Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Personalized Human Milk Fortification Strategies to Impact Micronutrition and Growth

✦ Course Transcript ✦

Editor's Note: This is a transcript of a live conference presentation on November 15, 2022. It has been lightly edited for clarity.

Christina J. Valentine, MD, MS, RD: I want to review in a little more detail, beyond protein and calories, is what I always tell my team. What's in preterm milk? What's in donor milk? What are our baselines, so we know what we're fortifying? And what are other gaps that you can address in your unit that can really accelerate growth, and most importantly, that linear growth, and if you do have an air displacement plethysmography (ADP) system (Pea Pod™), that fat-free mass?

Nutrition Gaps

We reviewed this in the last lecture. It really is apparent that mother's own milk is preferred. It's why I've spent my career thinking about how I can make the mammary gland healthier for those moms, as well, and thinking about supporting her, and having that supporting your NICU [neonatal intensive care unit]. Having pumps at the bedside, having those discussions with moms and families. To be honest, one of the discussions I always have is what are your plans for pumping human milk? We can help you with the act of breast-feeding later. When I started to do that, it really is a different connotation for moms. I do have some moms who do not want to direct breastfeed ever; whether it's [due to] abuse in the past or they just don't want to do it. So, when we were first saying, do you want to breastfeed, or we had this excited young resident asking the mom, she would say, "No." I mean, even to this day, I've had moms say, "No, I don't want to breastfeed." They also [may] have assumptions they can't breastfeed because their baby is so sick. So, start with this mother's own milk opportunity to educate her. Then, we do have our own academy recommendations that when mom's own milk is not available or a pasteurized donor milk source is the next-best thing, at least for that first 30 days of life, to bridge mom's own milk when it's not available.

The reality, however, you saw this in more detail, here's the reality. We do have a medical emergency. These babies are going home from the hospital small for gestational age, and that connotates that the brain has been missing a lot of key nutrients. Their bodies have been missing key nutrients. Their immune system has been missing key nutrients. It's a medical emergency. We've got to stay on top of our growth charts and our measurements and make sure you can see that every 10% increase in donor milk… Look at the deficits in your growth. It's meant to be fed to a baby at 4 months and above, eating solid foods. It's nutritionally inept. We have to be as strategic with our human milk feeding as we are when we look at ventilator strategies, and that's how I talk to my peers about it. We really need to look at the science and capture it.

We know this development correlates with linear growth, with fat-free mass, yet we're not doing a good job. Why is that? Why is this happening? Well, we have found that human milk foundation is a moving target, and all of our nice recommendations that we get on a glossy card that says how many nutrients breast milk averages, you know, from our academy or from older publications, and truly it's not that number. A lot of the industry make fortifiers to build on that number, but the baseline numbers are wrong. So, I want to give you some numbers you can use in your own setting and start to strategize around it.

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Also, donor-milk processing affects not only the anti-infective properties, but you'll see in the data I'll present, it will impact nutrient availability. Not only is it a late lactational stage, but in my area of research, [what] I have been very disheartened by is it affects fat availability. We've got to think beyond some of these key nutrients.

Fortification Practice

We know the mom's diet, which I just reviewed, but I'll share a little bit more with you, and our fortification practice is limiting. Folks say, I'll do 2 packets for 50, 4 packets for 100, or if you have the liquid available, I'll draw off what I need and put it in this, and that's what I'll get. You have to start looking at the literature, and looking at things I'll show you today, to think about your fortification practice, almost like parenteral nutrition compounding. If we're going to use human milk, we really need to think of ourselves as being better in our bedside mixing or in our milk rooms with some of these ideas that I'll give you so we compound that milk to be more nutritionally appropriate.

This is 1 of my little babies I had at Nationwide [Children's Hospital] saying, "Please target my nutrition, please think about it." Understanding breast milk baselines—and I'll review some nice data for you—but also how does processing and mixing change that? Look at your process in your unit. How many steps? How many freeze/thaws? How many heatings? Who's mixing it? How many steps, and how many times is this milk being touched? Also, is your fortification practice diluting mom's milk? We heard earlier that not only is mother's own milk important, but we know there's a dose-response effect to the protection against NEC (necrotizing enterocolitis). So, don't fool yourself, if you keep adding all this stuff to your breast milk to get growth, you're making an unsterile formula on the unit. So, really be aware of how your process is happening.

Informed Choice

What we've found in our research and through others, you'll see this [in our] updated reference list, is that the donors in the US are healthy, and they do have nice screening. The North America milk banks are under lots of…, they do cultures; they have a very clean system; they use a Holder pasteurization process, many of them; but we do know that people have variations in how they pool, what the mom's diet is. There's so much variability, that you have to make sure where you get your donated milk. How are they pooling it? I'll show you some data that's very clear, which shows you need to have a lot of mothers in 1 pool to get rid of that variability.

Then there's a lack of standardized terminology. I've heard parents say, well, I thought you were giving me preterm donor milk. We need to be more clear when we do our informed choice with our families on what donor milk is. What we typically say is it appears there are some components in pasteurized donor milk that could be protective in this first month of life. There are oligosaccharides, there is a little bit of activity of the anti-infective properties, there are things in there that are still there postpasteurization that aren't currently in preterm formulas. We believe, in this risky time period when your milk's not available, this would be appropriate; however, we do know from large, randomized trials that if your baby's on donor milk too long, they won't grow as well, and there are developmental sequelae from that.

In our unit, we found our risk of NEC was in the first 30 days of life, in a 10-year retrospective review, so we use 30 days as the trigger point to take them off donor milk and start using a "nourishing preterm formula," is how we say it when we get consent. When we started to do that, I felt it was a true informed choice for the parents. Then, when we put them on preterm formula at a month of life, they don't freak out and get afraid that we were going to cause NEC now. Our NEC rates, at the time of those

publications, were less than 2%, and we also used the bovine fortification. So, make sure you have that conversation with your families.

All right, let's do a deep dive. What are the components in human milk? This is a picture, I spent a lot of years with the Mothers' Milk Bank of Ohio. I was very fortunate to work with a nurse who was also a lactation consultant, Georgia Morrell, and we went around the US, and she was the prime mover. I was just there to support and build the evidence in really building a lot of the North American milk banks. It's clear that when you get into this business and you deep dive, there's a lot we can learn and still to learn.

Preterm Milk Gaps

As you heard from the previous lecture, there are gaps not only in donor milk, but [in] preterm milk. We're going to go through the preterm milk, and then I'm going to show you the donor milk. Then we'll talk about fortification strategies.

When you look at colostrum, when you look at preterm milk on day 7—and this is an updated, great preterm evaluation of milk that was published last year from the University of Augusta—you look at mom out to day 28, and then you also compare it to donor—if you look at that lighter beige color, that's the amount of calories, that's a gap. You need to make sure, if you're using early preterm mom's milk, month-old preterm mom's milk, or donated milk, that you think about the energy gap and make sure your fortification strategy is covering that. So, that's energy.

Here's one of my pet peeves. When we do parenteral nutrition, how many of you, when you're on rounds, you want the bedside nurse or the resident or the fellow to present and say, "calories per kilo, protein per kilo, fat per kilo"? How many of you, when you do enteral nutrition, continue to say, "How many fat grams per kilo the baby's getting"? It's such a huge, important component for this little person. We've started to do the fat. I tell the resident and the bedside nurse this is part of therapy. We've got to know how much of each was given to this baby, and you need to calculate, based on our data. What are the grams per kilo that baby got in fat, just like we would TPN [total parenteral nutrition]. And you're going to be so surprised. One of the biggest things we found was that these babies aren't getting enough fat. We were doing good with energy; we were doing good with protein, but I think some of the reasons protein is so important, if you don't give enough fat, you're not going to have enough nonprotein calories. And that protein is going to be used for energy. So, part of our process, you'll see in a little bit when I tell you the strategy, is that you've got to cover the gap for fat. It can be almost 2 g/kg. So, think about that.

I always emphasize quality in these milks, as well, and we need to learn so much more about the quality of the nutrients we're giving. When we did this cross-sectional examination of the North American milk banks, California, Colorado, Michigan, Ohio, Texas, we also had some milk samples from New England. I wanted to see how those moms were doing. We found that there were significant qualitative differences across the milk banks, inter-mom variability. If you look at the bottom 2, which is the arachidonic acid (ARA) and the DHA [docosahexaenoic acid], and you think about the total dose in milligram per hundred, and if you're feeding this baby this milk at 150 mg/kg, they're nowhere near what Dr. Koletzko just said should be the guideline. The donor milk not only has low fat, but, qualitatively, it also has low fatty acid for that little baby.

You can do this in your area if you're interested. In Ohio, we did a trial with our donors and gave them the 1,000 mg and saw a significant improvement in the donated milk. And those moms are always jazzed to help do anything. So, you can make a difference, even in your donated milk, qualitatively.

Protein: this is just a snapshot, a summary, because I know you were going to see it earlier, but if you look again, this lactational stage is a big deal. Early milk, about 2 g/dL, but it falls rapidly over the next period of time that the baby is in the NICU, and this is preterm breast milk. Even your preterm breast milk is not going to fill the gap for those babies' needs.

Donor Milk Limitations

When we did the donor milk protein, we found even more striking problems. We did this in our own Mothers' Milk Bank of Ohio, but we also did the cross-sectional examination. The mean protein, because of the way the milk is pooled, a lot of times you'll have milk anywhere; you'll have maybe a few preterm moms donating, but the majority are late-lactational-stage moms, sometimes out to 13 months. That protein was only 0.9 g/dL. So, get with your milk bank. Where are you getting your donated milk? Find out how much protein you're getting in those pooled samples if you don't have a human milk analyzer.

Now, striking, and I haven't heard anybody talk about this, and I think, as we move forward, we need to think about this: qualitatively the amino acids are not sufficient in donor milk. I think it's not just a quantitative problem, but if you look at some of these key amino acids—we did all the amino acids—but these are key that I wanted to point out. If you look at lysine in the bottom right corner, babies should get about 130 mg of lysine. Do you know, the World Health Organization and the protein experts at the FAO [Food and Agriculture Organization], they use lysine as a biologically appropriate protein. If you don't get enough lysine, you don't grow. That's not a good protein. You've got to start adding more protein. We're giving donor milk with extremely low lysine to these little babies. We've got to make sure we also consider, as we move forward, maybe they need some more free amino acids if we're going to use donated milk, and it just emphasizes, try to get your babies off donor milk as soon as you can, and you're outside, whatever your risk is in your unit.

Sodium Impact

I became very interested in this when I was at the University of Cincinnati. We did a study where we looked—blinded, prospective—looked at sodium because it is so clear babies need calories, they need protein, they have to have sodium or they will not grow. They will not grow. So, we were looking at urine sodiums, blood sodiums, and it was very apparent that our preterm babies were sodium insufficient. They were not getting enough sodium. We were giving all these calories, and all this protein, they still weren't growing. We gave them fat, they weren't growing. Well, don't you know, they needed more sodium. In this preterm milk composition, it went hand in hand with what we were doing at the time at Cincinnati. This is the Augusta data, and it was clear that even in preterm moms' milk, you can see how many milligrams per deciliter are in mom's own milk. When you look at the donor milk, it's about half that or less. Half that or less. So, keep that in mind as we go through fortification.

When you look at the gaps then, if you have colostrum, there's like a 4 mg gap, 25 mg gap in preterm milk; late-preterm milk, 33 [mg gap]. Look at donor milk. That's a huge gap, it's a huge gap. Then, what if you have that baby on furosemide, too, and you're losing sodium? Keep in mind, calories, fat, protein, and now you've got to keep in mind sodium, particularly if you're on donor milk. This is again why I counsel, and I loved the talk this morning, give your families that educational opportunity. Give them that awareness that donor milk is like this, and for sure, anybody using donor milk in the term nursery, you'd better sit as a diet committee and see what you're doing because it is not nutritionally fit.

Think About Zinc

Now zinc. We also looked at zinc, and we found a similar correlation. This is a study from Augusta looking at the zinc in the milk, but we were also looking at zinc in our babies and their status. We did metallothionein; we did zinc levels; we did all kinds of stuff, and it was very clear that not only is the zinc low for intrauterine recommendations in preterm milk, as well as donor milk. You'll be shocked in a minute, but think about it, as mom's lactational stage goes, by about 4 to 6 months' lactational stage, zinc, iron, sodium, magnesium, all those nutrients fall low because anthropology-wise, we start to get teeth, and we're supposed to start eating protein-containing foods, to cover those gaps in zinc and iron, protein. And we're giving that milk to little preemies. Here's what it looks like compared to donor.

Here's the gap compared to the 2021 new guidelines for early mom's milk, mature mom's milk, and then look at the donor. It's so significant. You cannot grow long if you don't have enough zinc. You cannot grow long. Think about zinc, and it's so important for immune properties and homeostasis. So, you have a baby who keeps getting sepsis, and he's on donor milk a long time, you'd better think about zinc.

Donor Milk Duration

So, just as a snapshot, I wanted to show you when you look at the percent of nutrient intake, depending on the human-milk source. Blue is the preterm mom's milk, the beige is the donor milk; you can see calories, we can do a pretty good job with the carbohydrate, but look at the protein, the magnesium, the sodium, the zinc. These are things that, when we finally changed our feeding protocol, and we found out when our risk of NEC is, and I really encourage you to look back, have a young fellow, a young faculty help you, dietician, nurse practitioner, and look to see when your risk is for NEC. How long are you using donor milk? Don't just believe somebody's paper that says you should use it to 34 weeks. That's a long time to have these kids on donor milk. I don't know what yours will be, but our risk was a month of life. Try to get them off as soon as possible, or else you're just going to have to fortify a ton.

In the summary for the first part of my talk, it's clear we need mom's own milk but there are still nutrient gaps for moms, and there's significant nutrient gaps for donor milk. So, what can we do to think about adding these nutrients?

Pumping Foremilk and Hindmilk

I want to convince you that the fortification concepts, you should start first with is pumping. Counsel your families on pumping and your moms, as long as she's passed her colostrum in that first week. Talk to her about pumping, and we'll talk in a minute how to do that, then make sure her diet's good, really look with the fortifiers. I tell my team, take the brands off, look at the nutrients. See what's going to dilute mom's milk the least. That's what we need to use. The supply chain guy can't tell us what we should be using for a baby that needs to grow. Then, you need supplements if and when you're addressing some of those gaps with donor milk. I'll talk about that.

To begin, I published this many years ago now when I was at Baylor with Rich Schanler and Nancy Hurst, and it was really clear that when our moms were randomly pumping their milk and bringing it in, we'd thaw it, we'd feed it, we were seeing some horrible growth, and then I thought about the concept of Dr. Neville's work. She does a lot of basic science with human milk in Denver. It was clear that in the first 2 minutes after letdown, the milk is foremilk. It's high in carbohydrates, and it's really sweet. Anthropology-wise, it probably tastes sweet, and the baby wants to get going nursing, but then after 2 minutes, it continually rises and rises and rises in fat, so you get the sweet cream at the end of that

feeding and I always call it, it's like Dairy Queen cream. It's sometimes 30 cal/oz. And all those nursing babies are supposed to get that beautiful fat.

What we started to institute was having moms pump hindmilk. What you do is you tell her to pump for 2 minutes, save that in the freezer at home, label it bottle number A, because it's sweet. Then when the mom is going to put that baby on solid foods later down the road, she can thaw it and mix it with the food, so it's not going to be wasted.

Bring in the rest of the milk. It is extraordinary. You don't even have to measure anymore. We were measuring the milk and doing creamatocrits, and it was very clear that every mom's milk is different. Some of the moms' foremilk was 13 cal/oz. If they're bringing you that milk, you're not going to get that baby to grow. But if you get them to bring hindmilk, you use a standard fortifier, a lot of the moms' own milk, babies will grow like crazy in weight, length, and head circumference. It's amazing. You don't have to add anything. Maybe some vitamin D. So, mom's own milk, just by pumping and getting her on her diet, often you will see, with a good dairy fortifier, those babies will grow really well.

I want to point out that there are some human cream data also available that Dr. Hair and her group at Texas Children's published, and we know anecdotally MCT [medium-chain triglycerides] oil can work well, too. The bottom line is to make sure your baby's getting enough fat because they won't grow despite how much protein you put into that kid.

Maternal Diet

Mom's diet: you'll want to go through these with your moms in your unit. We have a couple of residents I'm getting on the case and helping me do this. It's fun. They love it. They love talking about it. Even my moms on the Women, Infant and Children program, they want to know what they can eat. It's fantastic. If you go to my name on PubMed, Valentine CJ, I use my middle initial, you can download a lot of these papers for free because of the NIH funding. This paper I did with Katie Copp with the maternal diet is here. We found what moms were missing in their diet, and then what was, in our area, food sources they would eat.

My moms are very poor, they have a very limited palate, they have very limited resources. We had to think of things that would meet the needs that they would eat. Then be careful of mom's dentition because you don't want to say, well, just eat some raw vegetables and this, that and the other, and she doesn't have good teeth. We were really humbled because we were trying to do these kind of things fresh, and fresh is best, but for our moms, we had them bake a lot of these to make them a little soft. So, keep that in mind.

Evaluate Nutrient Quality

You heard, in more detail, what fortifier to use. I can say that, in practice over the last 20 years, and looking at this very carefully, and unbranding things, and looking at the data, I want everyone to be a very good critical thinker. Make sure you evaluate the percent of NEC in the studies. Evaluate [whether] the mom has chorioamnionitis, what kind of moms were they with what kind of babies. Because my amniotic fluid studies, which I didn't show at all today or the sampling we've done, these babies are swallowing stuff already in utero setting the stage. I think a lot of the things we've got to think early on for prevention of NEC, and 1 of those things is to prevent preterm birth. But really look at this because, as shown clearly, there are no differences in outcomes in the powered, randomized trials. Also, evaluate the source of the nutrients, the quality of the nutrients, as I suggested, and then we use preterm formula when mom's milk's not available after those 30 days.

Here's the other strategic supplements you need to think about. Barb Isemann is the first author of the

sodium paper that we did at University of Cincinnati, and I'm not one of the authors. I was one of her supporters in the unit. I was on service a lot during that time, and it was very apparent, if you have a baby on donor milk, our new protocol is this. Make sure that fortification is a good fortifier, think about the higher protein fortification opportunities, then you need to do 2 mg/kg of sodium, and even with the BPD [bronchopulmonary dysplasia] kids because they're not getting baseline sodium. You're not giving them supplements; you're really giving them their baseline. You need to follow their sodium levels, and you can do spot-urine sodiums, if you're concerned.

Make sure these kids get enough iron, 4 to 6 mg/kg/d. If you're not using a fortifier with iron, make sure they get enough. The zinc, I had a nice PDGI [pediatric gastrointestinal] fellow who we did this paper with, and it's in the JPGN, (*Journal of Pediatric Gastroenterology and Nutrition*) 2014. In that paper we found that you don't have to measure a lot of metallothionein and zinc levels. What we found was very clear. If you give that baby at least 2 mg/kg of zinc—and this included any donor milk-fed baby and your chronic lung disease babies—they will waste zinc because of their diuretics. So, you need to put the fortifier, you need to make sure you've got enough sodium, and make sure you've got enough zinc.

Then we monitor 25 vitamin D levels to make sure we're giving adequate D. I found, since I've been doing that, I was inspired at the University of Cincinnati and Cincinnati Children's because they had some of the gurus in vitamin D research, and it was clear our babies sometimes need 600 to 800 IUs of vitamin D. Think about measuring this and making sure they have enough.

Then finally, DHA and ARA. We are also very excited to start—now that it has commercial availability—DHA and ARA in our babies from the beginning. We do the mom's DHA, but we also know there are still gaps, particularly if they are on donor milk. Making sure your babies are getting enough DHA and ARA to think about reducing that likelihood of severe ROP (retinopathy), as well as for brain maturation.

Finally, if you think about how to measure these things, I had the best training at Baylor when I was young. I was excited. I already was a nutritionist, and I was like, what can I measure. The Children's Nutrition Research Center was there, and Dr. Heird was very much a pioneer in the area of parenteral nutrition development. I asked, "Dr. Heird, what can I measure, what can I do?" and he said, "Christine," in his Texas accent, he said, "If you can get a baby to grow long on an accurate length board, a centimeter per week, they don't got no deficiencies." And it stuck with me. So, you need to get a length board. Your units, if you're not using a length board, let me know. I'll show you how to get a grant for one because we're measuring the most important outcome for these babies, and we don't have the right device. It can't be a paper tape. It has to be a length board. Okay? You have opportunities for some quality improvement.

Then finally, if you do have body composition opportunities, an ADP system (Pea Pod™) costs less than a ventilator, is what I told my bosses. So, if you can possibly get an ADP (Pea Pod™), it really is helpful in measuring fat-free mass. Now, I want to point out; however, we did find that fat-free mass correlates very well with good linear growth. If you can get a good length board, and every week make sure the mom or the dad can help you measure. The dietician, the nurse practitioner, [because] it does take 2 people to make sure you're laying the baby just right, but you can do it even if the baby is on the oscillator. You just slide it under them and stretch them a little. We can do it on any sick baby.

Finally, you can really impact that fat-free mass with those types of feeding strategies in the hospital with human milk. Think about the maternal diet, think about fortification. And truly we have found, we do

use a human milk analyzer, and we currently, except for research purposes..., you can use it 3 times a week if you have it, but truly we use good BUN [blood urea nitrogen] to make sure we're giving enough protein, good linear growth, and that's about all we do except for the vitamin D. You can do a lot of these things in your unit despite resources.

And really think about your baseline of human milk. And please, I stalk my email, let me know if you have any questions, concerns, comments. I'm so happy to share anything. I have to acknowledge my Nationwide mentor, Dr. Lynnette Rogers. We still work together after all these years. Dr. Amy Gates, who was the author on a lot of the Augusta information, and my University of Cincinnati folks. I'm now at the University of Arizona; I'm a Wildcat, and all 3 of my daughters are Sun Devils, so we have a little fighting going on in our family. We are setting the stage to drive fortification to impact growth and development. Thank you so much.

Abbreviations

ADP	air displacement plethysmography system	**MCT**	medium-chain triglycerides
ARA	arachidonic acid	**MOM**	mother's own milk
BPD	bronchopulmonary dysplasia	**NEC**	necrotizing enterocolitis
BUN	blood urea nitrogen	**NICU**	neonatal intensive care unit
DHA	docosahexaenoic acid	**PDGI**	pediatric gastrointestinal fellowship
DHM	donor human milk	**ROP**	retinopathy
FAO	The Food and Agriculture Organization of the United Nations	**TPN**	total parenteral nutrition

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