Pediatric Nutrition
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Human Milk Fortification – Evidence Related to Bovine vs Human-Milk Derived

Transcript

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Classifications of Fortifiers

Brenda Poindexter, MD, MS: I don't personally have any disclosures. I did want to pause and talk a little bit about how the FDA [US Food and Drug Administration] classifies human milk fortifiers. There's been a lot of activity recently related to probiotics and a lot of concerns that marketing claims for the impact of probiotics are being marketed as though they were a drug to reduce disease, namely NEC [necrotizing enterocolitis]. I thought I'd start by saying that infant formulas are considered exempt, and they are labeled for use by infants, either who have inborn errors of metabolism or low birth weight, which really is the focus of our talk today with preterm infants. I think we do have to be careful when we're talking about the use of a food, namely a human milk fortifier, to reduce a disease, such as NEC. So, I just thought I would set the stage there.

The objectives are to review why fortification of human milk is necessary for preterm infants. I think Sarah did a beautiful job setting the stage for me. We'll then summarize the current evidence related to human milk-based human milk fortifiers, including the impact on NEC, growth, and other important outcomes. I want to talk about special considerations for the use of donor milk. Then I hope to convince you that future studies are urgently needed to determine what specific human milk fortifier nutrient profile and source may be most beneficial for our vulnerable preterm infants.

So again, I can't think of a better person than Dr. Taylor to share this session with because she's already done a beautiful job of outlining the benefits of human milk for you. It's a species-specific diet, decreases infant mortality, reduces the risk of NEC. The composite of NEC or death is associated with decreased in-hospital morbidity, including lower rates of late-onset sepsis, BPD [bronchopulmonary dysplasia], and ROP [retinopathy of prematurity], and has also been shown to be associated with a shorter hospital stay and a lower incidence of rehospitalization than preterm formula.

We know that there are also many nonnutritive components of human milk, and a lot of these translate into anti-infection for antiviral, antibacterial properties. The oligosaccharides in human milk, in particular, have important prebiotic effects. There are also other trophic factors, hormones, and cellular components. And, in the context of being asked to talk about differences in human milk fortifiers, between the human milk-based and bovine-based, I think this is a really important slide to keep in mind because pasteurization, we know, alters many of these components. I think that when you're looking at the human milk-based fortifiers, they also undergo the process of pasteurization. We have to think about whether they are equivalent to human milk that has not undergone pasteurization.

Impact of human milk

It was lovely yesterday to hear Dr. Shankaran give such a wonderful tribute to Dr. Charlie Bower. Charlie was one of the network PIs [principal investigators], when shortly after I finished fellowship, I had the opportunity to lead a trial for the Neonatal Research Network on parenteral glutamine supplementation. People talk about different turns your career takes, and we had thought, because glutamine is such an abundant amino acid in human milk, that giving it earlier in parenteral nutrition might help with reducing sepsis and other outcomes. I always say that this was the largest negative trial that I could have possibly imagined (and Cristina [Navarrete] was involved with some of our growth work in that trial), but the upside was that we had 1,400 ELBW [extremely low-birth-weight] infants who had detailed daily nutritional intake data. It enabled us to do several secondary analyses looking at the impact of various aspects of nutritional provision. One of the

Human Milk Fortification – Evidence Related to Bovine vs Human-Milk Derived

substudies that we did with Betty Vohr was to look at the impact of human milk on neurodevelopment at both 18 months and then at 30 months. This study was done at a time where no units had donor milk yet, and 75% of our study cohort received human milk in the hospital. Sadly, only 30% were still receiving human milk at the time of discharge. Fortunately, I think we have gotten better than that.

Dose-Dependent Impact

We assessed growth and neurodevelopmental outcomes, again at 18 months and at preschool age. This study showed that there is a dose-dependent response with intake of human milk. For every additional 10 mL/k/day that the infants consumed of maternal milk, we had improvement in the Bayley, MDI [mental developmental index], and PDI [psychomotor developmental index] that translated to almost 1 standard deviation of improvement. What was interesting is that we saw the impact at 18 months, and it persisted at 30 months. And so I think this observation really formed the basis of why then we proposed the Network Milk Trial to see if babies who received donor milk would have that same benefit in terms of neurodevelopment.

We've said that human milk is the preferred diet for preterm infants, so why is it important to fortify? Well, as Sarah again already set the stage for me, it's nearly impossible to meet the metabolic demands and the recommended nutrient intake without the addition of fortifier. Specifically, we need higher intakes of protein, calcium, and phosphorus to optimize growth and to mineralize bone. And although there's been no definitive association between the addition of human-milk fortifiers and long-term neurodevelopmental outcomes, greater gains in growth in the NICU [neonatal intensive care unit]—both weight gain and linear growth—are related to better developmental outcomes.

I know we have several people in the audience who are using translator services and I wanted to make sure that the interpreters had a list of my abbreviations that you'll see in a lot of the other slides. And so, maternal breast milk, donor breast milk, human milk fortifier, and then we'll have HM-HMF for the human milk-based human milk fortifier, bovine milk-based human milk fortifier, an exclusive human milk diet. By that I mean you have a base of maternal milk or donor milk, and the fortifier given is one of the human milk-based fortifiers. And then preterm formula. So, I hope that's helpful as you look at some of my future slides here.

Fortifier Products

There basically are 2 types of fortifiers that are available. There's multi-component and single component. As the name implies, multi-component provides a range of nutrients, including protein, fat, carbohydrates, vitamins, and minerals. The protein source may be whey or casein. It may be intact or hydrolyzed. But it's important to know that even if you're taking different fortifier products and following the recipe to make it a particular caloric density, different manufacturers are going to achieve the same caloric density in very different ways, in terms of how much protein or how much fat they are adding, and in the distribution of the macronutrients.

Single-component fortifiers are typically used in conjunction with a multi-component fortifier to enhance delivery of individual nutrients. So, examples of this would be a modular protein fortifier or a cream-based supplement to add extra fat. In terms of the milk source, it can be bovine- or human milk-based. Then In terms of the formulation, it can be either a powder or a liquid. Again, the main focus, with the time we have this morning, is going to be on the evidence or lack thereof for the differences between bovine- and human milk-based as the milk source.

Human Milk-Based Human Milk Fortifiers

With donor human milk being the preferred alternative to preterm formula when efforts to provide maternal breast milk are not available, the use of a human milk-based human milk fortifier to promote an exclusive human-milk diet has been evaluated. The human milk-based, human milk fortifiers are expensive liquids that are offered in a range of caloric preparations. One of the most important things to realize is that when you are adding the liquid-based HM-HMF, especially at the higher caloric densities, you are displacing a significant amount of maternal milk. So, if you're going up to 30 cal, you are adding the fortifier to maternal milk in a 1:1 ratio. If you

have a very limited milk supply, that may be okay; but if you have a lot of maternal milk, I think it's really a shame to dilute the amount of active maternal milk that you're giving.

And, at least as of a few years ago, a survey showed that the human milk-based human milk fortifiers [are] currently available in just over 20% of neonatal facilities in the United States. I know that that's different worldwide.

The proposed benefit of the human milk-based human milk fortifiers, and an exclusive human milk diet is extrapolated from studies demonstrating the association between preterm formula and an increased incidence of NEC. The advantages of an exclusive human milk diet have been suggested primarily in comparison to preterm formula or to supplementing maternal milk and formula and bovine fortifier. We're going to review some of those studies because I think it's really important if you're trying to make a decision between the 2 types of fortifiers that you carefully consider the evidence.

Trial Evidence

There has been 1 randomized trial by Debbie O'Connor that we're also going to discuss, called the OptiMoM [Optimizing Mothers' Milk for Preterm Infants] trial that has compared an exclusive human milk diet to human milk with bovine fortifier. As we go through this, it's important to also think about what the primary outcomes are for these trials and what the sample size was powered to detect in terms of a difference in the primary outcome. The spoiler alert is that none of them have been powered to look at a primary outcome of NEC.

DoMINO and NRN MILK Trials Impact on NEC

Before we dive into the studies looking at the exclusive human milk diet, I just wanted to give you a contemporary look at the rates of NEC in a couple of large clinical trials. The DoMINO trial [Donor milk for improved neurodevelopmental outcomes] was done by Dr. O'Connor in Canada, and the MILK trial was led by Tarah Colaizy for the Neonatal Research Network. These are both large, randomized trials, 363 babies and 483 babies. They enrolled extremely low-birth-weight infants of about 26, 27 weeks. The DoMINO trial had babies that weighed just under a kilo at birth, whereas the MILK trial, they were a little bit smaller, 840 g. In both studies, they took moms that were having limited milk supply in the first few weeks after birth, and they randomized them. In addition to the maternal milk, they would be randomized to receive either donor milk or preterm formula. Both studies, again, were powered to look at differences in neurodevelopment. Again, not being sure if pasteurization might alter some of those properties that had conferred neurodevelopmental advantage in earlier trials looking at the impact of human milk.

In both of these large trials no differences were found between the study diet groups in terms of the primary outcome, which was the Bayley-III at 24 months corrected age. But again, just to give you a little bit of grounding, the incidence of Stage 2 NEC or greater in these trials, in the DoMINO trial, it was 1.7% incidence of NEC in the donor group and 6.6% in the group receiving preterm formula. And in the recent MILK trial that Tarah [Colaizy] presented at PAS [Pediatric Academic Societies] last year—I think that paper should be coming out in the next few months—the incidence of NEC was 4.2% in the donor group and 9% in the preterm formula group. It's important to note that in neither of these trials did babies receive the human milk-based human milk fortifier. Both of these trials used bovine fortifier.

Just keep those numbers in mind because some of the studies that I'm going to show you looking at the human milk-based fortifiers have rates of NEC that are much, much higher than this, and I think it raises some questions about the generalized ability of the findings.

Exclusive Human Milk vs Preterm Fortifier

The first study I want to talk about is by Dr. Cristofalo. This was a study where they randomized extremely preterm infants whose mothers did not provide any maternal milk. Thankfully, this was a small study, only 53 babies, and they were randomized to either an exclusive human milk diet or to preterm formula. The study was powered, the sample size, on a primary outcome of the days of parenteral nutrition. NEC, which was only a secondary outcome, occurred in 1 infant in the exclusive human milk group, and in 5 infants in the preterm formula group. Again, I am not sure how relevant this is

because I think we do all agree that in the absence of maternal milk, we should be using donor human milk, if available

Exclusive Human Milk Comparted to MBM and Bovine HMF

The study that I think excited me probably the most is the Sullivan trial, and this was a randomized, clinical trial. They enrolled over 200 babies, again birth weight of 900 g, gestational age 27 weeks. The aim of this study was to compare an exclusive human milk diet with bovine-based fortification. The study started out with 3 different groups. So, all babies in all 3 groups received maternal milk, if available. Then they had 2 different groups where the intervention was to give the human milk fortifier, and the difference was when fortification was started, either at 100 mL/k/day of enteral feedings or at 40. [For] those babies, if maternal milk supply was not adequate, they received donor milk and then the human milk fortifier. So, a completely exclusive human milk diet.

The babies who received the bovine fortifier, however, if they didn't have sufficient maternal breast milk, they received preterm formula. I really think that this particular aspect of the study is the fatal flaw, because I wish that this had been donor milk, and then you could have had a true head-to-head comparison of the impact of bovine vs human milk-based human milk fortifier. So, it's really not possible to make this comparison.

The primary outcome of this study, again, was the days on TPN [total parenteral nutrition]. The investigators found no difference in the days on TPN, the time with the central venous line, weight gain, length of stay, or a combined outcome of late-onset sepsis or NEC.

Secondary Analysis of NEC

What they did do, though, was a secondary analysis just looking at NEC and, for the purpose of this analysis, because there really was no difference between the groups in terms of the timing of fortification, they combined them into 1 group. So, you had 138 infants who were in the human milk group and 69 in the bovine group. The incidence of medical NEC is shown in the white bars, and NEC requiring surgery in the black. By doing these gymnastics to look at the groups, the incidence of NEC in the bovine group was 16%, and 6% in the human milk group. Surgical NEC was 10% in the bovine group, and just under 2% in the human milk group. This is the study that I hear cited most frequently to justify why we should be using the human milk-based human milk fortifier. I think that it's unfortunate because I really don't think that you can attribute the differences seen here to the fortifier when there was also a difference in that the bovine group received preterm formula.

Based on some of these, I think, very valid criticisms, the investigators went back more recently and did another subgroup analysis. In this secondary analysis, they focused on the infants who only received 100% of mother's own milk-based diets. The maternal supply was okay. They didn't have to add the donor milk or the preterm formula. And so, they felt like they could do a head-to-head comparison. There were 114 babies: 82 in the exclusive human milk-based diet and 32 in the bovine fortifier group. Again, they did find statistically significant differences between Stage 2 or greater NEC and in surgical NEC or death. But again, this was very much a post-hoc analysis. When we've done calculations to think about if you were designing a head-to-head comparison of fortifiers in an exclusive human milk diet, to see a reduction in NEC, we think that you would need about 600 infants. I think this is not only a secondary analysis, but just also likely to be very underpowered.

OptiMoM Trial

I mentioned that there has been 1 trial that I think was well designed and did a true head-to-head comparison, and this is the OptiMoM trial, again done by Dr. O'Connor in Canada. Their group randomized 127 infants. These were babies less than 1,250 g at birth, average birth weight of 880 g and 27 weeks. They received a base diet of either maternal milk or donor milk. The fortifier was added when enteral feedings reached 100 mL/k/day, and it was either the human milk-based or the bovine. The primary outcome was the percentage of infants with feeding interruption for more than 12 hours or more than a 50% reduction in feeding volume. So again, this study was really designed to look at feeding tolerance and not really NEC.

Human Milk Fortification – Evidence Related to Bovine vs Human-Milk Derived

They found no difference in feeding tolerance, which was the primary outcome or on what they were calling a morbidity and mortality index that included death, late-onset sepsis, NEC, BPD, or severe ROP. I did note that if you only looked at Stage 2 NEC or greater, it was 4.7% in the human milk group and 4.9% in the bovine fortifier group. So again, this is a relatively small study in terms of what you would need to truly power for an outcome of NEC. But I think it's probably the best evidence we have that we do not see a signal with NEC with the human milk-based fortifier.

Summary of Evidence

Cristina [Navarrete] very nicely has pointed out the textbook, and there's a wonderful chapter in there on human milk fortification. I took 2 quotes from this chapter that I think summarize the evidence we've reviewed so far. "The use of bovine milk-based fortifiers is the current standard of care and represents an essential step towards covering nutrient needs." "At this time, there's no evidence to justify recommending a preferential use of human milk-based fortifiers, which are also far more expensive than bovine-based fortifiers."

Sarah [Taylor] already mentioned that there has not been any evidence to suggest that the human milk-based fortifiers have an impact on the preterm infant microbiome, and that microbial diversity is really influenced primarily by exposure to maternal breast milk.

Growth and HM-HMF

I'll briefly touch on growth in terms of the use of the human milk-based fortifiers. In the OptiMoM trial they found no difference in growth z-score trajectories, but it is important to note that to achieve those growth outcomes, a higher caloric density was needed, so again, thinking about dilution of milk. Amy Hair has done really nice work looking at the human milk-based cream product, which can provide caloric enrichment. In her data, there is a suggestion that this may worsen linear growth which, again, has been associated with adverse neurodevelopment. In the more recent study, the growth velocity was lower in the group that received the human milk-based fortifier vs the bovine, and again, this was a retrospective study, but they also saw no difference in NEC.

Donor human milk

We'll talk a little bit more in my talk later this morning on growth faltering, about the reasons why babies [who are] receiving donor milk may need special consideration for fortification. I know I'm running a little bit out of time, but the point I really want to make is that the milk processing and pasteurization can result in fat loss and in a reduction in bioactivity and concentration of nonnutritive factors.

This is a slide to show you that the more times we handle milk, from the donor who pumps the milk and takes it to the milk bank, and then it's pooled, and it's put into larger containers to go to your unit. Then it's further divided for individual feedings, you really see a very dramatic decrease in the concentration of fat. Especially if you're using continuous feedings, the fat can adhere to the tubing. I've found that explaining that to the nurses in the unit, because I feel like any little spit, and we're asked, oh can they go on continuous feedings? I've found that explaining the detriment in terms of nutrient delivery, they're like, oh no, well, we can live with the spits. I think that's an important thing to make sure that your frontline providers understand.

When to fortify? Gosh, this is something that we just don't have great evidence on. I think there is no evidence to say that early fortification is harmful. With donor milk, again we'll talk about this a little bit more in the talk on growth faltering, but I think adding a liquid protein in your milk preparation room to bring the donor milk up to preterm milk concentration is a reasonable practice.

Conclusions

I will conclude by saying that human milk is the preferred nutrition support source for preterm infants and should be fortified with a multicomponent fortifier to support short-term growth during the NICU course.

At present, there's insufficient evidence to support the choice of a human milk-based human milk fortifier over a bovine-based product. Either may be used, and we need more studies

Human Milk Fortification – Evidence Related to Bovine vs Human-Milk Derived

on the long-term impacts. Additional fortification or modular agents may be necessary to attain optimal growth in high-risk infants, especially those who are receiving pasteurized donor milk.

I would just make a plea that we need additional studies for newer generation fortifier products, including those with partially or extensively hydrolyzed protein. I think there's so much that we need to learn in how we approach post-NEC refeeding. One of my colleagues at Emory, Heidi Karpen, is doing some nice work looking on alternative diets for babies with congenital gastrointestinal disorders. I've really not touched on that at all, but [there's] still a lot of work to do. Thank you very much for your attention.

Abbreviations

BM-HMF	bovine milk-based human milk fortifier
BOV	bovine
BPD	bronchopulmonary dysplasia
BSID	Bayley Scales of Infant Development
BW	birth weight
CVL	central venous line
DBM	donor breast milk
DoMINO	Donor Milk for Improved Neurodevelopmental Outcomes
EHMD	exclusive human milk diet
ELBW	extremely low birth weight
EP	extremely premature
FDA	US Food and Drug Administration
GA	gestational age
HM	human milk
HMF	human milk fortifier
HM-HMF	human milk-based human milk fortifier
MBM	maternal breast milk
MDI	mental developmental index
NEC	necrotizing enterocolitis
NG	nasogastric
NICHD	National Institute of Child Health and Human Development
NICU	neonatal intensive care unit
NRN	National Research Network
OptiMoM	Optimizing Mothers' Milk for Preterm Infants
PAS	Pediatric Academic Societies
PDI	psychomotor developmental index
PF	preterm formula
RCT	Randomized Clinical Trial
ROP	retinopathy of prematurity
TPN	total parenteral nutrition
VLBW	very low birth weight

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