The relationship between NICU experience of VLBW infants and their microbiome at 2-3 years old.

Samia Dutra, MSN, Maureen Groer, PhD

University of South Florida, College of Nursing

Background

The infant gastrointestinal microflora is likely to significantly contribute to the core community that makes up the adult 'signature microbiome', which may participate in physiological and pathophysiological interactions with the host. In addition, the literature indicates multiple consequences of very low birth weight on health outcomes (Caesar et al., 2016; Eichenwald & Stark, 2008). This study examined the association of variables initially studied as VLBW infants in the Neonatal Intensive Care Unit (NICU) with their gastrointestinal microflora collected when they were 2-3 years of age. The gut microbiome was measured longitudinally during their NICU stay and then later when they reached 2-3 years of age.

Purpose

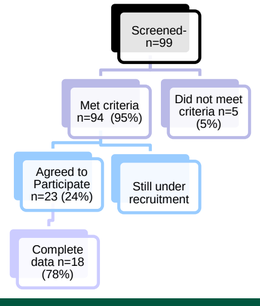
• The proposed study explored the relationship between NICU experience and characteristics of VLBW infants with their bacterial taxa at 2-3 years of age.

Methods

•Data from a parent study of a cohort of 99 VLBW infants with measures of gut microbiome, human milk intake, milk immunology, fecal calprotectin levels and later health outcomes collected when they reached 2 years of age.

•We followed VLBW infants (<1500 Gms) during 6 weeks of the NICU stay and followed up with home visits and stool collection at 2-3 years of age on 23 toddlers and their mothers.

• This study analyzed measures collected while the infants were in the NICU (gestational age, antibiotic intake, amount of human milk, birth type, and infections) with their bacterial taxa at 2-3 years old.



Acknowledgements

•This work was supported by National Institutes of Health [R01NR015446]

•An additional acknowledgment of the financial support to Samia Valeria Ozorio Dutra from the Brazilian Federal Agency for Support and Evaluation of Graduate Education (CAPES).

Methods

•Stool swab samples were stored at -80ºC prior to use. Microbial genomic DNA was extracted using the PowerSoil-htp 96 Well Soil DNA Isolation Kit (MoBio). DNA *Samples were forwarded to the lab of Dr. Jack Gilbert (Argonne National laboratory and University of Chicago).* The microbial content was profiled with 16SrRNA sequencing. PCR of the 16S rRNA V4 region (515F-806R) was performed and sequenced using the Illumina MiSeq platform to generate ~100,000 250 bp paired end reads per sample. Approval for this study was obtained from the university Institutional Review Board. All participants gave informed written consent to access their electronic health records and donate their children's stool samples prior to their participation.

Results

•23 VLBW infants (<1500 Gms) with equal gender distribution

•Fourteen (60%) of the sample suffered respiratory distress syndrome

Characteristics	Mean	Range
Gestational age (weeks)	27.9	25.3-32.4
Birth weight (gms)	1080.25	675-1485
Length of stay (days)	83.91	22-215
Days on Oxygen (days)	24.43	0-101

•Prenatal factors included maternal steroids.

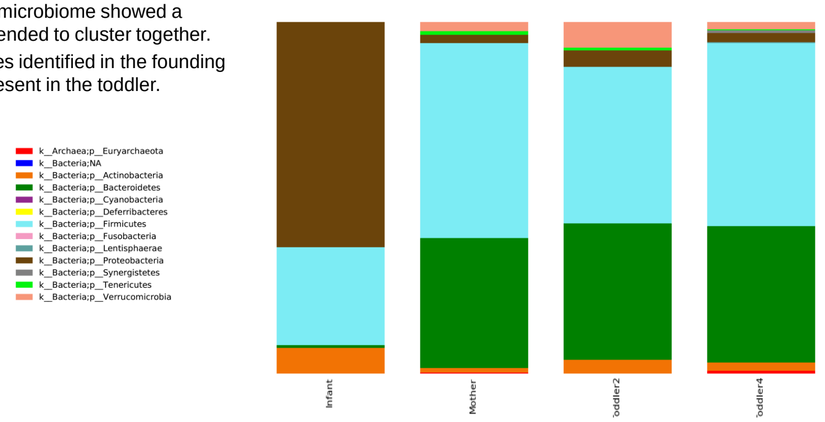
Parameter	Estimate	Std. Error	p-value
Intercept	24.06	22.35	0.284
C-section delivery	-23.63	7.65	0.002
Antenatal steroids	-23.57	11.47	0.042
Antenatal magnesium sulfate therapy	15.38	7.81	0.051

Regression model of alpha diversity in first 4 weeks of life

Results

•Principal Component Analysis of microbiome showed a potential genetic effects as twins tended to cluster together.

•In addition, some of the sequences identified in the founding microbiome of infants were still present in the toddler.



Discussion

•Preterm infant microbiomes confirmed an association between low gestational age and the microbiota profile.

• The predominance of *Proteobacteria* characterizes a dysbiosis that is linked with detrimental outcomes for preterm infants.

• In addition, the hospital environment, common use of antibiotics, and the use of infant formula rather than mothers own milk can contribute to dysbiosis.

• Oligotyping of the Enterobacteriaceae and Bifidobacteria found that certain substrains present in the stool in infancy were retained in the toddlers' stools.

•Enterobacteriaceae consists of virulent organisms capable of producing human disease (gram-negative bacteria that includes *Salmonella, Escherichia coli, Serratia,* and *Citrobacter)*, and increased proportions are found after antibiotic use.

Conclusion

•Toddlers show increased alpha diversity retaining some of the same Enterobacteriaceae "oligotypes" from infancy.

•Pre and post-natal factors significantly influence later childhood phyla composition..

•Feeding status is not predictive of community composition, but effect of antibiotics may be predictable.

•As an important regulator of physiological and pathophysiological effects, it is relevant to develop intervention approaches to decrease dysbiosis and increase diversity in the VLBW. In pursuit of appropriate interventions, studies which explore microbial influence, diversity and succession are crucial.

References

•Caesar, R., Boyd, R. N., Colditz, P., Cioni, G., Ware, R. S., Salthouse, K., . . . Hurley, T. (2016). Early prediction of typical outcome and mild developmental delay for prioritisation of service delivery for very preterm and very low birthweight infants: a study protocol. *BMJ open, 6*(7), e010726.

•Dogra, S., Sakwinska, O., Soh, S.-E., Ngom-Bru, C., Brück, W. M., Berger, B., . . . Chong, Y.-S. (2015). Dynamics of infant gut microbiota are influenced by delivery mode and gestational duration and are associated with subsequent adiposity. *MBio, 6*(1), e02419-02414.

•Eichenwald, E. C., & Stark, A. R. (2008). Management and outcomes of very low birth weight. *New England Journal of Medicine, 358*(16), 1700-1711.

•Groer, M. W., Luciano, A. A., Dishaw, L. J., Ashmeade, T. L., Miller, E., & Gilbert, J. A. (2014). Development of the preterm infant gut microbiome: a research priority. *Microbiome, 2*(1), 1.

•Groer, M. W., Gregory, K. E., Louis-Jacques, A., Thibeau, S., & Walker, W. A. (2015). The very low birth weight infant microbiome and childhood health. *Birth Defects Research Part C: Embryo Today: Reviews*, *105*(4), 252-264.

•Hollister, E. B., Gao, C., & Versalovic, J. (2014). Compositional and functional features of the gastrointestinal microbiome and their effects on human health. *Gastroenterology, 146*(6), 1449-1458.

•Karlsson, C. L., Molin, G., Cilio, C. M., & Ahrné, S. (2011). The pioneer gut microbiota in human neonates vaginally born at term—a pilot study. *Pediatric research, 70*(3), 282-286.

•Sharon, I., Morowitz, M. J., Thomas, B. C., Costello, E. K., Relman, D. A., & Banfield, J. F. (2013). Time series community genomics analysis reveals rapid shifts in bacterial species, strains, and phage during infant gut colonization. *Genome research, 23*(1), 111-120.

USF HEALTH COLLEGE OF NURSING UNIVERSITY OF SOUTH FLORIDA