

Very Preterm Infant Nutrition: Parenteral vs Enteral Transcript

Editor's Note: This is a transcript of a live conference presentation on November 14, 2023. It has been edited for clarity.

Outcomes From Nutrition



Sarah N. Taylor, MD, MSCR: When we think about nutrition, there are so many options and so many different ways we can nourish babies with parenteral nutrition, the enteral nutrition, protein, carbohydrates, all the macronutrients as well as all the micronutrients. It can be overwhelming. When I sit back and think about what is the best way and what does the evidence show for us to nourish infants, I think we have to consider what is our goal. Our goal is the outcomes.

So, feeding is giving the nutrition. The nutrition [provides] food for health and growth. Then we look at how that relates to outcomes, and specifically these are the outcomes that I consider important. Of course, their body [is] growing. What are they going to look like as a 6-year-old? Are they going to look like the other students in their class with weight and height and such? Neurodevelopment, of course, is incredibly important to families and to the outcomes of the infant to protect and grow and mature the brain. Their bones—this is something I'll go over a little bit—why very preterm infants are at increased risk for difficulties with bone mineralization.

I won't go over this as much, but when we're talking about human milk as a feeding type for preterm infants, we have to consider the anti-inflammatory mechanisms. And even our adult colleagues are starting to see nutrition for its anti-inflammatory effects. So, this is not foreign to the world of nutrition. For us, it often centers around human milk. And then, with this being an infant, it was supposed to still be in the fetal life, how that relates to their organ system maturation.

We then think of those outcomes in relationship to the gold standard nutrition for the term uncomplicated newborn, which is maternal milk, mother's milk. I will use terms, such as maternal and breastfeeding in this talk, and you'll hear those all through the morning. I do respect that not every individual sees themselves as a mother when they're lactating. Some people do

prefer parent milk or chest-feeding terms, but I'll be using maternal milk and breastfeeding throughout this talk.

What about the very preterm infant who is in the middle of having been, supposed to still be a fetus, yet is now a newborn baby? I am going to use calcium and phosphorus as an example of what a very preterm infant can be missing from fetal life. This is because 80 percent of the calcium and phosphorus that a fetus accrues is accrued in the third trimester. The peak accretion is 36 to 38 weeks, so a lot of these important minerals for the bone are coming at the end of pregnancy. Starting at 26 weeks, you see there's high intake of calcium, phosphorus, and magnesium. Most of the bone is going to be deposited from 24 weeks up until term age. So, a lot of bone growth is going on in the very preterm babies in our units.

Mismatch in Nutrition

When we give human milk, this gold standard nutrition for the term uncomplicated infant, when we give the human milk to the very preterm infant, how does it match up with their needs? Talking about that enteral intake—that intake by mouth—the very preterm infant daily needs are there of energy, protein, calcium, and phosphorus. In red, I have where human milk being delivered at 150 mL/k/day or even human milk delivered at 200 to 300 mL/k/day where it falls short of the very preterm infant's needs. So, even if we are giving huge volumes of milk at 200 to 300 mL/k/day, which is a lot of volume for babies to take, we're still falling short sometimes with protein, and definitely with calcium and phosphorus for the very preterm infant. There are other minerals and vitamins that are also low for what the very preterm infant needs.

Not only do we have this mismatch in nutrition that the very preterm infant needs and what is available in the milk, but also think about the mismatch of what is being made by the mom every day. We encourage moms to be making somewhere between a half to a liter of milk a day. So many of our very preterm infants are taking much smaller volumes of milk, and so they're not even getting what the mom is making for that

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infant. Her body is developed to give the full-day nutrition in a 24-hour period, but the infant isn't taking as much milk as she is making. So, there's a mismatch. Then additionally, when babies are in the neonatal intensive care unit, the milk is pumped, it's often put into a container, and then put into another container to be prepared for feeding and often goes through a feeding tube. So, there's loss of nutrition with all of that, as well as refrigerating, freezing, thawing. [There are] so many ways we have this mismatch between the nutrition that is being made for the infant and what the very preterm infant needs because they still need to be growing as a fetus.

Parenteral Nutrition

What do we do because we have these limitations in our ability to give enteral nutrition? Because of those limitations, we often rely on parenteral nutrition when it's available. What about the parenteral nutrition? I'm just going to go over little pieces in this 30-minute talk, but I want to highlight a new standard, a new guideline—or I guess it's a statement—from ASPEN, which is the American Society for Enteral and Parenteral Nutrition. This was published just this year, in 2023, with Daniel Robinson as the first author. If you're interested in parenteral nutrition, this is a nice summary of the evidence available regarding parenteral nutrition. So, like many of us, I grew up in neonatology, which focused on giving good protein, especially good energy. And Brenda Poindexter, who's speaking with me today, I read all that she was writing about, and others, about the importance of that good protein early on, and it is so important, and we saw improved growth with that.

But when we look at the randomized controlled trials that have been done, when we are giving early, higher nutrition, these are 3 studies where they gave amino acids and lipids early and then compared that to giving it later, or increasing it more incrementally, increasing it slower, they saw a change in how quickly a baby returned to their birth weight. So, a baby, say born at 1 kilo, is going to have some weight loss in the early days. How quickly, how many days does it take for that baby to return to being a kilo? That is where we saw the difference. We're able to have less of a weight loss early on, giving this early nutrition.

It is surprising, I will say, that we're not seeing other outcome improvements later on. We all thought if we gave this intense nutrition early, we would see better long-term growth and better neurodevelopment, which has been shown in some cohort studies when we look back at how babies grew and relate that to their brain development, and what they're able to do in their neurodevelopmental testing. But when we do board studies and randomized controlled trials, we mostly see short-term outcomes, and that's what's seen here. A faster return to birth weight with giving earlier amino acids and energy.

I want to mention, just to show what it means to be returning to birth weight more quickly. It means the line that is the growth patterns of babies at different gestational ages is going to have less of a dip and a quicker upward trajectory. We're looking for more of a quick hook there to get a baby back on their growth trajectory from birth.

Protein Goals

The parenteral nutrition guidelines were published in 2018. These are consensus guidelines. They weren't necessarily based on high-quality evidence, but it was the evidence that was available, as well as expert opinion. Here are the recommendations for parenteral, so IV [intravenous], energy, and protein goals for preterm, late preterm, and term infants. I do want to mention, though, that I believe when this guideline came out in 2018, it was not a full understanding of how much IV protein we should be giving. There's a follow-up, and a lot of this comes from our colleagues in Europe, recommending not going above 3.5 in the parenteral, with the IV protein. And I'll show you why.

This is also from the Robinson paper. They took the trials that have had protein above 3.5 g/k/day. You see one of them had a max of 4 g/k/day, another added 1 g/day, which got it over 3.5 g/k/day, and the third was 3.6 g/k/day. This is a forest plot. If you're not familiar with forest plots, if you look at your left-hand side, if the line and the box and the diamond are more on the left-hand side, that would mean the outcomes favored the higher amino acid. On the right-hand side, that would mean that the outcomes were better with the lower amino acid. As you can see that diamond is over on the lower amino acid

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showing, overall, it looks like we are not getting benefit and potentially harm when we go above 3.5 g/k/day with how we're currently giving parenteral nutrition. So, I do caution going above the 3.5 [g/k/day].

One of the big reasons this concern was raised, and again this came up more in Europe than it has in North America, so we've been talking quite a bit in international circles about the upper limits of protein. But I do respect this study that was done that looked at early aggressive or early increased nutrition, including giving amino acids at 3.5 g/k/day. This study was stopped early because, in the intervention group—in the infants getting the increased nutrition—there was a higher prevalence of or incidence of sepsis and hypophosphatemia—so low phosphorus, low potassium and high calcium. I'm not quite sure what to make of the sepsis outcome that hasn't been replicated in other studies, but the phosphorus, potassium, and calcium abnormalities are something to pay attention to.

This is another study that was published in 2013 [Bonsante et al. 2013] to look at intakes of amino acids. They had a high amino acid group, which is in red, a medium amino acid group, and a low amino acid group. When they looked at their phosphorus levels and their calcium levels, they saw significant hypophosphatemia, so low phosphorus and high calcium, and it seemed to be dose-dependent. The prevalence of the low phosphorus and the high calcium was higher with the high amino acid group and lowest with the low amino acid group. So, why was this?

Well, back in older times when parenteral nutrition was not being given, when we were giving just dextrose and not giving amino acids, in that circumstance, when we are doing that, the cells are in a dormant state. They are not undergoing metabolism. So, that first picture, when you're not giving amino acids early on, you see the amino acids and the phosphorus and the potassium aren't being given, so they're not going into the cell. When that happens, then the cell doesn't need potassium and phosphorus. The potassium and phosphorus can be in the circulation, and they can be excreted by the kidney, and they can go to the bone. The phosphorus can go to the bone, which is wonderful for bone mineralization. When we're not giving early amino acids, that's better for our electrolyte's stability, the

homeostasis in the body, the circulating levels of potassium and phosphorus, and better for the bone.

When we're giving amino acids, so the amino acids are going there into the cell, but we're not giving phosphorus and potassium, then the cells have the amino acid substrate. They can be metabolically active, so they need potassium and phosphorus. That's when the potassium and phosphorus come from the circulation into the cell. Then the circulating phosphorus level is low, and that means that phosphorus is going to be pulled out of the bone. Phosphorus and calcium have to go into bone together, and they have to come out of bone together. So, when the phosphorus is coming out of the bone, so is the calcium, and that's why you have hypercalcemia because it's coming out with the phosphorus. So, we would see the low potassium, the low phosphorus, and the high calcium. I saw this clinically around this time, 2013, not knowing why we had so many low phosphorus levels. We even had fractures in my unit, babies in the first week of life, which was very unusual, and it related to giving the amino acids without giving the potassium and phosphorus.

This is called by the group that worked on this, I believe it was in France, "Placental Incompletely Restored Feeding Syndrome," which is a tough name in English. Hopefully, it sounds better in other languages and it's because we're giving the amino acids without the phosphorus and potassium.

Phosphorus in Parenteral Protein

To provide a little more [information] on phosphorus delivery, we really need—if you're giving parenteral nutrition—you need to focus on how much phosphorus you're giving. [It is] very important to work to get 2 mmol/k/day of phosphorus. In order to give that much phosphorus you may have to come down a little on your calcium, or at least be mindful of your calcium-to-phosphorus molar ratio, and the recommendation for that molar ratio is there at the bottom [see slide 20]. It is 0.8 to 1 of calcium to 1 of phosphorus in the first week, and then a little bit higher calcium, 1 to 1.3 to 1 of phosphorus after the first week. So, paying attention to phosphorus is important when you're giving parenteral protein.

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Last thing I want to mention on parenteral nutrition is to be mindful when you are decreasing parenteral nutrition as you're increasing enteral feeds. We do a good job of getting in protein and energy in the first days of parenteral nutrition. We do a good job of protein and energy once we're giving full supplemented feeds to our very preterm babies. But in the middle of that, when we're making the transition, we often fall short of our protein and calorie goals. The enteral recommendations are there [see slide 21; Miller et al. 2014]. I won't go into the evidence behind those, but there's some nice evidence about giving 3.5 to 4.5 g/k/day of protein in enteral nutrition.

Human Milk Intake

[Let's] talk a little about the importance of the human milk intake for our preterm infants. There are so many ways in which the human milk relates to the development of a healthy intestine, both the epithelial permeability as well as the immune function of the intestine. This is a nice review that I feel summarizes so much of the human milk literature. It was published in 2018 [Miller J et al. 2018]. To sum that up, they saw in this review a decrease in necrotizing enterocolitis (NEC) in a dose-dependent manner with intake of human milk, decrease in late-onset sepsis, and decrease in severe retinopathy of prematurity. Again, the NEC as well as the late-onset sepsis was in a dose-dependent manner, and the severe retinopathy was looking at an exclusive human milk diet vs exclusive formula.

Microbiome Benefits

Donor milk is available in some places in the world, and it is associated with a risk reduction in necrotizing enterocolitis when it's given rather than formula. I want to highlight that we really need to consider focusing on efforts to get maternal milk—so, the own-parent milk—and be aggressive in that work. Donor milk is important, but what is most associated with improved outcomes from our babies is maternal milk.

These are 2 studies that were published in the last couple of years [Ford et al. 2019] highlighting that the diversity, the microbiome, is different between babies receiving maternal milk and donor human milk. The diversity is, and the difference

is, greater when the bacteria are there. The different bacteria are greater when babies are exposed to antibiotics, which a lot of our babies are. So, [it is] important to recognize that potential benefit to the microbiome with maternal milk over donor milk.

The study on the right was looking at the human milk fortifier vs the cow's milk, the formula-based fortifier [Kumbhare et al. 2022]. They didn't see any difference in the fortifiers except for one small change in the microbiome. What they saw in this study—and they didn't expect to see—was more of a difference in the microbiome related to whether babies received maternal milk or donor milk as the base upon which the fortifier was given. So, again, important that we enforce efforts to get maternal milk.

[Here is] another way to show this. This was from the Neonatal Research Network. It is older, but it is still one of my favorite graphs. Most of these babies...this is looking at human milk. That dose of human milk in the first 2 weeks, this was maternal milk for the most part, rather than donor milk. And you see how dose—that volume intake per kilo of maternal milk—relates to surviving free of NEC. So, again, that dose-dependent benefit of maternal milk.

How do we get that maternal milk to babies? Well, I'll show you at least from some work we did. This is what I would consider the highest level of a study. It was a retrospective cohort study, but we moved from feeding babies in the first 48 hours to feeding babies in the first day. We ended up with a median time of initial feed of 13 hours. This is in extremely preterm infants. In that work we did not see an increase of necrotizing enterocolitis. We saw a decrease in the diagnosis of feeding intolerance with exposing infants to human milk in the first day.

Feeding Intolerance

Talking a bit more about feeding intolerance, it's difficult to diagnose. We have a new study to look into better methodology for diagnosing feeding intolerance. When you think about what is a belly, an abdomen, what is that physical exam? The concern, as neonatal care providers, distended, glistening, tight, dusky, bilious emesis, hematochezia, which is the bloody stool. If you have a baby with those symptoms, you are very, very concerned about that belly. We all should be. That is very concerning that

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this infant has necrotizing enterocolitis. But when you take each of those components individually, they're not quite as meaningful.

Abdominal distention, our babies can have significant changes in their abdominal girth just in feeding. It can vary up to 3.5 cm during a feeding cycle. Emesis, we may see more emesis when we're not checking residuals, and that can be fairly common in different individual babies. Green can just be a marker of poor motility in the first days. It doesn't necessarily mean that there's inflammation in the gut in a preterm infant. Now, if it's bloody emesis that would be more concerning. When you just have some blood in the stool, it can be a milk protein allergy. There are other potential diseases that are causing that in the stool and so, individually, these can be hard to realize what they predict. Necrotizing enterocolitis? Not necessarily. So, that's why it can be so difficult to diagnose feeding intolerance in our population.

So, we end up with different NICUs, and sometimes different NICU providers, have different approaches to feed. So, in neonatal care, in my experience talking to people all over the world, I'm assuming it's also what you experience, we have people who are very scared to feed. That old mantra of nobody who's NPO gets necrotizing enterocolitis. If I don't feed, this baby will not develop NEC. And this newer approach, which you can probably tell I'm in this camp of feeding and providing human milk to that intestine. I don't have time to go through the details, but I do think that feeding is the preferred approach. It is done best when there's a protocol, when there's standard approach to initiating, advancing, and a standard approach to diagnosing feeding intolerance.

When to Start Milk Expression

If we're going to feed maternal milk, we need to get maternal milk. I just wanted to show the evidence quickly regarding maternal milk, how to obtain maternal milk. Expressing milk by 6 hours and expressing it often. I have here the Lisa Parker study from the University of Florida [Parker et al. 2020]. Some of you may be here from Gainesville. Wonderful study. She looked at expressing milk. So, pumping early in the very first hour, the early time was within an hour, then it was more

around 2 hours, and then the final time was less than 6 hours. She saw no difference in milk volume. So, this is nice to know as healthcare providers. We're okay to wait and support moms if some of the moms aren't able to start expressing milk until about 6 hours. That's okay. We have a lot going on with a sick mom and a sick baby. So, yes, it's important to start milk expression, but it doesn't have to be the first hour. It can be in that first 6 hours.

Hand expression is a wonderful way to obtain colostrum. Skin to skin is very much an evidence-based method to support mother's milk coming in, her milk volume. And then other studies have shown the importance of having lactation specialists to help with problem-solving and helping with maternal comfort with pumping or hand expression. Moms who are more comfortable are more likely to make milk.

Nutrition Mismatch

Going back to one of my first slides, again showing this mismatch. I've talked to you about parenteral nutrition, and then the importance of human milk for enteral nutrition, but there does need to be supplementation, at least of energy, protein, calcium, phosphorus, some micronutrients, and vitamins. And since I'm almost out of time, it's wonderful that Dr. Poindexter is going to go over more of the ways, the fortification available to give these extra nutrients to our very preterm infants who need this nutrition because it was so important for the fetal growth they've missed.

In summary, start parenteral nutrition in the first day, giving that protein or those amino acids and the fat and the energy, carbohydrates, as well. I also suggest starting enteral nutrition in that first day to be exposing the preterm infant gut to human milk. The doses of amino acids, starting 3 g/k/day—some people do start lower and show a good growth velocity, and going up to 3.5 g/k/day, but not to 4.

The phosphorus, again, is if you're giving protein, very, very important to be giving phosphorus. Then the enteral nutrition. Prioritizing maternal milk. Donor milk, when maternal milk is not available, to decrease the risk of necrotizing enterocolitis. Providing the calories and the protein as well as the extra



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calcium and phosphorus for bone. Some other micronutrients, which will mean that you'll need to supplement above what is available in human milk. Even if you are feeding at incredibly high volumes of human milk, we still need these supplements.

ABBREVIATIONS

ASPEN	American Society for Enteral and Parenteral Nutrition
Ca:P	calcium to phosphorous ratio
IV	intravenous
NEC	necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
NPO	nothing by mouth
RCT	randomized controlled trial
ROP	retinopathy of prematurity

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