Bridging the Protein Gap: Navigating Variable Milk Composition and Delivery in High-Risk Neonates and Infants

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Introduction: Why the Emphasis on Protein?

Dr. Ting Ting Fu: We're going to start first talking about protein, which is one of my favorite topics. If you're sitting here this early in the morning, you are very well aware that amino acids and protein are really important to our human physiology, and especially critical during our period of fetal development. It serves not only as an energy source, but also a building block, and a signaling molecule, which is really important for organ growth, cell structure, remodeling, and immune system development.

Protein accretion in the fetus increases throughout gestation and pregnancy. You can see in this graph how that really ramps up towards the end of gestation. This is through the placenta, delivering it directly to the fetus, in order to have that highest impact, especially in the last trimester. Unfortunately, preterm birth abruptly cuts off that supply. Most of our preterm babies are missing out on that last trimester, and that really important critical period of protein accretion.

Protein intake is incredibly important for growth in preterm infants. This is a systematic review and meta-analysis of 10 randomized controlled trials (RCTs), and probably one of my favorite graphs. And again, if you guys are here, you've probably already seen this before, really showing that the amount of protein that you get is associated with the weight gain that you subsequently see. In this study, they found that you see an increase in almost 9 g/kg/day in weight velocity, for each 1 g/kg/day of protein intake.

Protein requirements in infancy and childhood: we're going to kind of map this out throughout this talk today, but for our very low birth weight preterm infants, I usually think about 3½ to 4 g/kg/day is the intake I'm trying to provide, and up to 4 g/kg/day. I will say, as my bias in our unit, we shoot for 4½. And then, as you can see, as babies get older and as children get older, that protein requirement goes down over time.

Human milk, as you are aware, is the ideal nutrition for newborn infants. I think a lot about human milk composition. Milk primarily is actually water (88%) which obviously makes sense, because this is how our infants are staying hydrated. Carbohydrates make up about 7%; fat, 4%; and then, protein makes up about 1% of human milk. We usually think about concentration in terms of grams per deciliter—that's the unit we usually use—but you can kind of think of it as the equivalent as percentage in protein content, and preterm milk is typically higher than that of term milk. And term milk, we've put in parentheses, is donor human milk, because donor human milk most commonly comes from mothers who have had term infants. Protein intake, we'll kind of map that out to, if you were feeding it, that infant, 140 kg/day, up to 200 kg/day, and what that would look like, if you were unfortified. You can see those values are pretty far off from that 4 or 4½ kg/day. Feeding unfortified milk, you're going to have a gap of up to 3 g/kg/day, if you're shooting for those appropriate targets. If you don't have enough protein, you build up a protein deficit.

NICU: Human Milk Composition and the Protein Gap

Dr. Ting Ting Fu: I'm going to spend a fair amount of time talking about human milk composition and the protein gap today. One of my favorite phrases that I tell all of my trainees is that not all human milk is equal, or 20 kcal/oz. The composition of human milk really differs, based on a lot of different factors. Part of it is maternal, including her age, body mass index (BMI), her own diet. A lot of it depends also on the infant. Again, as I mentioned, term vs preterm milk is different. There's a physiologic stage of what lactational stage you're in. If you're talking about milk expression in the morning vs at night, that protein and fat content's going to differ. The amount of time in between feedings or milk expressions matter, as well. On the right, you can see a picture of really how that milk progresses in the first month of life, going from colostrum, that liquid gold, through transitional milk and that mature milk, on the far right. And even just visually, I think you can tell that the composition of these substrates is very different. At the bottom, just actually, a personal picture, this is foremilk vs hindmilk from my own pumping sessions. The foremilk on the left there, you can see is more watery. It's actually quite rich in protein. And then, the one on the right is hindmilk, which is higher in fat content.

I've already mentioned once that protein content differs by gestational age, but it also differs over time. This is a really nice graph looking at a prospective study of about 38 moms who delivered preterm. So not even the term moms, but just in preemies. You can see how that protein content really decreases steadily over time. Even though I'm not showing you what it would look like for a term infant, mother of a term infant, that graph essentially shifts down, if you can imagine that. Our protein content is decreasing.

This is really relevant, as I mentioned earlier, that donor human milk typically comes from others who've had an infant at term. You're talking about more mature term milk, compared to preterm milk, and that's going to look very different. This was a study that looked at 15 different donor human milk samples from 7 different sources. I believe 2 were commercial, and 5 were from Human Milk Banking Association of North America (HMBANA) nonprofit milk banks. When they looked at those, again, they compared it to both early preterm milk and mature preterm milk. What they found, in showing the donor human milk concentration, is that it is significantly less than that of the early preterm milk, which is in blue, and still less than the mature preterm milk on day 28.

There is some nutrient variability that can also come with donor human milk. That can come from both the donor level, and also the milk bank level. From a donor perspective, it matters, again, who your donor is, her lactational stage, their lactational stage, and also their diet, how they collected the milk, and again, morning vs night, and all of that can contribute to these different deposits that they bring into their milk banks as they generously donate. Within the milk bank, they typically pool the milk from multiple donors; although, this process can be actually varied from milk bank to milk bank, and then it undergoes pasteurization. The prepooling process can be different from milk bank to milk bank, and some milk banks have also incorporated human milk analysis to help them with that pooling, but every milk bank is different. Another key point I always tell everyone is, just talk to your milk bank, ask them what they do, and learn more about their practices, and I think it'll be really informative for you. The last point here, is talking about mixing practices. As milk banks have developed and increased the technology that they use, I can tell you, I took a field trip to my milk bank, when I was early in my training, and back then we were using Erlenmeyer flasks, giant flasks, to actually pool, and swirl, and combine all the milk. Now, there are actually machines that help automate, and make sure that the distribution of the nutrients is more equal.

Some key characteristics of donor milk to consider. That heat pasteurization step that the HMBANA milk banks utilize is really important for destroying the microbes. Those pathogens—they're really wanting to provide a product that is sterile. Unfortunately, this heat treatment also reduces the activity and the levels of the bioactive components of human milk, which I haven't even talked about today, but there are many, and abundant. The second point we've talked about before, that milk is primarily expressed by healthy mothers of term infants at later in lactation, but there is that pooling practice that can help reduce some variability, but that can also be different across the milk banks.

The changes in bioactive components can definitely impact the milk composition. Certain ones to consider would be enzymes. Lipase—probably one of the most important ones, I think—is affected by pasteurization. It's completely destroyed. When you think about fat absorption, and its impact on fat digestion, it’s a really important loss of that enzyme. There are also cells in human milk that are destroyed by that heat pasteurization. We also see reduced activity levels of many other important components, including enzymes, cytokines, growth factors, hormones, immunoglobulins, etc. There are also micronutrients that are sensitive to heat, including vitamin C and vitamin B6.

I've alluded to Holder pasteurization for a little bit now. This is a heat process, in which that milk is heated to 62.5 degrees for 30 minutes, and it is considered the gold standard in human milk banking. It's what is recommended as a standard from HMBANA, but there are other commercial sources who utilize different methods to process their milk. Another key point to remember, when we think about and review the science and literature on donor milk, is that most of those studies are looking at milk that's been Holder pasteurized, and may or may not be able to be generalized to other methods of heat treatment.

When I think about protein, we talk a lot about that total protein, or just protein in general, but what you actually have to think about, is that there are 2 buckets of nitrogen sources. Because when a milk analyzer is analyzing milk, it is essentially trying to pick up that nitrogen content, if you remember, from amino acids in biochemistry. There's what we call true protein, which is nitrogen from those amino acids, which reflect what we're using for growth and nutrition. Then, there are also these nonprotein nitrogen sources, which include urea and ammonia, and also nucleic acids. And nonprotein nitrogen is estimated to be about 20% to 30% of the nitrogen in human milk. When I see a protein content, whether it's on a milk label or whatnot from like a milk analysis, one of the questions is always, is this the total protein, or is this the true protein? And if it's the true protein, is this an actual measurement of the true protein? Or is it just an estimate where we think, again, just subtracting 20% of that content from what was actually measured as total protein? I think we don't talk about this a lot, but as you guys progress, hopefully after this talk, you will inquire and think

about that component as you're making your clinical decisions.

Donor human milk labels are also not completely standardized in the milk banking process, but many of them do label their milk. If you've never looked at a milk bank label, you typically can tell where it's come from, which milk bank, the lot number or the batch number, if you will. Some may indicate if it's term vs preterm milk, which is really nice. If they are analyzing their milk, they'll also tell you the calories and the protein content, but again, not necessarily distinguishing what's total vs true. Again, I encourage you to talk to your milk bank and ask. Not included on the labels are, typically, your fat or your carbohydrate, although, for my milk bank, when we get our packing sheets, that information is actually on there. It also doesn't tell you anything about the micronutrients, the bioactive components, or how they pooled their donor milk.

Are the milk labels accurate? This is something I've wondered for quite some time. There are a couple of studies out there on this, and I will tell you, the first study I did on this was not the best method. So I kind of redid it with some of my current ongoing work. When we looked at a hundred or so of our current samples from our current study, which we analyzed with the mid-infrared milk analyzer, we looked at what we call the concordance of what we measured with the labeled values. Then we looked to see how many of these samples were within 20% of the labeled value, which is what the US Food & Drug Administration (FDA) requires those labels to be, based on nutritional facts, but 20% is a pretty big variation. We also looked at 10% and 5%. You can see on the top graph here, in terms of the calorie concordance, all of the samples are actually within 20%, which is great. Even within 10%, we had a high proportion. Once you get to 5%, it's a little bit less, but still pretty good, and probably better than some of the other studies out in the literature. That protein concordance is a little bit lower, as you can see in that bottom graph. And the other thing I haven't pointed out is, some of the values were higher, and some of the values were lower. It actually swings both ways.

One caveat to this is, again, knowing my milk bank, and being collaborators with them, I actually know that a lot of these samples were before they introduced that automated mixing. I imagine that, as I continue to do these analyses, that these values may in fact be different now versus when I started this study 3 years ago.

This was another study that looked at how protein may be overestimated. I actually really liked the study. I relied on a human milk analyzer that uses infrared technology, and there are some limitations to how that can be measured. In this study, they actually went back to the wet lab, and measured protein content through biochemical methods. They measured the total protein, and they also separately measured the nonprotein nitrogen, and the amino acids. To walk you through these graphs, and the sample sizes were a little bit limited, but I still think quite informative. The reference protein on that bottom axis in the first graph, that is actually their measured protein. The labeled protein on the Y axis is what's on the bottle. For all of the 6 samples, or for most of them, the labeled protein was in fact higher than what they measured in the biochemical methods, with the median of the overreporting of 0.15 g/dL. When they looked at the total nonprotein nitrogen vs the total nitrogen content, they actually found that there was a higher amount of nonprotein nitrogen than we commonly think. So again, most people think about 20%. And they found that their samples had 33% nonprotein nitrogen. All of this to say that the labels can overestimate your protein, but that doesn't mean that you can't use that information provided you, again, know the limitations of that information.

The takeaways from this section for me, and hopefully, for you guys, is that human milk alone does not meet the protein targets for preterm infants, and that human milk composition is definitely variable, and those differences in protein levels is exacerbated by preterm vs term vs donor milk, among other factors. We really need nutritional interventions to address the protein requirements and make sure that we're able to optimize our nutrient delivery, in hopes of providing good growth, and promoting healthy development in our preterm infants.

NICU: Bridging the Gap With Fortification

Dr. Ting Ting Fu: I'm going to talk a little bit about fortification now, and some of the strategies that we've tried to implement.

For some context, I think as neonatologists, we know a lot about standard fortification, and then there's also what we know in the literature, and commonly with our neonatal nutritionist, adjustable and targeted fortification. Standard fortification is probably what you're all familiar with. We're adding a fixed amount of fortifier to a fixed amount of human milk, and this is typically based on the manufacturer's directions, although it is important to note that manufacturers are also typically assuming that your baseline

protein and energy content is 1.5 g/dL, and 20 kcal/oz. Remember, not all milk is 20 kcal/oz.

There's also the concept of adjustable fortification, where you add potentially additional protein, based on the blood urea nitrogen (BUN) measurements you're getting from the patient. This is a little bit more of a cumbersome process, in making sure that you're able to measure those respective customized levels of protein. I think the other caveat is that BUN can sometimes be a reflection of hydration status, but nevertheless, babies do grow a little bit better on adjustable fortification.

Lastly, targeted fortification is the most accurate, but probably the most cumbersome to implement, in which the macronutrients are measured with the milk analyzer. Based on those values, you can calculate how much of the additional modulars they need to add, to make sure that the protein, fat, carbohydrates, etc, all are able to reach those targets that you're trying to provide. I would say that standard fortification, at least from my standpoint, I sometimes wonder if it's enough. We'll go into one of my studies a little bit later, about why I'm convinced that standard fortification, in fact, does not give us enough protein. And so yes, I personally am trying to challenge this. As a preview, only 11% of the samples that I studied, once fortified, actually were able to reach that 4 g/kg/day target, and none of the samples of donor milk actually was able to reach the 4½ g/kg/day with standard fortification.

I do want to talk a little bit about targeted fortification, because this was one of the strategies that really changed how I thought about providing protein and nutrients to babies. This is a really important paper that came from Niels Rochow and Christoph Fusch, and it's a double-blinded RCT, looking at standard vs targeted fortification. And they enrolled infants less than 30 weeks, and they compared those 2 groups. In that graph in the middle there—their analysis of the protein content—they do report everything in the actual paper, but again, thinking about just the protein today, you can see that the protein content in that standard fortification group is spread, and kind of settles out around that 3½ g/kg/day with the standard fortification. For the targeted fortification group, again, they show you what that group looks like, first with standard fortification, and how once they are able to add the additional protein modulars, they're able to bring that protein level up to closer to that 4 g/kg/day, which was their target. And then for their outcome, they were looking at growth in the interventional period and at 36 weeks postmenstrual age. Infants in that targeted fortification group did have better weight gain and net weight at 36 weeks postmenstrual age. Targeted fortification is a great strategy to demonstrate higher weight gain. Again, there are certain challenges with its use as well.

I work in primarily level 3 NICU, and then I'm also affiliated with another level 3 NICU. And we've tried a few different strategies to address this protein issue because one has a milk room, but I don't have the milk analyzer there. The other one where I have access to a milk analyzer, doesn't have a milk room. Again, working with some practical constraints that hopefully sound familiar to you guys. So how do I actually accomplish this? From one of my initial works, I looked at a cohort of almost 70 very low birth weight infants who were receiving target-pooled donor milk. Milk that we were purchasing from our milk bank that was labeled as 20 kcal/oz. And what we found was that the protein content was still 0.9 g/dL, so akin to mature milk. What we noticed was that in this group, their change in *z* score, that decline in *z* score from birth to 36 weeks was about 0.5 for weight. Then their length *z* score decreased by a whole *z* score, which is pretty profound to us. We were trying to think, again, how can we provide extra protein?

This was actually a bit inspired by the fact that the donor milk that we got—that 20 kcal/oz—again, being friends with their milk bank really pays off. I knew that they were actually skimming the fat off of some lower-calorie milk and putting it in milk that was closer to 18 to 19 to bump it over to 20 kcal/oz, essentially their own method of lactoengineering. Our thought was, can we engineer a higher protein donor milk effectively? We called this donor milk plus, and we developed it actually for clinical use by adding a liquid protein product. It was 6 mL to 90 mL of donor milk. You can see in this table what that would look like for an assumed protein content of 0.9 g/dL—that raises your baseline protein content to 1.9 g/kg/day. Then when you do standard fortification on top of that, that gets you closer to 3.2 g/dL, which at 150 mL/kg/day gives you that 4.5 g/kg/day of protein target. This donor milk plus, we actually started feeding it as early as babies started with their trophic feeds.

Then we wanted to look at how these babies actually responded to it. We continued to follow out this cohort, and we then compared babies who received primarily that original donor milk, donor milk plus, and then also we had a third group of babies who received primarily mom's own milk. We were evaluating both the safety and the growth piece of it. Throughout this, I don't have this on this slide here, but there was no increased incidence of necrotizing

enterocolitis (NEC) or feeding intolerance with donor milk plus.

Then if I can walk you through the graphs. The first one I want to show you as a highlight is the weight *z* score over time. Both the donor milk plus and donor milk group decrease in their weight *z* score, and they're pretty parallel. I will say we did have a higher incidence of growth-restricted babies in that donor milk group, the original one, which is why it's shifted down. The growth in terms of weight gain was actually pretty similar between those 2 groups. That mom's own milk group actually increases and is the only one that demonstrates any catch-up growth, which I think is really important to note.

The other thing is the length. I was really impressed that, despite the difference in weight gain, we were actually really able to tightly parallel the linear growth in the mom's own milk group. Statistically speaking, the donor milk group, the original one at the bottom, is not statistically different from the other 2, but there is a widening of the gap that we were likely underpowered to fully detect. Our conclusion from this study was that this is likely a safe practice in stable, very low birth weight infants and that the weight gain was still, again, greatest with mom's milk, but we could at least mimic linear growth.

The other study that we've been doing is actually a study called MAGIC where we're looking at very low birth weight infants and a fortification strategy that I'm calling enhanced fortification. This was born out of the fact, again, without being able to implement that targeted fortification, could we just give more protein and simplify it by adding more fortifier and therefore increasing not just protein, but also calcium and phosphorus and providing perhaps even more energy overall to utilize that protein. For this practice, we actually started this in 2019, doing this for 7 years now, and we essentially fortify all of our very low birth weight infants to 26 kcal/oz, so changing that standard of care for them. We did this after they get to full feeds. And the recipe that we use—this is technically an off-label recipe, but as you guys all know, any higher calorie recipe is off-label. I don't know that this is any more off-label than any of the other recipes that other people may be using. Again, for this, we use a higher proportion of that fortifier to the amount of milk that we're giving. Then even though I don't have milk analysis in the unit, I have a milk analyzer in the lab. We actually collected maternal milk samples that were pooled for over 24 hours. That really gets rid of that morning, night variation you might see. Then we also collected the donor milk that the babies were receiving as well, just to give us an idea of what our baby is actually getting. Then I do have the enrollment inclusion and exclusion criteria right there for curiosity.

What we found, and we presented this a couple years ago at Pediatric Academic Societies (PAS), and thankfully this paper is now published, we found that our protein intake was actually very different based on enhanced vs standard fortification. The lowest targets of the macronutrients were all met consistently with both standard and enhanced fortification, but protein was definitely where it got interesting. If you're aiming for that 3.5 g/kg/day target, you reach that with both enhanced and standard, but that standard is definitely a little bit more pronounced with maternal milk. That's that light blue bar vs donor milk. If you're shooting closer to 4 to 4.5 g/kg/day, which as I told you earlier we do in our unit, you're really only able to accomplish that with the enhanced fortification. In that middle column, even if you're just shooting for 4 g/kg/day, none of the donor milk samples met that target, or maybe it was 1%. It's very low. You cannot see the green very well. Then in the 4.5 g/kg/day, none of those targets—either donor or maternal milk—were able to reach that with standard fortification.

In fact, you do need additional protein. For us, we think that this is a really straightforward and efficient way to provide that extra protein source. Limitations from our study is we did assume these are the theoretical calculations. We will be going back and doing all the actual intake calculations once we're done enrolling for this, and we're pretty close, but the results can differ based on the fortifier product that you're using and less so for protein, more so for the fat and carbohydrates, and then it can also differ based on your total fluid goal. We assumed a fluid goal of 150 mL/kg/day. If fluid restriction is a common practice in your unit, this may in fact look a little different. Lastly, our donor milk comes from our regional milk bank. Again, I'm going to sound like a broken record now. Every milk bank's a little bit different, so there are some caveats to that.

There are a few other strategies, also not exclusive to donor milk feedings, that I'm going to talk about where we can increase our protein intake. One of them is actually just to start your fortification earlier and really kind of ramping up and then making sure you're not accumulating that protein deficit over time. These are a couple of studies. The first one is the Tillman study that I have on the left where they had close to a hundred very preterm infants and they started fortification with a bovine milk–based powder at the onset of feeding. And in that study, there was no difference in weight

gain, but there was also no difference in the incidence of NEC. The other study that came out a couple of years ago that I thought was really nice, was where they actually started that fortification also at the onset of feedings using the human milk–based fortifier, and then compared to the control of when they introduced the bovine milk–based fortifier at 2 weeks. In this study, they showed improved length and head circumference with that early fortification group. Unfortunately, no difference in the fat-free mass accretion, but again, no difference in NEC or spontaneous intestinal perforation. Definitely some potential ways that probably need some more studying and validation, but definitely empowering us to think about creatively of how to provide that protein.

Another way to do it is to just increase your total fluid goal. Again, our group is pretty tight with the 140 to 160 mL/kg/day, but I'm open to consider other options. In the study where they actually compared the usual volume of 140 to 160 mL/kg/day to a higher volume feeding target of 180 to 200 mL/kg/day, not surprisingly, because they're increasing the nutrient intake, they actually saw a higher growth velocity in that intervention group. There are other ways to think about it that challenge how we typically practice. If we keep an open mind, we may find other ways to do this. I feel like I personally have not implemented this routinely, but definitely for some of the kids who don't tolerate certain things, and this makes me feel more comfortable feeding at those higher volumes.

A common question we get is, what about safety with protein intake? We could probably spend quite a bit of time talking about this, but for the purpose of time, we looked at this systematic review from 44 randomized and quasi-randomized clinical trials. They did look at protein intake from both parenteral and enteral sources, but overall, there was a slightly decreased risk of neurodisability-free survival with a risk ratio of 0.95. There was a slightly increased chance of cognitive impairment at toddler age with an elevated risk ratio of 1.36. Of note, there was increased growth parameter *z* scores at discharge, and there was no significant differences in NEC, late onset sepsis, which I feel like are the ones that people ask me the most about.

Some limitations to this meta-analysis is that they did conclude a low level of certainty for most of the findings. I'm going to highlight again that these studies evaluated both parenteral amino acids and enteral protein, which are not comparable. The quality of amino acids has changed over time, and there's definitely some increasing body of literature that enteral protein may in fact be a better nutrition source than parenteral amino acids. Overall, there is a lack of adequately powered studies of nutrition intake in preterm infants, and we, again, need to think about it relative to all the other nutrients we're providing, not just protein alone.

Otherwise, for us, the routine fortification to protein levels of 3.5 to 4 g/kg/day is pretty well-established and safe and beneficial for growth. Consider your fortification up to 4.5 g/kg/day on an individual basis, but especially for infants who are not meeting growth targets, especially for your extremely preterm or your very low birth weight infants. For those of your infants who are on exclusive human milk diets, definitely again, know that that protein gap is going to be more magnified and make a more concerted effort to make sure you're delivering enough protein. Then our surgical neonates with other critical illnesses may in fact need those higher levels of proteins, even if they're not premature.

Some other takeaways: in general, just be knowledgeable about the donor milk you're purchasing, understand that process and the limitations. Acknowledge that the labels aren't perfect, but they still can be your resource to you in terms of your clinical practice, especially if an infant is showing growth faltering, you could potentially look for pools that have higher protein or energy, but ultimately prioritize mom's milk as much as possible and then tailor your fortification strategies as needed.

Protein Metabolism and Requirements in Critically Ill Infants and Children

Dr. Sarah Fleet: I am going to round this out and shift gears a little bit. Full disclosure, I'm not a neonatologist. I am a pediatric gastroenterologist and physician nutrition specialist, so we're actually going to focus now and shift gears to slightly bigger children in the pediatric ICU and talk a little bit about some of the details about protein provision there. Dr. Fu really nicely summarized for us that the protein requirements of very low birth weight and preterm infants are at their highest, and then these start to decline as patients get a little bit older, right? And really, in adolescence, we see goals that are less than 1 g/kg when we look at recommended allowance (RDA), and that's what you can see here on the right hand side. What we also know now is that in periods of critical illness, the RDA goes out the window a little bit, and we really strive for much higher targets, upwards of 50% higher than the RDA. At this point in time, we're really recommending not using that as your goal, but rather using these higher targets closer to the 50% greater

for all ages. This really means that we're targeting an absolute minimum of 1.5 g/kg in the pediatric ICU, regardless of age.

We're going to talk about physiology, okay? To really think about protein provision in the ICU, some very smart people thought about actually breaking critical illness into a series of stages when it comes to nutrition. This really helps us understand why we sort of have these protein management decisions that we have in the ICU. In the very acute phase of critical illness, within the first 72 hours, we have this activation of the hypothalamic-pituitary axis, right? Catecholamines activate this axis. We have sort of this massive anabolic-resistant stage, and this is defined truly by this massive catabolism that we cannot overcome regardless of how much we give. Regardless of how much nutrition we give, you cannot overcome the catabolism of those first 72 hours. In this stage, we actually recommend lower protein targets. Then as this stage starts to wane after about 72 hours, we start to see this more recovery phase where inflammation starts to come down, stress response comes down, and then the body is actually able to have us to sort of perform anabolism, and this is where we target those higher protein goals.

This slide also kind of demonstrates what I was just mentioning, but this one really kind of delineates a little bit more about this resistance to anabolism in those first 72 hours. The cortisol results in proteolysis of skeletal muscle, right? Your proteins are being broken down into amino acids, and this leads to a loss of lean body mass overall. In those first 72 hours, we sort of accept this just because we know that regardless of how much we give, we're not going to reverse this. In the liver, we have gluconeogenesis, right? We take noncarbohydrate sources and make glucose out of those, which is great. It preserves brain function. However, it also can lead to some blood sugar swings that are a lot harder to respond to in those first couple of days, which again is why we have some slightly lower nutrition targets initially in the ICU. Finally, we have lipolysis, which releases glycerol and free fatty acids, which have their own metabolic consequences, but the focus of today is protein, so I'm going to stick to that.

What I want to delineate, though, is that although we recommend lower protein targets to start in those first 72 hours, once we hit the waning of that acute phase, that's when we really need to be conscious that we're providing enough and that we are giving this absolute minimum of 1.5 g/kg, upwards of 3 to 4 g/kg in a critically ill infant, because of the results of muscle loss that can occur over time. If you do have that continued catabolism of skeletal muscle, we start to lose things like cardiac muscle function and we start to have wasting. When you have muscle wasting, this can lead to a longer time on a ventilator because you can't wean off ventilatory support. You can also have difficulties with dysphagia and swallowing difficulty, which ultimately lead to an increased length of stay.

Our goal is to take all of this and say, "All right. Well, we need to account for the metabolic stress response and be very careful early on. We also need to preserve this muscle mass because that ultimately is what's going to get us out of the hospital. We also need to avoid complications of enteral and parenteral nutrition." Those are all somewhat competing sometimes, but this is where your multidisciplinary team really comes in. It's really, really helpful. All of our different specialties can help us account for each of these different problems.

I really cannot talk about protein in the ICU without talking about my dear colleague, Nilesh Mehta, who in 2015 put out this landmark study about protein intake and its results on mortality in the ICU. He and his colleagues included over 1,200 children from 59 ICUs all over the world, and they looked at children ages 1 month to 18 years who are on a ventilator for at least 48 hours, and they evaluated mortality based on the percentage of the prescribed goal of energy and protein and found this direct correlation between protein adequacy and mortality.

You can see here in the graph on the left-hand side that was sort of all-comers, those who were receiving less than 20% of their prescribed protein had a 60-day mortality of upwards of 9.9% vs those who were getting more than 60% of their prescribed protein goals, they were down to 3.2%. This actually bore out much more significantly in children who were the most ill. In children who were the most severely ill, so at severity level 4, they had almost a 22% risk of 60-day mortality when they got less than 20% of their prescribed protein. And you can see how that fell pretty dramatically once they started getting more. Overall, there was an 86% decrease in odds of 60-day mortality among the patients getting greater than 60% of their prescribed protein.

When we're thinking about nutrition delivery in the ICU, which is admittedly a little bit different than when we're talking about the neonatal ICU, we don't use RDA values when it comes to protein, for sure. The gold standard for determining energy needs is really indirect calorimetry,

which I understand is not available to everyone all the time. But it is our preferred method here at Boston Children's where we really do use this to target our energy delivery for each patient in the unit. The minimum protein intake, if you take nothing else from my little part up here today, is that it should be a minimum of 1.5 g/kg, but you can really target 2.5 to 3 g/kg for some of the younger children in the ICU. Because of all this, and we'll dive in a little bit more, based on what Dr. Fu just talked to us about and all the things that she just said, you can start to understand how that protein gap with human milk can now also translate into the pediatric ICU if we're targeting these higher protein goals.

Infant and pediatric formulas when standardly prepared are on average about 1.4 g/dL of protein. When you start to think about providing enteral nutrition to critically ill children, you can see how this may actually not meet protein goals, similar to what's happening in the neonatal ICU that we just talked about. To meet those, you need to think about adding whether it's modular protein or standard fortification to formulas or using a high protein formula if it's available and tolerated. But this often comes up against things like fluid restriction, which I think is, at least in my practice, one of our biggest issues with protein provision is coming up against wanting to enterally feed, however, being limited by the protein content of that enteral feed.

I was remiss in mentioning that in that paper by Dr. Mehta, that sort of associated protein delivery with mortality, that was only for enteral feeding. It was not borne out for parenteral nutrition. For many reasons besides that, but for all the reasons, we really prefer enteral feeds, but you can see how we really start to get ourselves up against a wall with fluid provision when we're thinking about protein. Nutrient-dense formulas are really going to be a mainstay as long as they are tolerated.

Considerations for High-Risk Populations

Dr. Sarah Fleet: There are some high-risk populations within the ICU. We take the sickest of the sick and then we stratify them further. One of those is patients with congenital heart disease. A lot of this actually stems from their general malnutrition that occurs in congenital heart disease. Prevalence of malnutrition in these children ranges from 15% to upwards of 64%. This is attributed to many things, right? They have increased cardiac demand, so they have an increased energy expenditure. They have this relative hypoxemia. They have pressure overload. They have feeding intolerance. They are on and off nutrition all the time based on all of those symptoms, based on critical illness and based in their hemodynamic instability.

The risk factors for their malnutrition, things that can make them even more susceptible are things like low birth weight, preterm birth, pulmonary hypertension, pneumonia, congestive heart failure, and just being an infant with heart disease. We know that malnutrition in heart disease can lead to longer hospitalization, greater infection risk, higher mortality risk, higher risk of adverse neurodevelopmental outcomes, and a worsened quality of life. This is true probably of all children who are critically ill, but it's born out particularly in those with heart disease.

This is not necessarily an actual protocol, but it's more of a thought protocol about how do we think about infants and children with heart disease? They are at risk for NEC, and it's a slightly different beast than the NEC in the neonatal ICU, right? The NEC that you get in the cardiac ICU and especially with older and full-term infants, but they are at risk for NEC because of their hemodynamics and because of their heart disease. They're also, most of the time, incredibly fluid-restricted. So we have this push and pull. We need to really stratify these patients as far as their risk, based on their cardiac lesion, based on their age, based on their protein needs, and their sort of baseline level of malnutrition, and start to parse them out. You can think of a million ways that you can start to think through that relative risk/benefit discussion, but really taking all of those into account and really making protein provision and nutrition provision one of the things that you think about when you're talking about risks and benefits in the cardiac ICU.

There are a couple of studies that I think are worth just mentioning around this topic. One of them was this registry-based study back in 2023 where they looked at infants with single ventricle heart disease. There's quite a lot of them, almost 2,500. They looked at human milk–fed infants during the first 2 surgical stages of single ventricle disease, right? So, they looked at them before their first stage, after their stage 1, and then during their stage 2 hospitalization as well. Before stage 1 surgery, if they were receiving human milk, they were receiving exclusively human milk before their stage 1, they had a decreased risk of preoperative NEC and they had a decreased length of stay. If, after their stage 1 during that hospitalization, they received what was called mostly human milk, they had a decreased risk of postoperative NEC, decreased risk of sepsis, and a decreased length of stay. Then during their stage 2 surgery, if they received any human milk, they still had a decreased length of

stay. Again, as we're talking about this, sort of starting to balance nutrition provision, risk of NEC in the cardiac ICU, and then all of the other hemodynamic instability, we can show that human milk was really protective in multiple different ways in multiple different stages of illness. There was also a retrospective study that looked at infants with heart disease or isolated cardiac lesion who they felt were at high risk for NEC. This was a single-center study. It was a little bit smaller, but they looked at pre-op human milk feeding and its effects on NEC. They also were able to demonstrate a reduced risk of preoperative NEC after controlling for multiple different variables, right? So the cardiac lesion itself, race, volume, birth weight, and preterm birth status.

There's also this other population of children who have acute kidney injury (AKI). I can't tell you how many times we're rounding and we hear, "Oh, they have AKI. We've got to decrease protein, their BUN and creatinine are on their way up. We should wind down our protein provision." If they are on continuous renal replacement therapy (CRRT), the nitrogen loss is pretty significant. And in fact, it's upwards of 20% of their total protein intake. This does need to be accounted for in our provision, the fact that we're sort of pulling off a very significant amount of the protein that we're providing. There really isn't any evidence that a higher protein intake in AKI is going to delay kidney recovery. There are many other reasons that you might consider this, but if that's your only reason, I'd encourage you to think a little bit longer about it because we're pulling off so much in that CRRT circuit. Think about accounting for those losses. I love parenteral nutrition. In fact, that's the majority of my clinical job at Boston Children's. However, I'm going to also tell you that we try really hard not to do it. In this population, in particular, enteral feeding is really the primary goal.

The one thing I think I can drive home here is that post-op nutrition is mostly dependent on pre-op nutrition. If they come to you malnourished, your chances of actually helping, your chances of improving their malnutrition in that post-op period, are much, much harder than if you had dealt with it beforehand. In the population that I work with, we often will delay procedures until we can see an improvement in weight-for-length *z* score a little bit and pull them out of malnutrition territory. But we really need to address this. The malnutrition in particular, we really need to address preoperatively to result in good success postoperatively.

But after surgery, nutrition support is obviously very important. It helps with healing. It helps with return of GI function. And again, we really prefer enteral nutrition just due to the risks of parenteral nutrition. We do see that early enteral nutrition within 24 hours post-op can reduce the risk of malnutrition postoperatively. Again, it's very dependent on what type of surgery you're having and your ability to feed in those first 24 hours.

Finally, refeeding syndrome, which I think is getting a lot of attention lately. I think we're paying more and more attention to refeeding syndrome. I wanted to talk about it for a second. There is not a ton of data and evidence out there on what to do about refeeding except how to treat it. Our mantra is always to start low and go slow. The initiation of feeds, of enteral feeds or parenteral nutrition, is really dependent on the degree of malnutrition, their underlying disease state and their sort of resting energy expenditure. Factoring all that together can help you target a goal that is far less than what their needs are and then slowly working up to goal, because it is the release of insulin that causes refeeding syndrome.

There is some debate about protein. The classic teaching is that protein does not contribute to refeeding, and so we should just meet protein goals and just be really gentle with carbohydrate. There are some people that feel that protein actually may modulate refeeding syndrome a little bit. There are proteins such as leucine, for example, that are insulinogenic. In my personal practice, we have seen high protein provision precipitate a refeeding syndrome, but again, we're also still providing carbohydrate in that scenario. So just be gentle with it. What we generally feel is that it is carbohydrates that are primarily driving this, but the protein provision can sort of modulate that refeeding risk. If you have a very malnourished patient, you might be better off starting slightly lower and then working up again to that goal that you need to get to.

Thiamine and electrolyte provision are really the mainstays of treating refeeding syndrome. You just keep repleting until you get them in a safe zone. There are some guidelines put out by the World Health Organization (WHO) about thiamine dosing and refeeding syndrome in children. The only way we prevent this, again, is by identifying malnutrition and treating malnutrition appropriately prior to them getting sick.

That was the whirlwind tour of the kids you need to worry about the most in the ICU and kind of how we think about protein and energy and nutrition provision generally. In the ICU, in critically ill children, we want to define and then individualize those protein targets based on the stage of critical illness, as well as some of those underlying disease states that we talked about.

Bridging the Protein Gap: Navigating Variable Milk Composition and Delivery in High-Risk Neonates and Infants

I want to really talk about incorporating dietitians into rounds and really using a multidisciplinary approach to treat these critically ill children. Just based on these different disease states and their different metabolic states within the ICU, having somebody rounding with a dietitian can be incredibly important to making sure that we're adequately covering these patients with protein and energy, but also backing off when clinical status indicates targeting those critical care–specific protein goals. Not using RDA as your protein goal in the ICU but rather using those critical care–specific ones. Obviously enteral nutrition first, and then if you cannot use enteral nutrition, using parenteral nutrition with some trophic feeds, as indicated.

Really assessing adequacy of protein delivery specifically with enteral nutrition and fluid-96restricted patients and making sure that what you're providing is actually meeting goals similar to the protein gap that Dr. Fu mentioned, this also occurs in the ICU. Identifying those human milk sources and then looking at those updated macronutrient reference values to determine the goals for enteral feeding.

Questions and Answers

Do energy or protein needs change for children with obesity or a higher BMI when they're critically ill?

Dr. Sarah Fleet: At this point in time, the recommendation is to use ideal body weight to dose protein. It does lead to some permissive underfeeding as far as calories go, but we are using ideal body weight and then using those same higher protein goals for critically ill children. So rather than just using a lower goal, we use a different weight. We use the ideal body weight rather than true body weight. I don't know that it's perfect, but it's the best we have at the moment. If anybody has an interest, we'd love to look at it because I do think it's a little bit unexplored. There's a lot of discussion around energy provision in that population, but there's a little bit less about protein provision, especially in the ICU.

Mom's own milk grew best in your study, so why not just use mom's milk?

Dr. Ting Ting Fu: That would be great. If I could have all my babies on their own parents' milk, that would absolutely be ideal. The reality is, I think in our current world, and especially in our climate of supporting lactating moms, it's not realistic, at least not in my unit for 100% of their enteral intake to be mom's milk. That would be great if we could increase it, which I have colleagues that are actively trying to work on, and it's really hard to move that outcome despite all of our very concerted efforts towards that. I don't think donor milk is going away. The reality of what I'm focused on is how do we improve this nutritional alternative that we have. I definitely didn't go over today the indications and the evidence supporting the use of donor milk, but I do think this closing point of mom's milk is still the best. So, everything we can do to support that is ultimately ideal.

Does protein content in hindmilk increase at all or in foremilk?

Dr. Ting Ting Fu: The protein content is actually fairly consistent between foremilk and hindmilk. There's a bit more fat in the hindmilk itself.

In the pediatric ICU, what strategies are you using to increase enteral protein, concentrating formula to a higher density (modular proteins, etc)?

Dr. Sarah Fleet: I think a lot of this depends on the age a bit. We fortify infant formula just using sort of standard fortification recipes. Part of that is because of all the other nutrients that go along with it, right? You get more calories, you get more protein, but you also get more phosphorus, you get more calcium, you get all the other things that come along for the ride, which can be helpful. In older children, our practice, and it's by no means the be-all and end-all, but our practice is we don't use a ton of modular protein. We try to work within the formulas available to us and choose those that are going to meet needs. If that means it's a hypercaloric formula that has a higher protein amount, then we will. We'll also use some of the specialty formulas that provide some higher protein. Modular protein is a little bit less in our practice, but it may just be our preference and our practice. In young infants, we tend to fortify up pretty high before we shy away from the doing it by concentration. And we will go up to about 28 kcal/oz, and then we'll start to think about other things.

Growth often limits timing of surgical interventions in the NICU and PICU. How do you view protein targets in this population to decrease factors such as length of stay?

Dr. Ting Ting Fu: I think this goes back to Dr. Fleet's point that your pre-op nutrition is super important. I think that's what this is getting at in terms of, for example, you need to be a certain weight to meet certain criteria for a surgical intervention. I think making sure you're delivering adequate protein is incredibly important, but I think the other piece that we don't talk about—and we really, again, need to think about the whole bigger picture—is also just overall nutrient intake in order to get these babies to grow properly. And that

includes fat delivery. And things that we didn't talk about today is when you're using a feeding pump and how that reduces your fat losses with your nutrition, that impacts your growth. The focus of today is protein, but I think you have to consider fat and everything else you're delivering to grow those babies.

Dr. Sarah Fleet: Just to get on a soapbox for 1 second is that not all weight gain is created equal. Like very rapid weight gain is... We say like, "We just got to get them to 5 kg so we can get them to the OR." Five kg in a few days vs 5 kg in a couple of weeks, we really are trying to balance this accretion of lean mass as well as fat mass. And rapid robust weight gain we know is not usually lean mass. So just kind of being careful with those decisions and yes, keeping your eye on the prize, but also recognizing what we may be sacrificing to get there, and what does another 5 days buy you? So really just thinking thoughtfully about what type of mass we're building when we talk about those growth targets for OR.

What is the difference between doing that vs supplementing it separately with feed?
Dr. Ting Ting Fu: In the donor milk plus that I mentioned, we essentially added the liquid protein to that donor milk to, again, engineer that higher-protein milk in the milk room itself. We were doing that as early as initiating. Like your 20 kcal/oz, you're starting your feeds at 15 per kg, they're getting 15, getting that donor milk plus. I will say in that study at the time, because it was an observational study and it was based on our clinical decision. We did at that time, I think that was a while ago actually, we were not routinely resuscitating 22-weekers. The 23- and 24-weekers, it was based on the clinical team discretion whether or not they wanted to initiate it, but we actually had babies in that cohort down to 24 weeks. In the initial time period, I think there was some hesitancy, but it turned out that the stable 24-weekers could actually tolerate that donor milk plus.

We did not really observe feeding intolerance in that period, even initiating it that early. I literally went through all these charts and looked at how often the feeds were paused or did not progress and the indications. Usually, it was the delays were due to like they were getting ibuprofen for treating the patent ductus arteriosus (PDA) and they just didn't increase that feeding volume that day. But actually, no difference in the feeding intolerance. I will say, I think partly it may be the fact that the protein product we use is extensively hydrolyzed protein and that may be a reason for that as well.

You can certainly add lipoprotein later on, but the idea was that in donor milk plus, we started that early. The enhanced fortification strategy I mentioned is a little bit different, which is that we just did just regular milk feeds, fortification 24 kcal/oz. Once we got to full feeds, usually around 2 weeks of life, everybody went to 26 kcal/oz. All of our VLBWs went to 26 kcal/oz, again, just to change essentially the standard of what we were giving them.

When do you start using ideal body weight in large-for-gestational age (LGA) infants?
Dr. Ting Ting Fu: I think there's a huge emphasis on preemies and small for gestational age, and that LGA population gets overlooked. I have a colleague who is actually looking at how to approach growth in LGA infants because what should it be? And I think, to some degree, how do we help them kind of grow down, right? Catch-down growth.

Dr. Sarah Fleet: My clinical practice is young children with malnutrition. I often get these LGA babies coming referred by pediatricians for malnutrition because they're not growing. So outside of the hospital, it's still this discussion about how much sort of stagnation and stabilization do we tolerate before we actually call them malnourished. I don't have a good answer for you. If somebody does, I'd love to talk. But both in and out of the hospital, early on and then a little bit later, it remains sort of a big question as to what we do with those babies and at what point do we intervene?

What protein targets do you have for 22- to 23-weekers in the initial days and weeks of life?
Dr. Ting Ting Fu: I think that's incredibly tricky. I think we're initially supporting them with parental nutrition, which isn't the focus of today's talk. And then we didn't talk about refeeding syndrome in the neonatal population, which we can tend to see in both in the extremely growth-restricted babies who are born, but I think those 22-, 23-weekers sometimes give us an indication that they're not necessarily tolerating the parental nutrition we're trying to provide. I think we are still learning how to care for 22- and 23-weekers. If you have any insights, that'd be great. I think most neonatologists know they're very different than the rest of the preemies right now.

Should protein intake be increased in critically ill non-operative patients?
Dr. Sarah Fleet: I can defer to Dr. Fu for what you guys are doing in the neonatal ICU, but keeping in mind that goal target of no less than 1½ g/kg of protein in the ICU, sort of

regardless of disease state, and then using higher targets for younger children, I think is the guiding light here. Also thinking through though, we know that sepsis is a hypermetabolic state, and so you also need to provide more energy. And then keeping in mind those acceptable macronutrient distribution ranges (AMDRs), right? Your AMDRs is—we don't want to be providing 60% of our calories from protein. There's a little bit of a balancing act that has to happen because we don't want to overfeed these patients either. So, using that goal protein intake, but then once you hit your calorie target that you've determined, whether it's using indirect calorimetry or using some of the standards, then back-checking your protein provision to make sure that you're still within your AMDRs so that we don't exceed those recommended goals.

Dr. Ting Ting Fu: I'm going to answer that in kind of concert with this other question.

Do you target more than 4½ g/kg/day of protein up to 36 weeks?
Dr. Ting Ting Fu: I think one thing we didn't talk about today is looking at the patient and looking at how they're growing. And the most critical piece is making sure that you start with this baseline amount of nutrition and then adjust it to how your babies are growing relative to that. I do think we can all think of severe bronchopulmonary dysplasia (BPD) cases where they needed higher calories to help make sure that they weren't just getting rounder but also increasing their linear growth.

I think in sepsis, which is overall hopefully ideally a shorter burst of illness, I don't know that we routinely increase our protein, but again, looking at that growth over time, and especially even in your less critically ill, but your preemies who are in the NICU, again, just making sure how are they growing and responding appropriately and then not just their weight gain, but their linear growth, is really important.

Dr. Fenton did a nice paper that I really love when we talk about what should your growth velocities actually be. I think your weight gain, 18 to 20, is probably ideal. But the linear growth is really interesting when you plot out that constant of 1 cm per week that we quote all the time in the NICU for linear growth. I can't find a reference for it, but when you plot it out on a curve, you do not maintain your length percentiles. The reality is, in fact, we don't really back off of that 26 kcal/oz that we do for our babies, and we usually end up sending them home on higher-calorie feeds.

How to decide which fortifier is best, cow's milk–derived vs human milk–derived, hydrolyzed vs intact protein?
Dr. Ting Ting Fu: We use an extensively hydrolyzed protein product with our human milk fortifier. We do not routinely use human milk–derived fortifier in our unit. I think the literature has not yet demonstrated that from reducing the incidence of NEC in larger cohorts, that is not shown to be beneficial. I think it is a really complicated question, especially given everything that's happened legally in this country in the last year surrounding fortifiers.

The hydrolyzed vs the intact protein, I'm going to get a little nerdy right here, if that's okay. There's a paper that came out this year where they looked at an organoid, it was an in vitro model of organoid monolayer, and they exposed it to extensively hydrolyzed casein and intact protein and amino acid–based formula, elemental formula. Actually, the cells that were exposed to the extensively hydrolyzed casein had decreased intestinal permeability, so some potentially increased intestinal maturation. I thought that was really interesting. It was an in vitro study. I'd love to see more people tackle that question, but I don't think we know the right answer, but at least I can tell you from a clinical standpoint, our babies in our NICU tolerate this higher-calorie recipe really well, and it may actually be related to the fact that it's a hydrolyzed protein.

In the very low birth weight infant, what is their ability to utilize all of the fortified protein? That is, is it wasted? How about short gut, post NEC? Can it be avoided in this very low birth weight population?
Dr. Ting Ting Fu: I think this is also a really great question. When I did my donor milk plus study, I was really hoping that the linear growth would be better. I was really hoping to see a bigger signal than I did. Part of it was being underpowered, but it also made me wonder if we were at a ceiling effect with the protein we were giving. It made me go back to thinking about the studies that have kind of focused on that protein-to-energy ratio. Again, making sure you have enough nonprotein resources in the body to utilize that protein. Actually, the clinical outcomes for our enhanced fortification, that is still forthcoming, but one of the pieces I am planning to look at is actually that protein utilization piece.

Dr. Sarah Fleet: From a short gut perspective, a lot of it is going to depend on where the ostomy—if you have an ostomy, and where it is. If it's a very high ostomy, then you may waste more than if you have an ileostomy vs like a high jejunostomy, right? Because you really need the surface area for absorption. I think a lot of that is going to be like very

patient-specific, especially about their length of intestine, right? Do they have 10 cm or do they have 45 cm? Because it's a huge difference as far as their absorptive capacity. If they have surgical NEC, I think it's really quite variable as to how much they can use. The counter-thought to that is if you're limited by surface area and you have a very short transit before it's going to exit via ostomy, should you just give a ton so that you can maximize whatever absorption you have in that very short period. I think you could come at it from—you could make sense of it either way, but just again, it's going to be a little bit patient-specific based on length of intestine and location of ostomy as far as how much is wasted vs how much they can actually absorb.

How early do you fortify, at what volumes and how fast to advance feeds in extremely preterm or especially the periviable infants?
Dr. Ting Ting Fu: Our feeding protocol is publishing out there in the world, but we typically do 3 days of trophic feedings at 15 per kg for the very low birth weight infants and then we advance by 20 per kg per day till we get to 75. That's when we fortify directly to 24 kcal/oz and then we continue to go up by 20 per kilo per day. There is discussion in our group about potentially feeding some of those bigger preemies a little bit faster, especially based on the now slightly more older SIFT trial, but we'd love to start seeing them faster.

The periviable infant, I think, is really interesting. We still continue to do 20 g/kg/day. We extended the duration of trophics a little bit longer for that population, mostly based on consensus discussion between other units. I don't know that it's evidence-based to do 3 days vs 5 days vs 1 day of trophics, especially since we don't know, and I think people need to study that, but that is our protocol.

In low- and middle-income countries, what protein could you fortify with in neonates (peanuts, moringa, others)?
Dr. Sarah Fleet: One thing I would worry a little bit about is just the protein quality in some of these sources, right? We know that some of the plant-based protein, the sort of bioavailability and utility of it is slightly lower. Things like peanuts, we know like peanut protein, for example, is a lower quality than some of the cow's milk–based protein. I don't know that it means you can't use it. I just think it means that you need to think about how much you're giving.

Dr. Ting Ting Fu: In neonates, this is a really fascinating query. I don't know the answer to this. I am acutely aware that the products we have available here do not exist in other countries, even if the European products are different, right? I've gotten really into the weeds and read product labels for a lot of different fortifiers and different products out there. And it's really interesting, actually.

In the context of this question, I don't know that I have a good answer. I think the other thing to consider is always like your water source, right, and how that gets into it. I think that's why we really stress the importance of direct breastfeeding and mom's own milk in these lower-resource settings because in terms of cleanliness and water and access to everything, I think it's a little bit more challenging to answer. Yeah. Sorry, it's probably not what you're hoping for.

Can you comment on displacement of fortification to the 26 kcal/oz with mom's milk?
Dr. Ting Ting Fu: That's also a great point. I think any time you're using a liquid fortifier you are displacing human milk. I will say with the bovine milk–based fortifiers, there's less displacement than with the human milk–based fortifiers in terms of those higher calories. Our recipe is 15 mL of fortifier to 50 mL of human milk. So, some degree of displacement, I think not as profound, and it's something that we're willing to take with the balance of really trying to promote adequate growth and the benefits that come with having good growth.

With targeted fortification, how would this look clinically, per pool, per day, per week when examining?
Dr. Ting Ting Fu: I can only tell you what's been reported in literature because I personally, we don't utilize targeted fortification in our units because of the amount of work it would take. The initial study from the Fusch Group, they analyzed maternal milk 3 times per week, if I remember correctly. And I think there's been studies showing that 3 times per week is probably ideal, but at least once a week would suffice.

Dr. Sarah Fleet: I can also just say that in outpatient land, the be-all and end-all is growth. It doesn't necessarily matter how much you get, what it calculates out to, exactly how much it is. If they're growing, you're meeting their needs. And if they're not growing adequately, you're really not. I'm just going to go back to your comment earlier about looking at the patient and looking at growth charts and using corrected-age targets and things like that, outpatient. The be-all and end-all is ensuring that they're growing properly. Whatever it is that you need to do to get there, ultimately, is the right choice to make.

Do you have any long-term outcomes in preemies who receive the higher protein targets?

Dr. Ting Ting Fu: This is an interesting question to me because fortification in whether or not babies benefit from it improves their short-term growth. And I think the long-term outcomes of how they do overall, there's still a lot of lacking evidence that we still need to continue to look at.

I actually think one of the studies that kind of addresses is the MILk [Mothers and Infants LinKed for Healthy Growth] study that came out of the neonatal research network. And you would only realize this if you read the methods super closely. The MILk study, for those of you who are not familiar, was trying to address the difference in neurodevelopment potentially. Is there a difference in neurodevelopment at 2 years in infants who get primarily donor human milk vs preterm formula? These were infants of parents who were either not intending to provide their own milk or did so very early on and then stopped. Because one of the previous problems in other studies that evaluated this had a higher amount of mom's milk.

The reason why I mentioned this study is because if you looked really carefully, they actually made sure that the donor milk recipes ensured at least like 2.8 to 3 g/dL of protein, which equates to 4½ g/kg/day of protein. Their primary outcome of difference in neurodevelopmental outcomes, there was no difference between the 2 groups, but I wonder if that was only achievable because we actually gave all that extra protein. Again, not quite a direct answer, but that's how I interpret that study.

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