Variations in the Nutritional Content of Human Milk

Transcript

Editor's Note: This is a transcript of a live internet presentation on March 22, 2023. It has been edited for clarity.

Brian K. Stansfield, MD: I'm here with a vested interest in the composition of human milk and I think if we understand what we are giving in that context, then we can better support our preterm infants, so I'm going to focus there. I want to start with a little bit of background, but ultimately that's the endpoint that we're trying to drive towards. So, let's jump right in.

Human Milk for Preterm Infants

I think that this audience is very familiar with the idea that an exclusive human milk feeding is the ideal diet for all infants within the first 6 months of life. Just about every agency you can imagine has come forward with support for this type of statement and I think this is particularly true for preterm infants. And I believe that the vast majority of us probably believe that.

This is probably the most compelling rationale for a human milk–based diet in preterm infants—this was published over a decade ago now—but it was observational data looking at the exposure of preterm infants to human milk within the first 14 days and the incidence of necrotizing enterocolitis or death based on that exposure. So, as you can see here, these are sort of Kaplan-Meyer type curves, but you can see that, if you look at the absolute amount of volume provided in the left column or you look at the fractional percent of absolute volume provided in the right column, human milk is absolutely protective of necrotizing enterocolitis or death. And this seems to be a very strong correlation that is linear in fashion. So, this is probably, I think, 1 of the most compelling slides for widespread use of mother's own milk in our preterm infants.

There are other outcomes that are as important. There's an emerging paradigm that neurodevelopment is improved in preterm infants who are provided mother's own milk. This is just 1 example of 1,000 infants, looking at their neurodevelopmental outcomes at 18 to 22 months. What this study did was it broke the group of 1,000 infants down into quintiles, looking at those that received the least amount of mother's milk, those being in the less than 20th percentile, and then subsequently stair-stepping up to those that received the most amount of milk, being in the greater than 80th percentile. They use a no human milk exposure as a control. You can see a clear linear relationship between the exposure rate of mother's own milk and mean neurodevelopmental indexes. And this seems to persist well into the school-aged years, with follow-up studies looking at children and this relationship at 8 years.

We know that human milk is necessary, but we also recognize that preterm infants present a unique and challenging population to support growth. These challenges are apparent very quickly, with rapid growth rate of preterm infants reflecting a high metabolic demand and that can be estimated to be roughly twice that of term infants for a variety of factors, not the least of which is the work of breathing and other high metabolic demands. There is a suboptimal nutrient accretion, and they really miss out on that third trimester transfer of nutrients from the mother to the infant that can contribute to rapid growth. There is difficulty providing sufficient nutrients within a weight-appropriate volume of human milk and then, where I've sort of spent a good deal of my interest is in the variation in composition of human milk.

Adequate Growth and Preterm Infant Outcomes

Let's transition to talking about what are we actually trying to achieve in nutrition, and that is optimal growth, right? So, we know that growth faltering is the thing that we're trying to prevent. Beyond just being preterm, there are risks associated with growth faltering, including late-onset sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, and retinopathy of prematurity. And we know that our goal is to provide sufficient amounts of nutrients, using that term blanketly, that would approximate the rate of in-utero growth. That is an incredibly difficult thing to do. I think that this philosophy is well-stated, but if you spend any time in the neonatal intensive care unit (NICU), this is achievable—but it is difficult.

The benefit of achieving optimal growth is that we know that there are short- and long-term neurodevelopmental outcomes that are improved with optimal growth, so those kids who stay on their growth percentile have better outcomes on their 18- to 24-month Mental Development Index tests (MDIs). We also know that they do better in school. They miss less days. There's less need for accommodation. They have better grades. There are some suggestions that body composition either associates with or is a modifier of these trajectories. So, if we improve growth, we potentially improve their body composition. And what I mean by that is better lean mass, less fat mass, and better length; and therefore, some of these educational outcomes are obtained.

One example of this is shown here. So, if we look at weight gain and we track this along percentiles, or *z* scores as stated here, from a week at birth, assuming that first diuresis has occurred, that we've nadired in weight and now are looking at growth trajectory from that seventh day out to term, we can see that kids who maintain their *z* score or improve their *z* score have better neurologic and performance outcomes (psychomotor outcomes) directly and strongly associated with weight gain. BMI and head growth also have some modest association. But weight, the easiest thing to measure in the NICU, is a good correlation with future neurodevelopmental outcomes.

We know that there are some strong risk factors for preterm infants in experiencing growth faltering. The lower the growth rate and the younger gestational age, the more likely you are to develop growth faltering in the postnatal period. We know that males tend to experience this at a higher rate than females. Certainly, comorbidities, the things that we have to do to help preterm infants survive (particularly mechanical ventilation, steroids and diuretics) contribute to a higher metabolic demand. Those infants that have experienced intrauterine growth restriction really are set up to experience growth faltering, but also periods of rapid weight gain, which is probably detrimental as well. And then, 1 thing that we can actually do something about, which is nutrition. Infants who experience poor nutrition are at a significantly higher rate of growth faltering, but again this is—and the point of this talk—[that] hopefully we can do something about that modifiable risk.

Composition of Human Milk

I think, again, understanding what we're trying to provide and whether or not the milk meets those needs is the first step. There are a lot of factors—both maternal and environmental—that influence the composition of milk. There's a good body of evidence looking at both maternal prepregnancy BMI and postnatal weight loss as affecting the milk composition. Age, race and ethnicity of mothers, geographic location, diet, certainly genetics. I think 1 of the strongest influences is milk volume. We have some really strong trends—and I'll show this in a minute—the effects of milk volume on the content of human milk. Certainly, gestational age and sex play a role, and then a lot of attention has been paid to early and late milk, both in the preterm and term infant, and that obviously has some key differences in the nutrition content of those stages.

Then there's environment, and when I talk about environment, I'm talking about the whole thing. So, how do you pool your milk? Do you do sequential feedings? Do you pool 24-hour samples? What are your thawing practices? Has milk been pasteurized or heat-treated (as would be the case with donor milk)?

A couple of years ago, in 2021, we performed a sort of narrative review of the composition of preterm milk, really seeking to understand what had been done to that date. What was somewhat surprising was really the lack of good studies out there, particularly good studies done recently. We identified 27 articles dating back to 1984. You can see here on the right, we sort of labeled when these articles were identified according to publication date, and there was a smattering in the early 80s and then a few sort of hit or miss throughout the 90s and 2000s, and then, more recently, that return of attention has come back in the 2010s. But key to this was that the vast majority of these papers were published in an era when 28-week deliveries and survival were maybe a little less common. And certainly, there was an underrepresentation of Black women in all of these papers. And so, 1 thing that we sought to fill in the gap was to provide more data on those 2 particular populations.

With the help of Amy Gates, who was working on her PhD thesis at this time, we performed a prospective analysis of human milk from preterm infants. We identified women who delivered at less than 36 weeks. We enrolled almost 40 women in the study. We pooled the 24-hour milk samples at 7, 14, 21, and 28 days, and then we extracted a sample from that 24-hour pool in order to perform a macro- and micronutrient analysis. One key part to this, and I want to highlight, was that the mean gestational age was 28 weeks, but the range was 22 or 23 weeks up to 33 weeks, and about half or just under half were less than 28 weeks at birth. So, this was the largest analysis of the preterm infants that we're caring for today.

I also want to draw your attention to the fact that the vast majority of women enrolled in this study were African American or Black, and I think this was really a tremendous shortcoming in the literature. And I think you'll see why here in a few minutes.

So, just some observational points about the aggregate data. We took all the samples and analyzed the energy, fat, protein, and carbohydrate content, you can see these trends over time. Energy stays relatively flat; we know that to be true. We know that fat is sort of variable. Some of these peaks that we witnessed at 14 and 21 days dissipated by 28 days. Carbohydrates, similarly, very, very flat (roughly 7.5 g/dL, almost all lactate). But protein had clear trends of diminishing over time, and this reflects the known literature: early milk is usually protein-dense, and that protein content slowly dissipates over time and reflects more closely what we see in term infant milk.

What I think was most striking was some of the differences between Black and White mothers and in less than 28-week and greater than 28-week infants. One thing that stood out to us very clearly was the differences between Black and White mothers. Here in the left graph, you see the protein content at each time point in Black mothers (in brown) and then in White mothers (in blue). You can see that there is a statistical difference in those trajectories. Black mothers sort of persist with a higher protein content in their milk than Caucasian mothers. In fact, sort of sitting right over 2 g/dL vs our Caucasian mothers. What was also interesting was when you looked at the protein content of that milk and included the volume of milk that each mother was producing, not only was there a downward trend of protein content, which we saw reflected in the big aggregate group, but that trend was aggravated by the volume of milk. What I mean by that is that moms who produced larger quantities of milk at each of these time points tended to produce lower protein quantity within that milk, such that high-volume milk tends to be low protein in content.

What is striking is that, as you might expect and certainly in the Southeast where I am, Black mothers tend to produce less milk and certainly in this grouping of about 38 women, we saw significant differences, particularly in that 14- to 21-day time point, between the volume of milk that was produced. Now, mothers started and ended at the same time point generally, but in this cohort, we saw differences in the volume of production such that you could easily make an inference that Caucasian mothers producing higher-volume milk were then producing lower protein content within that milk, whereas African American or Black mothers who persisted in producing milk produced a lower volume of that milk, but that milk was protein-dense.

When we looked at less than 28 weeks or really small, extremely low gestational age newborn (ELGAN) infants and greater than 28 weeks, we did some of the same analyses. So, in the blue, you'll see in both of these graphs, the less than 28-week infants, and in the purple, you'll see the data from infants greater than 28 weeks. And you can see that the carbohydrate concentration in extremely preterm infants is higher, and it persists at that higher level throughout the first month after birth, whereas older preterm infants have a lower quantity of carbohydrates in that first early milk, and that carbohydrate content falls off dramatically as the milk matures.

Conversely, if you look at sodium content in using these same outlines, you see that extremely preterm infants, less than 28 weeks, produce really low quantities of sodium within the breast milk, and it's relatively flat (around 20 mg/dL), whereas older infants (28 to 32 weeks) produce a higher content of sodium in the breast milk, but also that sodium content increases over time. And I'll remind you that these categories were roughly similar, about 16 infants were less than 28 weeks out of the 38 total, and about 66% of the population was African American.

Variations in the Nutritional Content of Human Milk

When we look at the variation in mother's own milk composition, we like to do this comparison between preterm and term milk because I think that it really clarifies where the differences are. Now, I want to focus on the areas that have entertained the most interest when it comes to growth, and that's the protein differences, the differences in sodium, and—more recently—some of the data coming out on differences in zinc. As you can see here, we estimate that preterm milk is protein-dense with sort of a recognized concentration that, in some cases, doubles that of term milk. The sodium content similarly is roughly 60% to 2-fold higher in preterm milk, and then the zinc content similarly is much higher in preterm milk.

So, a couple of things that I want to highlight before we dive a little bit farther in is that the key takeaways from what we have shown is that preterm human milk is dynamic, particularly in that first month of lactation. There are some constituents that are relatively stable. Energy supply is stable. Fat and carbohydrates—relatively stable. But some of these contents are very dynamic. Protein diminishes over time. Sodium seems to be very volume dependent, so you have ebbs and flows in the amount of the sodium that's excreted into breast milk. There's a persistently low content of zinc.

Other factors that I want you to take home with you are that maternal race and ethnicity probably plays a role in the protein content of milk, and it's probably mediated through the volume that these mothers produce. And so I would really like to emphasize that if you're supporting your Black and African American mothers, trying to really support good volume production. Supporting lactation is going to be key to getting good milk and sustaining that. And then gestational age—there are going to be key differences in, particularly, sodium content, according to gestational age.

The big question I think in today's world is what do we do with donor milk and how do we consider that? Well, we know that the American Academy of Pediatrics (AAP) and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have come out with good recommendations that donor milk is the preferred alternative for mother's own milk when it's either unavailable or insufficient, and this is true particularly in the first days to weeks of life. We have to recognize that donor milk has some key characteristics that differentiate it from preterm milk or mother's own milk. Donor milk is primarily expressed from mothers of term infants. There are examples of preterm mother's own milk that's being pasteurized and pooled and available for purchase, but it's certainly not the majority. Most of this milk is actually collected at late stages of lactation, so these are term deliveries, and this is the excess milk produced at later stages. We also have to recognize that it's pooled from multiple mothers, so there are benefits to that. You're sort of evening out the playing field so those mothers that are nutrient-rich vs nutrient-poor—you're providing more consistency in the product. But there are some downsides to that too. That large volume of milk is going to make up larger parts of the pool, and we know those larger volumes are probably less nutrient-dense.

And then, importantly—and I think not to be overlooked—is the pasteurization, or the processing, that is important to destroy the microbes and to prevent any infectious risk. But recognizing that heat inactivation or sterilization process probably destroys other active components in milk.

So, what about differences in growth with mother's own milk and donor milk? This is a hot topic. I think there's a lot of good recognition—at least anecdotally and now some emerging research—to support that there's a population of kids on donor milk that appear not to grow as well. We know that donor milk is recommended because it reduces necrotizing enterocolitis. A lot of that data's based on comparisons to formula. We also know that there's some emerging evidence, as I mentioned, showing that short-term growth may be compromised in a subcategory of preterm infants exposed to donor milk. I wouldn't go so far as to make any strong statements here. I think that over the next several years, we're going to see more clarity on this topic, particularly with secondary analyses and some of the prospective studies coming along. And what is most unclear is what are the long-term effects. So, we have a widespread adoption of donor milk—there was a recent study suggesting that upwards of 95% of level 4 NICUs and 85% of level 3 NICUs provide donor milk. It is prevalent. The question is how does it work and what is it providing as far as outcome data?

This processing of donor milk has pretty clear effects on the milk composition itself. So, we know that there are clear changes in some of the bioactive components. The heat inactivation certainly inactivates enzymes, which are highly heat sensitive. There is suggestion, although I would say limited data, on the potential of the heat inactivation and sterilization process in cell death. You know, we know that breast milk is a tissue, it's providing not only nutrients and fat and protein, but it's an active living tissue, so there are cells and immunoglobulins that are transmitted. And so how the processing of that milk affects that composition is a little hard to know at this point. We know that there is probably a reduced caloric density. We also know that lipids are highly susceptible to heat inactivation, and disruption of some of the fatty acids, and there is good data now on some of the vitamins that are reduced, as well, in the pasteurization process.

In this graph, what we've done here is we've taken the recommendations based on preterm feeding guidelines from Koletzko and ESPGHAN and we've looked at our data for early preterm milk and mature preterm milk, and then compared that to donor milk. And what we're trying to show here is if we take those recommendations, what would it take for us, as far as the supplementation process, to achieve the midpoint of that target range. So, for instance, protein. We're targeting 3.5 to 4.5 g/kg of protein, and so the content of protein is variable, based on lactation stage and prematurity. What would it take for us to meet that midpoint as far as the content of protein within milk at these points? If you look at our early preterm milk, based on the content of about 2.2 g/dL, you're still going to have a shortfall of 0.5 g/dL to reach that 4 g/kg/d of protein. As that preterm milk matures, that deficit is going to grow to just over 1 g/dL, but when you compare that to donor milk, that deficit approaches almost 2 g/dL, such that the estimated protein content of donor milk at about 1 g/dL is roughly a third of the content that is actually needed to meet the recommendations set forth by Koletzko and ESPGHAN. You can see here that just achieving the midpoint is going to be difficult for protein in donor milk.

Similarly, if we look at the same recommendation for sodium, we see that sodium in preterm milk is going to be roughly half of the total sodium content needed for preterm infants. That sodium deficit will grow as preterm milk matures, but interestingly, donor milk provides very little sodium—on the goal of about 10 or 11 mg/dL, such that your shortfall in sodium is roughly 5- to 6-fold that amount in donor milk. So, while donor milk is insufficient in protein, it is much more insufficient in sodium and really warrants close observation of sodium and replacement.

And then zinc. Zinc has a really emerging interest over the last several years. Zinc is poorly expressed in milk of all stages, such that you can see in order to provide adequate amounts of zinc, you're really going to have to look to supplementation, whether it's preterm milk or whether it's donor milk.

Let's return back to looking at the comparison between preterm mother's milk, term milk and then the recommended preterm intake. As you can see here, the energy differences, the carbohydrate differences—not terribly different between preterm and term milk. The key differences are in protein, sodium, and zinc. We know that iron is poorly expressed in all stages of milk. We know that calcium is very low in both preterm and term milk. And in order to meet these recommended nutritional requirements, we really have to look to alternatives or supplementation of both preterm and term milk to reach these recommended values.

Best Practices for Human Milk Fortification in Preterm Infants

And this brings me to the point of human milk fortification. So, we know that term infant formula and unfortified human milk do not meet the nutritional requirements for preterm infants. I think that there's widespread adoption of this idea that we have to provide supplemental nutrition beyond either mother's own milk or donor human milk to meet these goals. And just to amplify this point even further, a meta-analysis of almost 1,500 kids showed that human milk fortification was associated with growth benefits during hospitalization. So, these are short-term outcomes. Better weight gain. In fact, nearly 1.5- to 2-fold difference in weight gain. Increased body length, which is critical for optimizing distribution of fat and mass, and then better head circumference growth.

The question then becomes: what are the best practices for fortifying mother's own milk or donor milk? And I think this is an area of controversy. I don't feel like I'm going to answer every controversy, but I do want to give you some food for thought.

So, if we look again at the rationale for fortification, I return to this graph that I just showed you a little bit ago. The most recent recommendations, published just in the last 2 years by Koletzko and ESPGHAN, recommend that we consider a feeding volume up to 200 mL/kg/d for preterm infants. In recognition of that fact, what volume would it take to reach some of these goals without fortification? Well, our protein volume in mL/kg/d for mom's milk would have to be nearly 220 mL/kg. Again, assumptions I'm making here is that you take the lowest content of protein in preterm milk, the lowest content of protein in term milk, and that is to meet the lowest recommended value. But 220 mL/kg/d of mom's milk or 390 mL/kg/d of donor human milk in order to reach the recommended threshold of 3.5 g/kg/d. That's a lot.

It's even more dramatic when you look at sodium and some of these other supplements or nutrients. To reach the sodium goals, you're going to need at least that volume, but what is most striking is calcium and zinc require over half a liter of fluid per day in order to meet the calcium, zinc, and phosphorus goals. Now, we know iron is poorly excreted in breast milk. I think almost every center recognizes that and supplements with iron. But the question is, how many centers are recognizing the shortfall of zinc and sodium and some of these other nutrients and trying to target better delivery of those nutrients?

So, what are our goals for human milk fortification, recognizing that fortification is necessary? Well, number 1 is to augment but not replace—so, to supplement. We don't want to take all of that important mother's milk that we're providing and replace it with fortifier. That's not the goal. The goal is to augment the nutritional balance. Avoiding displacement, particularly mother's milk, is important. We want to support mothers and their milk supplies, and the ultimate goal is to limit formula exposure when necessary. And, you know, all of this is in light of providing optimal nutrition in a limited volume milk.

Observationally, we know that it takes a while to meet some of these goals. This was a nice study done just a handful of years ago published in the *Journal of Parenteral and Enteral Nutrition* looking at how long it takes to reach the protein and energy requirements for our preterm infants. And if you look at both less than 1,000 g and our larger preterm infants, they sort of mirror one another. It takes us roughly 4 to 5 days to meet some of these protein goals and even longer to meet the energy demands. Most places have developed a cautious approach to nutrition, where advancing feeds is done according to a protocol in a staged approach that ultimately leads to these deficits that we experience every day.

When we're thinking about fortification, we recognize that we ultimately do need to fortify. There are 3 main buckets or schools of thought around fortification. So, the first, and I think most common, is standard fortification—that is, I'm going to provide a certain amount of fortifier to a certain volume of human milk, and I'm going to standardize that practice, regardless of the gestational age of the infant or other factors to be considered. This is easy and, I think, for most centers and for most babies, this is rational, cost effective, and reasonable. We know that there are some assumptions being made that human milk is standard and that it's roughly producing 1.5 g/dL of protein, and it's roughly 20 kcal/oz. In reality, we know that not to be true, but those assumptions are valid for most infants.

The second bucket is this adjustable fortification strategy. There is a little bit more labor to this, but it is cost efficient, and it's really targeting certain values. Some centers will use serial blood urea nitrogen (BUN) measurements in order to optimize the protein intake in the human milk. They will provide additional protein supplementation in order to drive that BUN north of 10 mg/dL. And there are variable caps on when they might reduce that protein content.

And then, more recently, there's been really exciting data on the idea of targeted fortification, and this really hones in on the variance between mother's own milk based on a lot of factors that we've already described, including lactation stage, but also recognizes that we, using standard or even adjustable fortification and analyzing milk on a regular basis, may still require more nuanced approaches. These approaches are intensive, from a personnel standpoint. They require specialized equipment, and they're definitely the most costly (in fact, somewhat cost prohibitive at this stage for many centers).

Variations in the Nutritional Content of Human Milk

If we look at standard fortification—again just highlighting some of the limitations—there's really no accounting for the variation in human milk over time, recognizing there are key differences in early milk and late milk. It may not always meet those nutritional requirements for preterm infants, and 1 of the key shortcomings will be in the protein. There have been observational studies—really some decent evidence but limited—suggesting that these practices result in slower growth, and that's particularly true probably for a subpopulation of kids who are already at risk for growth faltering.

One of the best studies to date was published just about a year-and-a-half ago and looked at standard fortification vs targeted fortification and the effects on nutrient composition within the milk. So, this was a double-blind, randomized, controlled trial of infants less than 3 weeks. Those in the control group got a standard fortifier and then, in the targeted fortification group, they received attention to protein, fat and carbohydrates, trying to meet certain goals of delivery. As you can see, protein, carbohydrates, and fat (in the red on the far left) is the standard fortification control. And the intervention is, on top of the standard fortification, the analysis of that breast milk before the addition of the targeted fortifying agent. And then the intervention where it says SF+TFO, that is the analysis of that milk after the targeted fortification. So, you can see here that this is preterm mother's own milk. It maybe marginally approaches the recommended goal range in both the control and the intervention groups. The protein content appears to be at the high end of that range after fortification. Similarly, carbohydrates experienced the same trend. But fat is really dense in all of the milk and did not change dramatically with the intervention.

Important to note here is that the authors or the designers of this study tried to target proper protein—the total energy ratios—and I think that that is really important in interpreting this study. When they performed the targeted fortification in raising the protein content, they similarly raised the carbohydrate content to maintain that balance of protein to total energy.

What were the results of this study? Well, when they looked at standard vs targeted fortification in the whole group, they compared growth trajectory at 36 weeks, and they saw higher growth (larger, better weight gain) in the targeted fortification group, a difference of roughly 200 to 220 g. And when they looked at the growth velocity over the 21 days after birth, they saw better growth velocity at 21 vs 19 g/kg/d in the standard. Now, 1 thing to point out here is that our goal growth velocity tends to be about 15 g/kg/d, and so the standard fortifying approach definitely was well within that goal range of 15 or better, and the difference here is certainly better. What we still don't know is: is there a ceiling effect growth velocity? Remember our goal of providing adequate nutrition to mimic in utero growth during these periods, and that is roughly 15 to 20 g/kg/d. So, the question remains is "good" good enough, or is better the optimal goal? I would say that, while there was a clear difference in the growth outcome here, both were well within the goal for growth velocity. And I think this also highlights that if you pay attention to something like this, you're probably going to get your preterm infants to grow better. So, participating in the study probably had a pretty decent effect on the control group.

Again, looking at other studies of adjustable vs targeted fortification, you can see here that when we pay attention and we do a much more intensive job of measuring protein and adding protein, we can achieve higher protein intake here at 4.5 vs 4 g/kg/d, and then we can see better weight gain (23 vs 18 g/kg/d). Again, both well within the acceptable range of 15 to 20 g/kg/d.

And then I've had this up on a couple of slides, and I just want to highlight that Koletzko recommends 3.5 to 4.5 g/kg/d of protein. If you haven't read the most recent ESPGHAN recommendations, which just came out late 2022 or 2023, ESPGHAN actually lowered their general protein recommendation to 3.5 to 4 g/kg/d. They do remark in there that for kids who experience growth faltering, 4.5 g/kg/d can be the goal. But I [will] just make the notation here to say that many of these studies were designed with the idea of providing the top end of that 4.5 g/kg/d range. Whether or not that's necessary for every infant is still up for debate.

Returning now to looking at deficits. If we look again at our early preterm milk, late preterm milk, and donor milk (again trying to reach these lowest measured values) how far short would we be if we sort of settled in at 150 mL/kg/d (which I think is a pretty standard goal volume for preterm infants)? Well, the point of this slide is to show you that you can clearly hit your caloric goals with any of the milk that you have. They're going to be somewhere in the neighborhood of 80% to 90% of your calorie goals at 150 mL/kg/d. So, a slight increase in the volume target, you can adequately provide sufficient numbers of calories to meet that goal. What is the major problem and the reason that calories should not be the goal of our nutrition program, but composition, is that protein deficits, particularly in donor milk, are going to come not even to 50% of your total goal, even at 150 mL/kg. Your sodium requirements are going to be tremendously high, particularly in infants who receive donor milk. Calcium is going to lag significantly. You're going to be somewhere in the neighborhood of 25% to 30% of your target goal at 150 mL/kg and, as I've said before, zinc is poorly expressed in milk, and you're going to come nowhere close to meeting your goals, even at max volume. So again, just setting the stage for fortification. Fortification is key.

When we look at this, I think 1 of the key drivers (at least in our unit) for why we choose the products that we do is the protein content and the composition. As you can see here, if you look at the 5 major available fortifying agents in the United States, you can see that the protein content varies between these products and that Similac provides an additional protein supplement to bring that content up on top of these fortifying agents.

So, if we said that sodium content is totally deficient, so if we look at the amount of sodium in these 3 major products, at each of these volumes, you can see that really only the human milk–derived product reaches the very lowest threshold of sodium content at 150 mL/kg/d. Another way to diagram that: sodium levels are not going to be met with standard fortification—we've really got to pay attention to sodium. So, even if you're providing fortifying agents, you really probably ought to be supplementing with additional sodium, and that's a practice that we perform here at the Children's Hospital of Georgia.

Finally, a couple of other considerations. This is unpublished research that we've performed in just the last year or so, but what we've tried to do here is to take into account: if you're choosing a fortifying agent and you're providing a number of different caloric densities for those agents, what are the effects on things like displacement? If you're trying to provide as much mother's own milk as possible, displacement is probably 1 of the key drivers in the decision making around what fortifying agent to use. And, as you can see and would expect, if you increase the amount of fortifier you're giving, you're displacing more milk. But what I want to draw your attention to is that, as you approach that 26 to 30 calorie goal, you're displacing somewhere in the neighborhood of 30% to 50% of mother's own milk. So, if we're trying to optimize our nutritional program to provide as much mother's own milk as possible, when you're using or trying to achieve 30 calories-per-ounce milk, you're going to be displacing somewhere in the neighborhood of 50% to 60% of mother's own milk. And this is particularly true for the human milk–derived products.

A similar consideration is osmolality. This has been gaining some traction here in the last little bit. If you look at these fortifying agents—and these are the standard commercially available liquid fortifiers—you can see here that we add more fortifier, the osmolality, or the amount of things in the volume of milk, goes up in a linear fashion. Well, the FDA recommends a threshold of 450 mOsm/kg H_2O. That is the maximal amount of things in the volume that we are supposed to provide to infants in order to prevent some of the associated effects, like feeding intolerance. If we look at these numbers, you can see here that several of these products approach this 450 mOsm number and surpass that relatively commonly used caloric density. And for the Similac products that have provided an additional protein supplement, even at low caloric densities, you're now over this recommended threshold.

Now, what this means for necrotizing enterocolitis or even the idea of feeding intolerance is still to be debated, and a lot of these recommendations are based on old data. So, I don't want to over-emphasize this, but it is a part of the consideration process in choosing a fortifying agent.

So, just to summarize some key takeaways when we think about how we optimize human milk. Well, I think the first thing that I want to emphasize is that preterm mother's own milk is dynamic, and I think that we recognize that. It's protein-rich, particularly in that first week, and I think this is a key reason for sequential feeding. Here, at the Children's Hospital of Georgia, we feed milk as it's produced: we label milk, and we provide the early milk first and the more mature milk later on. And I think this is a good rationale—not just for the protein but sodium and other constituents as well—I think these are good rationales for sequential feeding.

We know that there is higher protein, sodium, and zinc content in the first month of life, and that is dramatically different than what's seen in donor human milk. And then, as I kind of alluded to, I think that, even with fortification, we really need to pay attention to how much sodium we're providing, and we're probably not providing enough. Here and (I think) many centers are now routinely supplementing additional sodium, somewhere on the order of anywhere from 1 to 4 mEq/d. Here, we begin that process at day 10 of feeding.

Recognizing that there are some other factors that may influence composition of mother's own milk. I've alluded to 2: gestational age and race. I think we've well-described the influence of lactation stage, but I think these are equally important to consider. And then pooling. If you are pooling mother's milk, I think that that allows for even distribution of nutrients and is ideal if that practice is possible in your unit.

Preterm milk is not the same as donor human milk. I think that is another key takeaway, and I really want to discourage conflating preterm milk with donor's milk when you're reading the literature. A lot of early studies showing the benefits of human milk were really looking at mother's own milk, and some of that evidence has been extrapolated to donor milk. And I'm just not ready to be there just yet. I think donor milk is great, but I think we have to be a little bit restrained in what we think it can do. We know that, if pooled and pasteurized, I've discussed some of the effects of that may be true. We know that it's likely variable in composition. Some of that variability is evened out with pooling practices. We know that it has low amounts of protein, sodium, and zinc. We also know that there are particular considerations around the differences in fortifying donor's milk vs mother's milk. Displacement may be more important with mother's own milk than it is with donor milk, depending on the fortifying agent that you're choosing. Osmolality may be an important contributor to feeding intolerance, so if you feel like that is clinically important to your unit, really look at that data.

In our practice here, we use a high-protein fortifier when we hit 24 kcal/oz, and we use the standard protein for either early milk or milk as we move our caloric density north of 24 kcal/oz. And that allows us to really optimize the protein delivery to these infants. And then, I think it's important to recognize that, while powdered formula may meet the caloric needs of preterm infants, it's going to be woefully inadequate to provide sufficient amounts of calcium, sodium, protein and zinc.

Variations in the Nutritional Content of Human Milk

Audience Questions

Editor's Note: This is a transcript of live audience questions with the educator's responses from the presentation on March 22, 2023. It has been edited for clarity.

✧ If support and funding can be obtained, do you recommend human milk analyzers for all NICUs? Why or why not?

We don't have a human milk analyzer. I think it's something we're attracted to because our NICU not only values the information that can be obtained from a human milk analyzer, but I think we also have research intentions for its use. I think it's a great product, and if you have the resources and the personnel to use and obtain such a product, I think it's great. More information is rarely bad, but it is intensive. Most places will analyze milk once or twice per week. For research or clinical studies, as many as 3 or 4 times per week. I think it's sufficient to measure once a week if you do have a human milk analyzer. And I think if you're making good decisions and you're seeing better growth, then, yes, the information obtained is valuable.

✧ Building onto that, what fortification procedures do you recommend for NICUs that do not have access to milk analyzers?

I think that that's where, if we can expect a couple of baseline assumptions, there are differences in donor milk and preterm milk. And if you recognize those differences, then your fortification strategies have to be a bit nuanced. The beautiful thing about having products that are very similar but only different in the protein content (eg, the sodium, magnesium, and calcium are stable), but you're able to provide additional protein, then you can really have a slight nuance to your fortification strategies, where you recognize the low protein in the donor milk, you can then provide a high-protein human milk fortifier for infants who are receiving majority donor milk. For that early preterm milk, you can provide standard protein in recognition that it's already protein-dense. I think that having some slight variation in the tools that you're able to provide allows you to just take on some very simple first steps. If you're doing standard fortification and you're getting good results, go for it. I think there's no reason to change. But if you're experiencing a subset of kids that are growth faltering after birth, then maybe changing up 1 or 2 things might make a big difference. You know, going with that high-protein fortifier, particularly for donor milk, might be all you need. Or going with that high-protein fortifier for 24 kcal/oz might be sufficient as well. And again, paying attention to the other nutrients like sodium and zinc supplementation.

✧ There are so many important nonnutritive properties of human milk, such as antibodies, immune cells, and other bioactive components that can impact the microbiome. What do we know about how these might differ between preterm, term, and even donor milk?

That's a great question. I will say these are things that we are interested in, moving forward. I think we have some forthcoming publications that will highlight some of the activities that we've done in this area looking at composition, and we are now diverting our attention into some of the bioactive components. But I think that there's still just not enough to be known about whether there are key differences between preterm and term milk when it comes to things like the microbiome or the cells that are expressed in that milk. Whether or not there are key differences, whether those differences matter for the preterm infant, whether there're changes in the oral microbiome if they're feeding (as we see with the differences between vaginal and Cesarean birth—there are key differences in the gut microbiome in those 2 populations). Would it be true that infants who are provided mother's own milk might have different oral and gastrointestinal microbiomes compared to donor milk where it's been pooled and pasteurized? Those are key questions that remain to be answered.

✧ Do you add sodium supplements directly to feeds and, if so, how does that affect the osmolality and thereby the tolerance?

We don't. All of our supplements are controlled by the pharmacy here at the Children's Hospital of Georgia, so we do not add them directly to the feeds. We provide them as medication. We routinely supplement with sodium, zinc, and magnesium, and those are done as timed medications. We try to split that out into 2 times a day for most of those. I think magnesium is once a day. But the goal there is we do it away from the feeding, and the idea is to alleviate some of the concern about osmolality, and I think that's an important consideration. In an ideal world, I think we would have some sort of nutritive supplement that could be added to feeds directly.

✧ Do you have a protocol for transitioning off of human milk fortifier?

We don't. That's an area of interest for us. Right now, we transition our infants off of donor human milk at 1800 g. With that transition on to formula, that's sort of the end stage for that. We have a variation of practice here. Whereas we do send some infants home who have good growth on fortifying agents, and we'll send them home on mother's own milk with a fortifying agent. For much older babies, say at 44 weeks corrected, we tend to convert. If we need additional calories, we'll provide other avenues, maybe a high-calorie formula, 1 feeding per day, just to provide that extra nutrition and supplement some of those missing ingredients from mother's own milk. So, we have a little bit of variation of practice, depending on the age of the infant and the growth trajectory.

✧ We talked about mother's race, but do you have any new information regarding other factors that impact human milk content, such as maternal physical activity or pumping practices?

That's a great question. We talked a little bit about sequential milk, but I've had this idea of looking at hindmilk vs foremilk. You know, if you're taking a 24-hour pooled sample, and you're probably gathering more milk than you're actually going to provide in that 24-hour period, should we preferentially provide hindmilk or foremilk? And I think some of those questions are really interesting. They're just difficult (but important) questions to ask. And if we get to the point where we're fortifying well and we're providing sufficient amounts of nutrients, I think a lot of times those more nuanced questions probably only matter for a small subset of kids.

⦿ *To complete this course and claim credit, click here, or go to: https://pnce.org/Variations-Human-Milk*

Abbreviations

AAP	American Academy of Pediatrics	**ESPGHAN**	European Society for Paediatric Gastroenterology Hepatology and Nutrition
BUN	blood urea nitrogen	**NICU**	neonatal intensive care unit
ELGAN	extremely low gestational age newborn	**MDI**	Mental Development Index

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This activity is supported by an educational grant from **Mead Johnson Nutrition.**