Probiotics & Practical Use in the NICU

Featuring:

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TRANSCRIPT

Maura Bowen: If you're a longtime **Power of Nutrition Podcast** listener, you already know how we spend a lot of time talking about the value of probiotic use in the NICU, mostly because we work closely with experts around the world who've seen massive success in establishing probiotics programs in their NICUs and have the data to back that success. One of the prevailing notions, however, is that it's wise to proceed with caution when establishing probiotics protocols in the NICU. That's because there's a lot to consider. Like deciding which probiotics to introduce, or how they'll be prepared and administered, or how long will the treatment course be, and most importantly, which patients will receive this treatment. And all of these questions should be answered to gain alignment of the NICU team. Additionally, attention should be paid to how to measure efficacy. So, if you're working through some of those same questions for your practice, you've come to the right podcast.

Maura Bowen: I'm Maura Bowen with Abbott Nutrition Health Institute, and I've invited two **Power of Nutrition Podcast** regulars. That's Dr. Karyn Wulf, Abbott Medical Director and practicing pediatrician, and Dr. Adam Baker, Director of Science, Human Health Innovation from Chr Hansen in Hørsholm, Denmark for this discussion today. And we're also honored to host Dr. Arpitha Chiruvolu, a practicing neonatologist, who's joining us from Baylor University Medical Center in Dallas, Texas. We'll focus this discussion on successful protocols Dr. Chiruvolu has introduced it to her NICU, along with six months of data she's collected to help demonstrate the continued support of her probiotics program. Doctors, thanks for joining us today.

Dr Chiruvolu: Thank you, Maura. I appreciate the opportunity to share our experience on probiotics implementation in the NICU.

Dr Baker: Thank you, Maura.

Dr Wulf: Thanks, Maura. Happy to be back with you today.

Maura Bowen: So as usual, I'd like to give you all the opportunity to introduce yourselves. So, Dr. Chiruvolu would you like to go first?

Dr Chiruvolu: Yes, Maura. I'm a neonatologist in practice for over 15 years, currently working at Baylor University Medical Center in Dallas, Texas. I also serve as an assistant professor of pediatrics at Texas A&M College of Medicine. I'm a clinical researcher in the field of neonatal/perinatal medicine.

Maura Bowen: Wonderful. Thank you. And Dr. Baker, would you like to go next?

Dr Baker: Thank you, Maura. Yes. I'm a human molecular geneticist, who has been studying complex diseases and oncology for most of my career. And for the last 10 years I've been a Chr Hansen where I'm the Director of Science and Human Health. And there I'm really focusing on the human microbiome and how probiotic bacteria can support and help in different ways.

Maura Bowen: Great. Thank you. And Dr. Wulf, can you tell us about your background?

Dr Wulf: Sure. I'm a general pediatrician and for the past 18 years, I've been practicing clinically. I joined Abbott almost three years ago as the Medical Director for Pediatrics.

Maura Bowen: Perfect. Thank you. So, before we start, I'll note that I'm recording in the studio while Dr. Wulf and Dr. Chiruvolu and Dr. Baker are dialing in from their respective offices. And I'll also note that Dr. Wulf will be conducting today's interview, and she'll provide her insights along with Dr. Chiruvolu's and Dr. Baker's answers. So, Dr. Wulf, I will hand the microphone over to you.

Dr Wulf: Thank you so much, Maura. So, thank you to Dr. Chiruvolu and Dr. Baker for being here today. Dr. Chiruvolu, you recently established detailed protocols for using probiotics in your NICU. I'm hoping we can spend some time today describing that process and I'd like to take it step by step. So, the first question is what made you decide to embark upon a probiotics program in your NICU?

Dr Chiruvolu: Thank you, Dr. Wulf. So, the main goal of probiotics implementation in our NICU was to decrease the incidence of necrotizing enterocolitis. NEC is a multifactorial process of intestinal infection and inflammation involving abnormal bacterial colonization and overgrowth. However, we also believe by decreasing the dysbiosis, we may observe improved feeding tolerance and growth in our preterm patients. This may in turn lead to reduction in various morbidities and mortality.

Dr Wulf: So how did you determine which probiotics you wanted to use? Considering things like multiple strains versus single strain probiotic and a liquid versus powder formulation?

Dr Chiruvolu: We decided on multi-strain probiotic as increased diversity may lead to increased dysbiosis. The experts societies such as European and North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition Committees provided a positive recommendation for a multi-strain probiotic combination that may reduce necrotizing enterocolitis stage two or three. There is also evidence that if proven efficacious, two to three strains may be more effective than a single strain bacteria. Liquid versus powder did not matter as long as it is made safe and mixes well.

Dr Wulf: Dr. Baker, would you like to talk a little bit more about the liquid versus powder question?

Dr Baker: I think the way we're actually focusing on the difference between liquid and powder. For us, it is critical that we could actually get the safety, the hygiene, the monitoring and the quality of the product to the highest levels. And also, the way that we could actually deliver this product in a single dose format. And so actually for us, the powder turned out to be the best way that we can actually control absolutely stability, quality of the sort of ingredients within that--the absolute state-of-the-art monitoring we talked about, the ISO-seven hygiene monitoring. And actually, been able to make this so there's individual [unintelligible 00:05:20 - 00:05:25: _____ with a _____ _____ manufacture ____] for this process. So, for us, this was the best way for us to be able to deliver the strains.

And if I could say as well that we also agree with the single strain versus multi-strain, we're very proud about the science that can be developed as we just mentioned. And we can actually show the actual added benefit of actually using multiple strains is actually able to build even more efficacy, more scientific data to actually show that this is maybe a better combination to be using.

Dr Wulf: Thank you so much for that interesting information, Dr. Baker and Dr. Chiruvolu. Dr. Chiruvolu, how early and how long do your protocols suggest offering probiotics to preterm infants.

Dr Chiruvolu: We start probiotics on all the infants born less than 1500 grams as they are at higher risk for developing necrotizing enterocolitis. We aim to get the first dose within first 24 hours of life, soon after the infant receives mother's colostrum. We give one dose daily until infant is 35 weeks postmenstrual age. This is the age when the risk of necrotizing enterocolitis starts declining.

Dr Wulf: We all know that change is difficult and especially change in clinical practice. Dr. Chiruvolu, how did you start to talk to the decision makers about your probiotics protocol? How did you gain alignment? And can you describe what that process was like for you?

Dr Chiruvolu: We reviewed the research and evidence thoroughly and presented it to the group and hospital leadership as to how the probiotic implementation would benefit our preterm patients. We presented our smart goal and cost analysis based on previous studies. This process was not difficult as the leadership supported our passion to provide best care for our patients.

Dr Wulf: Could you describe a little bit about how you set up your program?

Dr Chiruvolu: We formed a multidisciplinary team consisting of physicians, nutritionists, hospital administration and nursing. After reviewing pros and cons of multiple probiotics products available, we decided on the best product for our unit. We then came up with an evidence-based protocol. We worked with nurses on feasibility for administration and to prevent contamination. We also involved microbiology for improved surveillance. We worked on resources for parents and had them in our admission packet. We were well prepared for the rollout.

Dr Wulf: That's really helpful to have you go through those stages. Thank you so much. With all new programs, there are some challenges. Did you face any challenges in the early stages, and are there any challenges you still face today?

Dr Chiruvolu: As with every quality improvement initiative, we had small kinks that needed to be fixed. Overall, the rollout was very smooth. We performed continuous surveillance, data monitoring, and addressed any issues immediately. This improves compliance and efficacy.

Dr Wulf: So, Dr. Chiruvolu, that's really interesting. You mentioned, as you were setting up our protocol, that you took a multidisciplinary team approach. How did you approach the microbiology question of what is needed for surveillance for potential of probiotic-associated sepsis in the preterm infant?

Dr Chiruvolu: We got together with microbiology and discussed this in detail to prepare a process. The multi-strain, probiotic, non-pathogenic bacteria that we use, although anaerobic, show marked growth in the presence of oxygen. Our regular blood cultures that are incubated in aerobic environment at 37 degrees Celsius, may be enough to detect these bacteria. The lab performs what is known as MALDI-TOF, Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry to identify these organisms. So, we do not routinely send anaerobic blood cultures to detect probiotic sepsis.

Dr Wulf: Dr. Baker, do you have anything you'd like to add to that?

Dr Baker: Yes Dr. Wulf. I think what Dr. Chiruvolu said is so important and interesting. And I think we know, and we study these strains so specifically. We have the genomic sequence of the entire strain completely sequenced, and we have the technologies, you just said MALDI-TOF or sequencing. So, we're able to take samples and sequence and understand absolutely without doubt, what is the strain or what is the cause of this sepsis. And this is the type of thing we need to do now to ensure and understand if it's due to probiotic or is it due to other bacteria.

Dr Wulf: So, understanding the protocol that you put in place, Dr. Chiruvolu, what are some of the outcomes that you've seen as a result of your probiotics protocols?

Dr Chiruvolu: It is very exciting to share our preliminary data Dr. Wulf. We had 100% compliance with the protocol. Our interim data analysis showed improved growth velocity in very preterm infants, decreased incidence of necrotizing enterocolitis, improved feeding tolerance with decrease in the median number of total parenteral nutrition days. We also observed decrease in our median length of stay for very preterm infants by 15 days. And there were no episodes of probiotic sepsis.

Dr Wulf: That's fantastic. Dr. Baker, do you have anything you'd like to add to that?

Dr Baker: Well, I would like to say that it's fantastic to hear these results. Some of the similar results that we have seen before, they were so positive to see with using these strains. And I think it's important to reflect as we go forward. These are the strains that are key. We've talked about that in this podcast to building a healthy microbiome. And you will see these strains being important also when we start to look at term infant or term babies and going into early infancy. So, these are strains that are so important in giving you a good start. And it's so great to hear how well they are doing in the preterm infant, but it doesn't just stop there, they continue as we go to term infancy and beyond.

Dr Wulf: So, Dr. Chiruvolu in your mind, what is the feasibility of continuing your ongoing probiotics use in the NICU setting?

Dr Chiruvolu: It was very feasible to use probiotics in our NICU. We have a process nicely set up and the flow is very smooth. In the morning huddle, the charge nurse confirms the list of infants needing probiotic dose for that day. Preparation is performed by a nurse at a dedicated place, and the syringes are delivered to the bedside. The nurses administer them to their patients.

Dr Wulf: We really appreciate you sharing your clinical experience because we know we got a lot of questions about that. I would really like to ask you a few rapid-fire questions now. So, if you don't mind, we're going to just share some of the questions we've heard when considering the use of probiotics in that preterm infant space. What are your thoughts on using probiotics to address virulent?

Dr Chiruvolu: One of the actions of probiotics is to cause modified immune response. They augment immunoglobulin air response, inhibit cell death, and stimulate cell regeneration. This is the reason probiotic bacteria also may have positive effect against viruses and fungi.

Dr Wulf: And what are your thoughts on probiotics and the development of antibiotic resistance?

Dr Chiruvolu: Probiotics may contribute in reducing the antibiotic-resistant pathogens. There's also a theoretical risk of probiotic, bacterial strains spreading the antibiotic resistant genes. However, there are no specific studies in preterm infants addressing or proving this.

Dr Wulf: Dr. Baker, Dr. Chiruvolu mentioned antibiotic resistance genes in this theoretical risk. What do you know when studying the strains that are used in the NICU space about virulence factors and resistance genes in those strains of probiotic?

Dr Baker: We study it actually very, very, very carefully and intimately. As you know, when we actually take these strains, one of the first things we do before we start working with them, we sequence them completely. And then using silicon technologies, which can then go into lab technologies, we're actually understanding [inaudible 00:13:25] how a whole or a half human genome, and then concerning antibiotic-resistant-type genes or virulence genes. If they have anything, we stop. It is not going to be used in the pre-clinical space. And certainly, we can go further and test that.

Sometimes you take a little test with them within the lab in these settings. But I think it is in a very interesting area. Dr. Chiruvolu also said it, but the recent ideas in that the probiotics and there's some very interesting science coming out on this now about the risk of antibiotic resistance in the microbiome and how probiotics can actually help keep this down or push it away whereas adding these types of bacteria and the effects they have, as Dr Chiruvolu said, making sure that we actually try and keep the [inaudible 00:14:08] resistance that's going off within the microbiome. It's a fascinating area.

Dr Wulf: That is really fascinating. I'm going to switch gears once again on you. And now I'm going to shift to the parent perspective. So, Dr. Chiruvolu, when you are talking to parents and trying to counsel them, and parents who want to know about the safety and efficacy of probiotics, what do you say to them?

Dr Chiruvolu: It is very important for the parents to be involved in their infant's care. So, we do mention about probiotics when performing antenatal counseling. We also counsel them after a patient is admitted to the NICU by providing resources. There is a detail handout in the admission packet about probiotics. Until now we did not have parents who refuse probiotics for their infants. In fact, we had parents for the infants who do not qualify according to the protocol, asking for probiotics for their babies.

Dr Wulf: So, it, in your experience, it's been generally well accepted by parents as an intervention in the NICU?

Dr Chiruvolu: Absolutely. No question about that.

Dr Wulf: Fantastic. So as always, we look to the literature to give us guidance on, on these practices. And there was a recent quote from the American Academy of Pediatrics. And to quote the article from just this past month in June 2021, "Given the lack of FDA-regulated pharmaceutical-grade products in the United States, conflicting data on safety and efficacy and potential for harm in a highly vulnerable population, current evidence does not support the routine universal administration of probiotics to preterm infants, particularly those with the birth rate of less than a thousand grams." Do you think your data could impact the statement? And if so, how?

Dr Chiruvolu: That's a great question Dr. Wulf. The American Academy of Pediatrics is being very cautious, given the vulnerability of the extremely preterm infants and the possibility of adverse effects in this population. One thing to remember is published studies have included fewer infants who were born less than a thousand grams.

Overall, there was no benefit reported with probiotics used in this population, but no harm was documented. Moreover, this population is at higher risk for necrotizing enterocolitis, sepsis, and other adverse effects of dysbiosis. Therefore, we included these infants in our routine probiotic implementation protocol. And so far, we did not see any adverse effects. And as I shared before, our probiotic implementation went very well. We started seeing benefits in preterm infants. But I do agree with American Academy of Pediatrics clinical report, that centers choosing to administer probiotics, especially in these extremely preterm infants should carefully monitor outcomes, adverse events, and safety.

Dr Wulf: Thank you so much, Dr. Baker, do you have any thoughts about this recent statement?

Dr Baker: Absolutely, fully agree with Dr. Chiruvolu. And if we're going any further, I'd like also to think that we actually consider very carefully, because I think some of the caution, which is absolutely understood, is to consider which strains of probiotics you're using as well. And once you've got those to actually add them in. And we have seen as well in the clinical studies that have been done with the strains that have been used, there was actually no specific data saying that it works better in these very, very underweight babies that they are included. And we also don't see any adverse effects or anything. So maybe more information is needed, more data is needed. But from a scientific point of view, there's no reasoning. As long as we have this very, very high standard of product, critical understanding of the strains, I cannot see why this particular group cannot end up benefit from the probiotic strain.

Dr Wulf: You both highlight really important parts to that question. And we go back to the concern that the AAP mentions on the manufacturing and safety and the lack of FDA oversight for that, and I know we've dedicated a whole podcast in the past to the safety and protocols that are in place for certain probiotic strains, including the one that Dr. Chiruvolu is using in her NICU. So, I think that really understanding the individual strains, research behind the strains, the genetic sequence, the presence or absence of antibiotic-resistant genes, the manufacturing process. There's a lot to consider when selecting probiotics for use in the NICU. And as the AAP statement suggests, we don't know that about all of the different strains that have been studied. So, it's a really important thing to consider when using the probiotics in the NICU. So, thank you both so much today. I think, I think that's all of my questions.

Maura Bowen: This was such a fabulous conversation, and I really want to thank you three for your insights. As I mentioned in the intro, we talk about probiotics all the time here at Abbott Nutrition Health Institute. So don't be surprised if we tap you on the shoulder to come back to the podcast so that we can talk about this more as the learnings evolve. So, thank you for being here today.

Dr Wulf: Thank you so much, Maura. It was a pleasure being here.

Dr Chiruvolu: Thank you, Maura. It has been a pleasure participating in this podcast.

Dr Baker: Thank you so much Maura. It's been a real pleasure just being here.

Maura Bowen: Thank you all again. And for our listeners. If you're looking for more podcasts, we have dozens and dozens across a variety of different nutrition-science topics, and you can find them on ANHI.org by clicking “RESOURCES” at the top of the page, then “PODCASTS & VIDEOS.” We're also on Spotify now. So be sure to subscribe to ANHI's Power of Nutrition podcast series, to hear the latest nutrition science news and share us with your colleagues and also be sure to visit Christian Hanson's, The Probiotics Institute. That's TheProbioticsInstitute.com to learn more about how probiotic strains can benefit the microbiome across the life cycle. I wanted to point out that the Chr Hansen team just launched a new global site as well as the site, just for its audience in China. So, visiting the site will be solid time spent. Thank you everyone.