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TRANSCRIPT

Supplementing Micronutrients and Trace Elements to Improve Growth and Outcomes in VLBW Infants

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The topic today is From Probiotics to Biotherapeutics in the NICU.

We know from very early ages that many cultures had associated the ingestion of bacteria with health, so different people used the fermentation to ingest bacteria. At least in probably the last hundred years, after the early observations made the association of the ingestion of bacteria with long life was when the research about bacteria microbial was started. And now we know and Dr. Hair showed another example of how the microbiome is related and implicated in our bodies, not only in the intestine, but all parts of our body are related to the microbiome, and the lack of a normal microbiome relates to diseases. Everything has been associated, Parkinson's, Alzheimer's and other conditions have been associated with the lack of a healthy microbiome.

Premature babies is the population that really are more prone to having dysbiosis. The preterm babies, the mode of delivery, many of them are born by C-section, so they don't acquire the bacteria through the vaginal channel. They are exposed to a different environment. They don't go with mommy to home and they don't breast-feed so they go to a NICU environment. We frequently use antibiotics and also diet composition. Dr. Hair has already mentioned some of the facts that prevent these babies from acquiring a normal microbiome. And in this population dysbacteriosis is very prevalent and a population that will most benefit from trying to prevent dysbiosis.

So, what have we done so far and what is the evidence on how we can prevent this type of dysbiosis? The first clinical trial was in Taiwan in 2005 and that clinical trial was very obvious and was very strong in terms of prevention reducing the microbiome probiotics and decreasing incidence of sepsis, incidence of necrotizing enterocolitis and mortality. After that study in 2005, people started to do all kinds of clinical trials and this is a meta-analysis from 2016. Probably there are many more clinical trials after this 2016 meta-analysis, but this meta-analysis compiled the results of 38 trials that included more than 10,000 subjects in this study. And the results of the meta-analysis show that the use of probiotics decreases the risk for severe necrotizing enterocolitis.

Out of this meta-analysis, there were 29 clinical trials involving 9,000 babies, in which the risk of mortality also decreased with the use of probiotics. Not only necrotizing enterocolitis, but all causes of mortality. So, after this meta-analysis compiling all the clinical trials at that point, the question was should we use probiotics as a routine in the neonatal intensive care unit? Many areas are starting to use probiotics. Colombia is one of the countries that uses more probiotics. In Europe also, there was more use of probiotics. In the United States, their use was not that expanded but a survey showed that 14% of the units—and that was in 2016—used probiotics. And in the 500 units that were asked, 70 used probiotics and the probiotics included 16 different products, differing types of probiotics. And of those 16 types of probiotics, only 2 were validated by clinical trials. What does that mean?

When we look at those probiotics, there were different types of *lactobacillus*, different types of bifidobacteria and there were different types of other bacteria, like saccharomyces boulardii and other bacteria that were used in those probiotics. When we talk about probiotics, are we talking about the same thing and, in some ways, we like to say antibiotics—the use of antibiotics—cures infections. But were the antibiotics all the same? And this is a meta-analysis that was (inaudible) separate the studies that were done with bifidobacterium species, that were done with *lactobacillus* species. We see that the results are great, significant. On both types of probiotics, they decreased the incidence of necrotizing enterocolitis.

But, for example, when they include in the analysis probiotics that include saccharomyces boulardii or bacillus species, even when these probiotics include *lactobacillus* and saccharomyces, they can decrease. So, those probiotics were not able to prevent or decrease the risk of necrotizing enterocolitis.

That's the first question is when we talk about probiotics, are we talking about the same thing or of the difference between one and the other? And the other important point when we talk about probiotics is shown in this study that was an independent agency analyzed probiotics that were in the market. So, there were 16 different probiotics that contained bifidobacteria. Of the 16 probiotics, there was pill-to-pill variability, there was variability between one bacteria and another bacteria. Some of them, they have a species that was not labeled and only one of

the probiotics matched whatever was on the label of the probiotics.

There are concerns in terms of safety using probiotics that are not well-regulated or they don't reflect whatever's supposed to be in the probiotic. But, at the same time, there is a question of efficacy. How effective are these probiotics? So, if all these clinical trials were done with probiotics that didn't have the bacteria they're supposed to have or didn't have the amount of bacteria they're supposed to have, the doses were not consistent with the same composition, so there is a question of can we be more effective, can we use a real probiotic with a real amount of bacteria or the right bacteria being more effective in terms of correcting the dysbiosis?

That leads to a statement by the European Society of Gastroenterology, Pathology and Nutrition and Parenteral Nutrition and also by the American Academy of Pediatrics, the committee that focused on newborns, and they called to regulation of the probiotics that were used. The European statement was more liberal and they claimed only products manufactured according to current good manufacturing practices should be used. In the States, the call was a little bit more restrictive and they talked about a pharmaceutical-grade probiotic product not being available, had not been studied, and the long-term safety of the use in probiotics was not proved. And they also make a point about the fact that about the use of probiotics in the NICU being was used for babies under 1 kilo. And no or most of the studies that were done did not include a population of this immature or more premature babies.

So, then the regulation is different for the use of probiotics and we are going to make the difference. So the probiotics are really dietary supplements. They are regulated by a GRAS notice which is generally recognized as being safe. Biotherapeutics are, if a probiotic is used for diagnosis, treatment or prevention of any specific disease, it's a drug and it's supposed to be considered like a drug, but it's a biological product and that's why it's called biotherapeutic. And this is not regulated by the same center; it's regulated by the Center for Biologics Evaluation and Research, the same center that evaluates the use of vaccines.

So, basically the difference between a dietary supplement which is what we call probiotics and a biotherapeutic is that supplements are considered safe until proven to be unsafe. The way that we use the probiotics and the way that the world uses probiotics to promote health, but not specific to cure a disease. A prescription medicine which is a biotherapeutic is something that is considered unsafe until proven to be safe or effective. And the difference, there's a long list of differences, so the classification of dietary supplements or live biotherapeutic, the proof of safety is not needed for the supplement, the proof of being effective is not needed for the supplement. There is no postmarketing surveillance after the product is used for everybody. There is no good manufacturing practice, they are different. One is regulated like a food supplement and the other is a pharmaceutical. Also there is no disease claim on the label of the 2 products. This is the theory of what we know about the 2 products.

This is a publication that came out early this year in 2025 and this is very interesting because all the areas in which the probiotics had been used, there is a little report, so maybe sepsis that happened or some complication. There are case reports of those things. There was, the latest case report was sepsis used by the bacteria that was given as a probiotic and that was what alerted the FDA to try to refrain and stop the use of probiotics liberally. But this is from the Canadian Neonatal Network and this reports the use of probiotics in Canada and they confirmed, they were using mainly 2 different probiotics one was a probiotic that contained 4 bifidobacteria and 1 *lactobacillus rhamnosus* and the other probiotic that was extensively used was a probiotic that contained *lactobacillus reuteri*.

So, the results and there was a large number of subjects, so there was babies that did not use probiotics was 15,000 compared with the babies that used probiotics was 18,000. And they also made a comparison between the babies, all the babies under 34 weeks of gestational age and babies who were under 1 kilo. And the results were really in some way amazing or surprising because in babies, when they analyzed the whole group, the babies less than 34 weeks, the incidence of necrotizing enterocolitis was higher on the babies who were exposed to probiotics. The sample size is very large, so probably the study, the analysis, was a little bit over-powered, but this was different in the whole group, but when they looked at babies less than 1 kilo, there was no difference in the incidence of necrotizing enterocolitis. The other interesting thing was mortality. In the whole group, there was no difference between the 2 groups, probiotics or no probiotics, but in babies less than 1 kilo, there was decreased mortality in babies who were exposed to probiotics and this is really significant. In terms of sepsis, there was also higher incidence of sepsis in babies who were more than, in the whole group of babies, less than 34 weeks.

Looking at the comparison of the groups, obviously the babies who used probiotics were a little bit smaller, but the rest of the things were more or less similar. But the interesting thing was

babies less than 34 weeks, 27 infants, there was 27 cases of probiotic sepsis. That the probiotic that was used produced sepsis and this sepsis in 41% of the cases was related or associated with the intestinal necrotizing enterocolitis or intestinal perforation close to the sepsis, before or after the sepsis. They were trying to relate this fact with the sepsis. And in babies less than 1 kilo, obviously, 24 of the sepsis were more in the smaller babies, 24 out of the 27 happened in babies less than 1 kilo and again, around 40% of the cases of sepsis that were also related with the incidence of necrotizing enterocolitis or single intestinal perforation. Three babies died of the sepsis.

This is the first report that we have about the extensive use of probiotics in a big area and these are the results reported that obviously it's a retrospective study which may have a lot of confounding factors, but the number, the Ns, are really, really large to take care of many of those confounding factors.

If we look at the other side, the use of biotherapeutics, this is the only study up to now in which probiotic or bacteria has been developed like a pharmaceutical, like a biotherapeutic, and has been studied in a clinical trial. This is a randomized, controlled trial in what they used IBP-9414 in premature infants. This is a product that is *lactobacillus reuteri*. *Lactobacillus reuteri* is one of the probiotics that has been used in many areas and is a probiotic or bacteria that has been proved to have some mechanism that combats dysbiosis, increases motility and also reduces the immune regulation on the gut. This bacteria has been developed and the FDA and European Medicine Association to be developed like a pharmaceutical under the criteria of pharmaceuticals. So it's dry, freeze dried. It's prepared right before being administered to the baby and the manufacturing process is developed on IND under the FDA.

With this product, they did a phase 2 study which was mainly to test safety and there were 3 cohort groups, babies of different birth weight, and they compared one with the other. There was no different on the incidence of adverse events, so major adverse events. And there was nothing major adverse event or side effect alerted in terms of the safety of the product. In other studies, also there was analysis of the intestinal, the stools and they proved that there was no cross-contamination between the control and the intervention group.

After the phase 2 study, the phase 3 was developed and finished like probably a year ago, the recruitment of patients. The phase 3 primary endpoints were the prevention of NEC and also the time to sustained feeding tolerance. This probiotic was proved to increase intestinal motility so one of the ideas was to see it promote feeding tolerance and the babies who were in the study would reach full fit sooner. Secondary endpoints was necrotizing enterocolitis defined and confirmed by laparotomy or autopsy, so we had the pathology of the intestine. I have to say, sorry, there's the prevention of NEC, the NEC was defined by report of the PI of the study group and confirmed by x-ray with 2 independent radiologists that when they were disagreeing in the reading of the x-ray was shown to another radiologist that will decide if the x-ray was a sign of NEC or no signs of NEC. The study consisted starting on the first 48 hours of life and the probiotic was administered until the baby was 34-plus 6 days, so 35 weeks of gestational age. It was a daily dose of this bacteria.

To be sure that babies under 1 kilo were included, it was done in different phases. There was a first phase in which infants that were recruited were between 700 to 1 kilo and then when a certain number of those babies were included, the study was expanded to babies less than 700 to 500 g and above and also to 200 so that we are sure that the population included in the study had all groups of birth weight and gestational age.

This is the CONSORT diagram. Out of the 1,000 babies, around 1,000 babies that were recruited inside, the 900 that completed the study and they had the follow-up. The follow-up was around 40 weeks of gestational age. After have finishing the administration of the product, they were followed up for any other adverse event. And the results show that for necrotizing enterocolitis, what was defined like general or total necrotizing enterocolitis, obviously stage 2 and 3 or more than 2, there was no significant difference between the groups. The study also had the primary outcome to analyze the results after 14 days. We are going to talk about that now.

When they refer to nonsurgical NEC, there was (inaudible) but also there was not significant, but when we analyze the results after 14 days, there was a significant difference. Same thing happened when we looked at necrotizing enterocolitis that was surgical, there was evidence by pathology by surgery all because mortality in both cases, they show the signs, pathological signs of necrotizing enterocolitis. And in this case, the *P* value was statistically significant. So, in reality, the use of this product decreased the risk of severe necrotizing enterocolitis when it was diagnosed by pathology or surgical path.

What was very interesting, it was the highlight of this study, I think is that the fact that, for the first 15 days of life, there was no difference. And then when we look at different outcomes or the outcomes that were secondary outcomes, the first 15 days of life, the first days, there was not so much difference. And then after 15 days, the results started to separate, the groups started to separate. We thought this is interesting because

really a probiotic or a bacteria need time to be colonized, a time for that bacteria grow. So, we cannot expect an effect of the probiotic the day after it is given or the second day or in 3 days. So—and this is something that previously was not taken into account—it's important that if we are thinking in using this product for the prevention of dysbiosis which starts as soon as possible because it takes a little bit to have an effect.

The other interesting thing is that mortality, all causes of mortality, was significantly decreased in between the 2 groups. So, starting from any time and then when we analyze after 14 days of life, the decrease in mortality was significantly decreased with a total of 27% decrease of mortality. So, this is interesting because the decrease of morality may be related with the severity of necrotizing enterocolitis, but probably not all the risks, all the reasons is that, but also open what we were talking at the beginning, like the bacteria isn't all body and probably there is many other organs that are associated or affected by dysbiosis or the use of prevention of dysbiosis.

There was no difference in the side effects when analyzed. Obviously, the adverse events that were reported by the PI, this is a study that included 70 different units in many different states, in Europe, in Israel, so the definition of these adverse events, they are not that strict. It was just reported, but it will be interesting to know if any, there was no difference between respiratory in general or gastrointestinal disorders or disease.

So, this is just a meta-analysis that happened in 2012. It's interesting because it was another one of these meta-analyses where they separate bifidobacteria of *lactobacillus* and bifidobacteria *lactobacillus* in the clinical trials. And we see that any one of the groups, there is a decrease in the risk of necrotizing enterocolitis, but however the decrease of mortality is only shown by the groups that have *lactobacillus*. The group that had bifidobacteria does not decrease mortality, but decreased necrotizing enterocolitis. The group that had *lactobacillus* alone or with bifidobacteria, there was a decreased risk of mortality which is consistent with whatever we see in the clinical trial and is consistent also with whatever the results of the Canadian use of probiotics report.

So, generalizing, we can do better but to do better, we have a lot of things, a lot of work ahead. And it's important that, to promote research that investigates a specific mechanism of action. Most of the clinical trials, the probiotic that was used was the probiotic that was available and without substantiated the choice with mechanism or reason of basic research to support the use of that probiotic. We have to define the strains or combination of strains that have clinical benefits. Probably not all have clinical benefits, so we cannot just use without thinking in this (inaudible) probiotics because maybe they are different and there are more that may be more effective or less effective. We have to be sure that there is regulation that guarantees the quality of the products in both sides, in terms of safety and in terms of efficacy. We have to explore strategies on how to prevent dysbiosis in premature infants and this is called from maybe giving the bacteria to the baby or maybe adding to the nutrition that the baby may have or maybe adding the bacteria, giving the bacteria to the mother and the mother may produce or may change the colonization of the breast milk.

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