add and the lack of maternal milk that you're going to provide. If you're having to use higher caloric densities, you're going to be giving more fortifier and less milk. That's just by definition, and this is a graphical example of that.

I would say if in your practice you're using a fortifier that requires 26- or 28-kcal/oz fortification, just by definition, you're going to be giving less of that mother's own milk than you would be if you could get by with a fortifying agent that only requires 24 or 26 calories. That's a consideration to be had if you're doing target caloric density as an outcome.

Osmolality. Osmolality is related to feeding tolerance. And while there's not a lot of great data around osmolality, and there's no evidence to suggest that osmolality is—no, there's very, very limited evidence that osmolality is related to any gut pathology at all, it's clearly connected to gastric emptying. I often ask the question to nurses, "What do kids do when they eat their multivitamin?" And most of them quickly respond, "Oh, well, they throw it up." Well, the osmolality of these multivitamins is 10,000 mOsm/kg of water, which is a crazy number considering that the AAP recommends that nothing ends up in the stomach in oral nutrition or supplement that's above 450 mOsm/kg, and that's represented by this dotted red line in this graph.

If the goal is low osmolality in oral nutrition, low osmolality in oral supplements, thinking about those things in a way that is both pragmatic. So, split the multivitamin, give it twice a day, give it on the back end of feed so that you have a dilutional effect. These are things that you can do that really require very little cost and just some education for the nurses that could actually make a difference, both in the baby getting the things that you're trying to do, but also nurse satisfaction. They're not cleaning up those messes nearly as much.

If you look at the fortifying agents, they all do a pretty good job of staying below this recommended threshold of 450 mOsm/kg, but there's some variation and obviously the more fortifier you give, the more human milk becomes osmolar. Baseline human milk osmolality is about 300 mOsm/kg, just to give you some reference point.

And then acidosis has been a big issue, I think, when we think about fortification. And 1 of the limitations in really starting early fortification was the concern for metabolic disturbances. If you look at the same commercial liquid milk fortifiers, many of them have an acid load that is really equivalent, with a few exceptions.

I think you can look at this data and say within the sphere of things that we normally do at 24 kcal/oz, maybe even 26 kcal/oz, the acid load from the fortification of human milk is probably pretty minimal, regardless of the fortifying agent we use. And it's maybe only at those higher concentrations that we might experience differences. Again, just some data to reassure you that the fortifying agent is probably not a major contributor within the physiologic uses that we have.

I think that some considerations for your feeding practices around fortification is to just start by, again, what's the base milk that we're using? And so, in my practice, if we're using mother's own milk, my primary goal is to get as much of that into the baby as possible. That's my primary consideration. Can I get more percent volume into the baby? I really think about displacement as the major driver. If I can do that at 22 or 24 kcal/oz, then that's where I want to be vs doing that at 26 or 28 kcal/oz because you're just by definition going to give less of that mother's own milk. And then I think if you have concerns about tolerance, if you have concerns about acidosis, maybe that's a driver of your fortification choice, but they do appear to

have less of an impact overall and no real clear connection to NEC or other major gut pathologies that are concerns.

The Latest Evidence for Overcoming the Unknowns

Fortification Types & Strategies: Feeding Protocols

We think about the latest evidence for overcoming the unknowns, we still want to think about feeding protocols. And so, again, everybody has their favorite feeding protocol. Hopefully it's yours and the 1 that you're using. But when we think about this, it's critical that we do standardized feedings.

There's numerous RCTs. We're just going to highlight a couple here that land the plane for us, so to speak. One aspect of this is, well, how do we fortify? Okay. We've got these multinutrient fortifiers. They work great, we can add them, but could we do a little bit better by target fortification? I think that's a popular term, particularly for centers that have the ability to analyze the milk that they're using.

If you look at this RCT just published last year, 114 preterm infants, they had an individualized nutrition vs an optimized nutrition. The terms are not really, in my book, correct, but regardless, the individualized nutrition was macronutrient. They were measuring macronutrient profile of the mother's own milk and then supplementing appropriately, I would call that targeted nutrition, I guess this is a more popularized term. And then optimized nutrition was based on just following growth and serum nutrients, the things that we all do. And I would call that the standard fortification strategy just to compare to other trials that use that language. And what they ultimately found was that, at 18 to 38 months, there was no difference in Bayley scores. But they did note—and again, I talked about adiposity—at least in this study, as a secondary outcome, there's modestly higher rates of central adiposity in those that experienced that targeted fortification vs the standard fortification.

I think you'll see that there's maybe some rationale for that here. This was a secondary analysis of the ImNuT RCT in 120 preterm infants. And essentially, they were standardizing their protocol to hit these target ranges. In the gray are the recommended ranges for protein intake and energy. And they were really looking at it comprehensively because there's a nice gap that occurs in the transition from parental nutrition to enteral nutrition where protein and energy supply to the preterm infant for a handful of days—there's this nadir where both are lost. And what they did here was really target optimizing both protein and energy nutrition delivery to maintain that goal. And you can see here that when they pay attention to that through a standardized mechanism with regular feeding involvement and addition of a fortifier at pretty commonly accepted time points (100 mL/kg) that you can see here, they were doing a pretty good job of staying within that target range, as noted by the darkest line.

But as you'll note, as they move farther and farther out, it's easy to drift above that target range. And I think that maybe targeted fortification has that as a potential drawback. That's still yet to be explored, I think, definitively, but that we could maybe pay attention a little too much and sometimes some benign neglect is beneficial to babies as well, particularly in that convalescent stage.

And then the question of, as I said, we're great at initiating things and terrible at stopping things, and so postdischarge, what do we do? This was a really nice trial thinking about if we fortify mother's own milk or don't fortify mother's own milk, is there some benefit once we discharge these infants? And they compare that to a group that was just transitioned to preterm formula. Essentially mother's own milk with fortifier, mother's own milk without fortifier, and then a third group with preterm formula. And there was no difference at 6 years in IQ between the fortified group and the unfortified group. That's really clear again, that diet is the key driver of a lot of these outcomes. If a baby's getting mother's own milk, that's a great thing. And then when they looked at this subanalysis, the infants in the fortified mother's own group had better verbal and motor development scores in comparison to those infants who are fed the preterm formula. Again, we want to emphasize mother's own milk is the key here. Anything less than that probably has some different patterns that we need to consider.

And then just considerations for your own practice: advocate for standardization of practice. The simplest thing you could walk away from at any of these meetings is to go home and write a feeding protocol that incorporates when do you start feeds, how do you advance them, and when do you add fortifier. And those simple things will make a tremendous

difference on any feeding-related outcome you're interested in. If you're not doing that, that would be probably the first thing to do.

And then just to look at thinking about when you leave the NICU, what's your follow-on care? What is your way of counseling parents and pediatricians about if we are sending them home on preterm formula or we're sending them home on fortified mother's milk, how long? What's the plan for that? And I think a lot of pediatricians are ill-equipped to particularly know when to take a fortifier out of mother's own milk. And I don't think—I know I can speak for our group—we don't do a good job of equipping them with that information. Think about it. If you have a plan in place that you're going to send a baby home with fortified mother's milk, maybe speak very clearly to both the parents and the providers about how long you anticipate that being needed.

And then sodium supplementation and other supplements. I think, this is a hot area. And if you're paying attention to the literature, there's really good data coming out about targeting things like sodium and zinc supplementation after that first week or 2 weeks of life; that may be beneficial. And I think over the next years, that's going to be a very common practice that's already starting to be implemented. And in a meta-analysis of zinc supplementation, zinc is a micronutrient that we really need to be thinking about. Improved weight gain and linear growth, better motor development scores. Zinc deficiency is 1 of the, I think, 12 or 14 leading causes of death worldwide. It's one of those things. Iron gets a lot of press, and zinc gets none. They're both 2+ cations, but we need to be thinking about zinc deficiency in our preterm infants and supplementing with zinc as well. I feel pretty strongly about that.

Emerging Solutions in Preterm Nutrition

Salas: So now, for this last part of the presentation, we're going to touch on the bioactives, the things that we are presenting in milk that could be beneficial for growth, for nutrition, to jumpstart the immune system for a lot of things that we want in a preterm infant and term infants as well. So here we're talking again about the fact that milk has things that are not necessarily nutritive, but very beneficial, and that's what we're talking about—mainly human milk oligosaccharides (HMOs) and other components like lactoferrin. As you can see, HMOs represent a good proportion of the carbohydrates that are in milk, but again, we're not looking at their nutritional aspect, so we're looking at how those are beneficial for growth and for the microbiome as well.

When they started using HMOs, the best way to start was just adding this product to infant formula. And as you can see here in RCTs, it was shown that this practice could lower some important outcomes in term infants like less bronchitis, less use of antibiotics in general, and even things more subjective such as softer stools. And when the same type of studies were done in preterm infants, there was evidence that this practice could actually favor growth, specifically length-for-age *z* scores. So consistent benefits in both populations, term and preterm infants. And the part that I like the most about HMOs: they seem to help diversity of the microbiome. Because when you look at how those 2 interact, HMOs and microbiome, you can see that, when you think about NEC, you do see some changes in the diversity in NEC, as we talked about when we touched on microbiome, but also the components and how babies that have NEC usually have low concentrations of HMOs. Now, this is very promising, HMOs. I think we're not talking about the concentration itself, we're talking about the function, and I think it'll be highly beneficial in the future as we learn more about its properties.

The other bioactive that seems to have a really good profile is lactoferrin. And again, this is a protein, and it's present in human milk but not in cow's milk and seems to be very beneficial for maturation of the GI tract and also immunomodulation (that I think is the most promising one) and also risk reduction of sepsis. There are several RCTs comparing lactoferrin supplementation in neonatal outcomes. And so far, 1 of the largest trials has not shown any benefits in risk reduction of late-onset sepsis. But the direction, as you can see here, it is not against, right? So it does suggest that probably there's a potential benefit—that maybe it's about finding the right population that could benefit from this practice. But they did confirm, again, that there were less respiratory symptoms specifically related to bronchiolitis in the supplemented group. And the largest randomized trial did not show any of those effects. But again, it included a different size population. It went up to 32 weeks. And if you look at the effects on this particular

outcome by gestational age in that publication, you see something interesting about how the effect seems to also be driven by gestational age. But overall, the conclusion of the trial was no difference between groups, which is irrelevant because when you combine all these trials and you look at the meta-analysis on it, that effect seems to be consistent. So, we're hoping that more research will be able to clarify that aspect.

Now, there's this—another concept that is also interesting—is what do you do when you offer this product to term infants? And on those trials, there is evidence that there might be long-lasting effects, specifically on neurodevelopment. And something promising for preterm infants specifically is this RCT that suggests that when you have this option—let's say, ideally, you want to be on a diet that is just maternal milk and nothing else and maybe exclusive human milk diet. And then let's say you don't have access to the alternatives; you don't have access to donor milk. Is there any way to make formula effective enough to emulate what you get in terms of the microbiome profile by adding this type of bioactives?

And in here, you can see in the figure in the middle that, when you compare the profile, specifically microbial diversity between infants that are exclusively breastfeeding vs those that received a formula, those that have formula with lactoferrin plus HMOs, seem to have a similar profile, at least at that time when the intervention is completed around week 4. Now, that doesn't seem to be a long-lasting effect, right? So, if you look at the changes in the microbiome after week 8, it seems different, but in preterm infants, sometimes even these transitory effects might be beneficial. So, I think there's definitely a lot more to be studied here and to try to identify these type of profiles.

So, formula. The take-home point here is that, if you modify formula in a way that you add these components present in human milk, you might be able to achieve at least some effects, specifically on microbiome.

Now, the other promising bioactive is bovine colostrum. So, colostrum has the potential, as shown here, that has multiple compounds unlike mature milk, and that probably has to do with the health that the preterm infant needs during that transition period from receiving amniotic fluid, swallowing amniotic fluid in utero, and now having to depend on a human milk diet, ideally. So, if you don't have access to human milk, is colostrum better than mature milk as an alternative? And if you look at these trials, even though there was no difference in time to full feeding, it's a practice that could be a good alternative for those that infants that are not receiving human milk.

The most recent trial, the FortiColos trial suggests that they target a really good population (26 to 38 weeks), and they didn't find any differences in terms of growth, but there were some benefits in terms of how much protein they were intaking. So even though this trial did not find any long-term effects on growth, at least it confirmed that by providing bovine colostrum as an alternative, you are delivering a good amount of protein with it. And again, about tolerance—maybe could be beneficial.

The question is, when you have donor milk, it's important to take this bioactive thing into consideration, right? Pasteurization, the processing, the handling of donor milk might actually lead to a reduction of these bioactives, and therefore that could be an opportunity to start looking at things that can be added to donor milk to make it more efficient and more effective. Supplementing with a fortifier that could provide those bioactives could generate an important change in practice.

Now, to summarize this section. In terms of bioactives, I think: very promising. Just that effect on the microbiome at least seems to be the first line of research that could be proven relatively soon. And the effects on morbidity, especially if you use them combined, right? So far, there've been trials about doing HMOs and outcomes, then lactoferrin outcomes, it's probably going to be more about combining those 2 and seeing if there's any effect on important clinical outcomes in preterm infants. Okay, so we're going to wrap up the session now with some key takeaways.

Key Takeaways

Stansfield: Yeah, so I think it's just important to recognize that donor milk, particularly, requires mineral supplementation. It's likely that mother's own milk requires some supplementation, but we have to be a little nuanced and splitting the hairs between those 2, that they really do represent 2 different entities. And then after optimizing volume, supplementations, fortification, that we really need to have a longer-term view of growth, not be so quick to pull the trigger on making changes,

particularly in that first handful of weeks. And then, when considering the transition from donor milk to formula, just evaluate donor milk availability and risk for NEC, the things that we're doing are important in making that transition.

Salas: Now, for the microbiome and the use of probiotics, I think it's important to recognize that the type of milk matters a lot, probably more than the type of fortifiers. So, if you look at all those trials, what really matters is how much maternal milk has been given because that takes care of probably a lot of that. The evidence seems to be pretty consistent, at least in terms of randomized trials. It could lead to a risk reduction of NEC. And now we have 2 recommendations. We have AAP, and we have ESPGHAN. They're slightly different, but I think both want the same thing. So, we want to generate a product that is safe, but also we want to give access to our patients therapies that have been effective.

Stansfield: Yeah, really difficult spot to be in. When choosing a fortifier type, there's a lot of considerations. For me, I think about displacement really around mother's own milk. With donor milk, I don't really think that's a big issue. And then as Ariel has shown, and now a couple of RCTs, we can be more aggressive with feeding volumes, those first feeding volumes, particularly in modestly low-risk population of preterm infants. And then the evidence suggests that stable infants may experience growth benefits. If we are thinking about that same group, then we may be able to combine the benefits of exclusive human milk feedings with early fortification.

Salas: Great. In terms of evidence from trials, very promising—the use of HMOs and lactoferrin could be beneficial in terms of tolerance as well. So that's something that we'll explore in the long term, right? There is evidence on term infants now that these products could facilitate, improve neurodevelopment, and that will be the next step in preterm infants.

✧ **My question would be for Dr. Salas and the microbiome. So obviously, we do a lot of these studies with looking at NEC, with fortifiers and so on and so forth. The problem is, I see it very similar to grabbing a lot of children with all kinds of different infections and then testing whether amoxicillin gets rid of the infections. Of course, it's going to get rid of most of them, but there are some children that may have an anaerobe and that antibiotic wouldn't work. I see that very similar with, again, the use of fortifiers. With the whole buzzword of precision medicine, individualized medicine, do you see a future within probiotics where we could actually test, even at a genetic level, the microbiomes of these individual infants and then basically prescribe, if you will, a probiotic that better gives you the diversity of that specific individual infant, and therefore, really reach a nice level of diverse microbiome for these infants, and hopefully with that, improve even better the outcomes for NEC and other things?**

✖ **Salas:** That's a great point. I think it's possible. I started in this field—I did get into the microbiome because I thought it would be sooner, but I think it's going to take a bit longer now because I'm worried about the things that I mentioned in terms of, again, it's probably not just the type, right? It is the function and maybe the combination of them. In order for us to generate that product, that probiotic, we're going to have to learn. I think, so far, we know about the types; we don't know about the function, the combined effect, I think. And again, it's a number. I definitely think that the future is multistrain products, but I guess the concentrations, I think, still need to be defined and probably will take years.

✧ **First, I want to say really appreciate your work on the early fortification. I wonder if you could just share with us what your NICU's current practice is and how you're feeding? And then additionally, are you using probiotics?**

✖ **Salas:** No, we stopped using probiotics after that FDA communication. Our practice after the trial, yes, that's a great question. We did get a bit worried about this question about displacement, right, because we were fortifying with the human-derived fortifier in both groups. Babies that were getting maternal milk and those that were getting donor milk, there are concerns that maybe by fortifying, maybe we're displacing, we're reducing the amount of maternal milk that has been given just to fit this profile of full fortification. So right now, what we do, we provide maternal milk (unfortified) during the first 2 weeks, but if we have to supplement with donor milk, we use fortified donor milk. The diet during the first 2 weeks for us, based on that trial, is either maternal milk, unpasteurized, and pasteurized fortified milk, and then fortification with the bovine product as usual.

Stansfield: So we've started fortifying early, first feeds, particularly for what I consider our more low-risk patient population, so over 1000 g. We've started fortifying first feeds, and we've never been probiotic users, so we didn't have to make a practice change, so I can't comment on that. And we're very attracted to combining those effects and going with more higher-volume feeds. So that's going to be the next consideration in our revision of our feeding protocols. I think we're trying to think about these populations separately, over a 1000 g and under 1000 or 750 g or whatever cutoff you feel.

✧ **Given the lack of evidence of improved neurodevelopment in fortified vs unfortified maternal milk—and if I remember correctly, the Cochrane of fortification RCTs postdischarge didn't show an improvement in growth metrics at 6 months either—how compelling of a case do you find it to routinely fortify postdischarge? And then my other question is, do you know if there's any evidence of the impact of postdischarge fortification on the duration of breast milk provision? Because I always wonder, these moms we send home and we say, pump for 30 minutes and then mix the formula in and then feed your baby for 30 minutes and rinse and repeat in 3 hours for 2 months. Does that impact their ability to sustain?**

✧ **Stansfield:** Yeah. Both good questions. We have rarely fortified mother's milk for the reasons in your second. We feel like, and I say this as … I've never breastfed, but it sounds like a very tiresome situation to not only pump, but then to mix and store and measure, and to do that over and over again sounds tiring. We've actually taken on providing a preterm formula to add additional calories or nutrients, whatever that is. Our practice is often moms breastfeed. We want to invigorate that discussion around breastfeeding and allow them to breastfeed on demand without this arbitrary 3 hours. And then what we do is we tell the dad, "Hey, when you get up in the middle of the night, you can give 24-kcal/oz preterm formula, and that can be the replacement." So, you win on both those fronts where you're not tiring out the mom, you're bringing dad in, and that's been our solution, but it's really just practical. There's no good evidence to support that practice.

Salas: Yes. For us, yes, a very common concern, right? So, when you're sending them home, the numbers don't look right. If you don't fortify, you start getting worried about how much you're giving. I think that comes up a lot when our dietitian feels very strongly about fortification. And then you try to be pragmatic in terms of, "How is this going to work at home?" We are trying to individualize, so we start a discussion about it a couple of days prior to discharge, because sometimes those decisions happen like the day baby's going home, and I think that's probably the worst-case scenario. But I do see, I think we need to promote breastfeeding—feeding directly from the breast. So even when they go on fortification, I think it's fair to give them at least 2 or 3 feeds directly from the breast so they can have the experience of that, and maybe that can sustain breastfeeding rates throughout postdischarge.

In terms of growth, I think when you look at it as a pattern, I think NICU growth matters a lot for long-term outcomes. Postdischarge growth of preterm infants—it's a pattern. I just see that you don't see the same effect. So even though you might improve, whatever happens with growth after discharge, probably is not influential in neurodevelopment. But I feel strongly about the other aspect, the one that we have control on during the NICU stay. I think we still need to be very focused on caloric intake, macronutrient intake. But if you said, "What do you do postdischarge?" We can have some flexibility just like it happens in normal life. Term infants also, I mean, we don't measure so many things in term infants. I wonder what normal is, truly, because every family is different. Everybody who considers normal, has a different definition of what normal is.

Interprofessional Panel Discussion

Kirsten Frank, RD, CSPCC, LDN, CNSC, IBCLC: We're a group of interprofessional healthcare professionals that were asked to speak on the role of interprofessional care, collaboration, and education and how that impacts our healthcare systems.

And that interprofessional collaboration and education model is comprised of 4 core concepts. The first 1 being roles and responsibilities, and that's the use of knowledge of one's own role and team member expertise to address individual and population health outcomes. And for me, I think my role as a lactation consultant and also as a dietitian brings 2 different roles and responsibilities to the interprofessional team atmosphere so that I can both speak on nutrition and then also the lactation aspect of care. That second core concept being value and ethics, which Dr. Stansfield will touch on.

Brian K. Stansfield, MD: Values and ethics are implicit to who we are and the various roles and expertise that we have and we bring to the interprofessional healthcare team. And the goal of recognizing these values and ethics is that we can promote the individual values and bring new perspectives to our care. It allows us to really value diversity; it helps us to look at people individually to recognize cultural differences and background differences that we're really navigating and specific to the patients that we're caring for. Within the healthcare system, recognizing the values of individuals allows us to collaborate together with honesty and integrity, striving for health equity, and improving health outcomes.

Frank: Excellent. And our third core competency is communication, which Michaela will touch on.

Michaela Berroya, MSN, RNC-NIC: It is really important as part of an interprofessional collaboration, to have great communication. If we are not all on the same page, none of these protocols or guidelines that we are trying to implement are going to work. We need to make sure that we are responsive to each team member's needs and that everyone has a seat at the table. We want to be respectful to all of our colleagues and all of the expertise and knowledge that they're bringing to this group. We want to give compassionate care to our patients, and we want to be compassionate with our colleagues. Everybody has different specialties, and this is why interprofessional collaboration is so important so that we have a whole picture for our patients.

Frank: Thank you. And the last core competency is teams and teamwork. And as Dr. Stansfield and Michaela mentioned about both value and ethics and communication, and as I mentioned about roles and responsibility, those all play a huge role in teams and teamwork. That aspect of bringing the principles of the science of teamwork together to come collaboratively together to make group decisions for the best care for that patient, talking through each of our roles and expertise and manage each other up in those decisions and those collaborative conversations that we have together. And also, to hold each other accountable as well with regards to the care that we're bringing to the table for our patients.

Michaela is now going to speak on the importance of interprofessional care and collaboration in the NICU setting.

Berroya: Thanks, Kirsten. So, we wonder: why do we need interprofessional collaboration, and what gaps might it fill for us in our varying settings and different professions? So, we know, without our interprofessional collaboration, we may have a fragmented health system. When we collaborate with each other, we are a more collaborative workforce, and this leads to a collaborative practice. We then, fortunately, have a strengthened health system, and the end result, which is what we all are working for and towards, is improved health outcomes for our patients. So, when we talk about this framework, we are looking at, what can we do in our own institutions, and how can we bring this to other places? Brian, do you have any examples of how this is done in your own health setting?

Stansfield: One place where this is really clear to me is in interdisciplinary rounding at the patient bedside where, as the physician, we incorporate both discussion opinions and comment on the care from nurses, dietician, respiratory therapists, parents, any social workers, or other staff that might have insights that we may not gather from our exam or from the electronic medical record. And what it does is, it allows us to really come up with a thoughtful and comprehensive plan of

care for each individual during each day. And I think it also brings the values and good communication from the team members so that everybody's on the same page when we leave the bedside. Kirsten, does your institution practice interdisciplinary care? And what are your thoughts about that?

Frank: We do actually. We host, every day, interprofessional rounds with each other. It is comprised of myself, a dietitian, pharmacist, respiratory therapy, nursing staff, sometimes our spiritual care providers, our case management team, and social work. We round every day, and we have an opportunity with each other to share our expertise and what we can bring to the table to help optimize the care of the patients that we're talking about. And a lot of the times, because we round throughout the unit and go room to room, if the family's present, we'll also include the family in our collaborative conversations with each other. And so, it helps all of us stay on the same page. We all are able to share our information and what we can bring to the table right in that moment. And it definitely, I feel, optimizes the care of that patient.

Berroya: And Kirsten, just like you were saying, as well as Dr. Stansfield, we do the same thing at my institution. And I think this is actually extremely helpful when families are present for our interprofessional rounds because there are so many team members there that are specialized in their areas, and they're getting an overview of the plan from everyone. And if the family has something that they would like to input or a question that they need to ask, this is a great space for them to do that and to also understand why we are doing what we're doing for their baby.

And to just sum up what we were all talking about, this framework is really important to give us the best healthcare outcomes for our patients. We have stronger teams; we more efficiently use our resources; and we are helping to improve access to healthcare and make sure that our patients get the best outcomes as possible. And that is what we're all here for and why we do our jobs.

Okay, so now I'm going to throw it over to Dr. Stansfield to talk about our interprofessional collaboration and the core competencies that we discussed and how they apply to the NICU.

Stansfield: Thanks, Michaela. Interprofessional care, I think we do this in many ways, but one place where I've seen it actually be very effective is in the thinking through of new information, particularly around, how do we feed and provide nutrition to preterm infants? It's such a complicated part of our jobs, and we're inundated with new information about the timing of when we start feeds, the supplements we may use, the addition of certain fortifiers by either type or timing. How do we measure growth and progress in our nutrition goals? And incorporating all of this new information into the standard practices within our units—the feeding protocols that we use to help streamline care and to make it predictable for the entire healthcare team. It can be difficult, and it really is an opportunity for interprofessional care to sort of highlight the various values and ethics, the expertise, that many partners in the healthcare team can bring to the table. And I think it's been one area where I've seen the importance of good communication across professions. I'm curious, Kirsten, as a dietitian, does your program incorporate new information into your feeding protocols?

Frank: Yeah, thanks, Dr. Stansfield, that's actually a really relevant question. We recently, in my institution, just got through a process of updating our feeding protocols, and we came together and put together what we called a nutrition expert committee in our unit. And it was made up of myself (dietitian), a couple of our bedside nurses that wanted to join the nutrition expert committee, 2 of our nurse practitioners, and we had a physician lead, one of our neonatologists. And we started off with doing an audit of our current protocols and kind of seeing where we were falling short and if what we were using was up to date with the current evidence. And with the new evidence that's out there, we decided to do a little deeper dive into the research based off of the audit that we put together.

And so, we had collective meetings. We tried to meet twice a month—it ended up being 1 to 2 times a month—with each other. And each of our meetings was focused on utilizing the information we got from our audit and doing a deep dive into our literature and how we could apply the most recent evidence to our feeding protocols. And we actually took a lot of the newer information to help provide a newer feeding protocol, and we broke down the different gestational ages a little bit more

tightly to be a little bit more individualized in care, as well as the weight classes for our babies. And then we used a lot of the information that's available now in the current evidence to help. We start fortification a little faster, a little sooner. And we also are shortening our trophic feeding days, and it seems like we are able to feed babies a little faster than we previously were, and we just went live with those protocols in the middle of April.

Stansfield: Wow. That's a really great example of how interprofessional care really helps to mold precise feeding protocol. Michaela, I'm curious as a nurse, how do you implement some of these changes?

Berroya: Yeah, so I think that's really great that you're doing that. And I think these interprofessional groups are so important because in the past, before some of these guidelines and protocols were established, as the nurse at the bedside, it was sometimes like, "Let's see, which attending is on today to see where they're going to go with this? Am I, as the nurse, going to have some say in what's going on?" And so, interprofessional collaboration is extremely important because we did the same thing with our protocols. Pretty much as Kirsten said, the members that were involved, we had those same members involved in our feeding guidelines. And so, the nurse felt like they really had a seat at the table to say, we may think that we want to do this, but how can it be actually implemented in practice in terms of timing and flow? And this helps to have a better workflow for the nurse because you've had a voice at the top of the table.

Stansfield: It seems like interprofessional care and good communication across professions is actually really helpful in bringing in new information and then implementing that information.

Frank: I like what you touched on there too, with keeping the nursing team involved. Because at first when we put our committee together, we weren't thinking through quite all the people that should be at the table because, like Dr. Stansfield said, we're here thinking about putting these protocols together, but then how does that impact the nurses at the bedside? So, when we pulled our nurses into our group, it was actually quite helpful because some of the newer evidence, talking about maybe increasing feeds a little faster at a faster volume than we have previously been used to and starting feeds a little sooner—it feels uncomfortable sometimes. And so, with our bedside nurses there and able to speak through some of those potential fears and hesitations that the rest of the unit may experience was incredibly helpful to us so that we could, again, look at the literature. What does it say? What does it look like in real life? How do we apply this? And that the bedside nurse input was incredibly valuable.

Berroya: Yes. I often say that sometimes the nurse is the gatekeeper because they are the person that is at the bedside the most out of all of the teams. And so, it's really important to be able to feel like you had a say, and like you said, to alleviate the fears of maybe some of your colleagues because they know that nursing was represented in this discussion to come up with these protocols.

Stansfield: Thank you both. That's really great examples of interprofessional care at work. Kirsten, do you want to wrap us up?

Frank: In looking at those 4 core competencies of roles and responsibilities, value and ethics, communication, and teams and teamwork, and how they apply in the NICU being so impactful to the care of our patients. But it doesn't just apply to the NICU setting. This is actually quite pertinent across all healthcare settings to make sure that we are optimizing the best care possible for the patients that we are helping and serving. So, thanks so much to Dr. Stansfield and Michaela for jumping in that conversation with me today. And I also thank the learners for joining us in this conversation.

Abbreviations

AAP	American Academy of Pediatrics
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
FDA	US Food & Drug Administration
GI	gastrointestinal
HMO	human milk oligosaccharide
NEC	necrotizing enterocolitis
NICU	neonatal intensive care unit
RCT	randomized controlled trial

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