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Neonatal feeding and developmental issues

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Prematurity occurs in more than 10% of live births in the world each year. This translates to approximately 13.4 million preterm infants in 2020, with nearly 1 million dying from preterm complications (1). Research has contributed significantly to advances in medical care of the fragile preterm infant, resulting in increased survival rates (2). Preterm infants often have long-term healthcare needs and may face multiple challenges during their care in the neonatal intensive care unit (NICU), including cardiopulmonary problems, infections, neurological, and oral feeding issues (2). Oral feeding is a complex sensorimotor behavior. The level of skill necessary to properly select, sequence and coordinate oral, pharyngeal, laryngeal, and esophageal subsystems for safe oral feeding render it as one of the most advanced neurological milestones facing the newborn (3,4). The demonstration of oral feeding competency in preterm infants is an essential requirement for hospital discharge. For some premature infants, oral feeding problems may persist into childhood and beyond (5–7). This emphasizes the importance of early diagnosis and management of feeding problems and periodic follow-up to address long-term challenges among children and adults born preterm. Therefore, the charge exists to refine and standardize diagnostic criteria and promote individualized therapeutic strategies facilitated using a comprehensive multidisciplinary approach to manage feeding disorders.

‘Neonatal Feeding and Developmental Issues’ is a special topic series which appeared in *Pediatric Medicine* [2021–2023]. This series includes eight original papers contributed by distinguished international scholars and their research teams. The shared expertise brought to bear on the challenges of prematurity and neurodevelopmental outcomes related to feeding development and disorders is impressive and includes neonatology, pediatrics, genomics, speech-language pathology, neuroscience, computer science, biomedical engineering, machine learning, and statistics. This exciting level of interdisciplinary

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collaboration brings new questions and experimental approaches, advanced technologies, and data analytics aimed at translational therapeutics to benefit the fragile preterm infant. A review of the papers contributed to this topical series illustrates a wealth of new information surrounding the complexities and multifactorial nature of the transition to oral feeds and safe swallows by premature infants including respiratory and neurological status, the significance of maternal stressors during this challenging process, and importance of home environmental factors to promote the development of vocalization, word usage, and speech. Machine learning of the biomechanics of ororhythmic patterning during non-nutritive suck (NNS) evolution complement studies of the viscosity and caloric composition of the nutrient bolus. New information of the relation between sensory-driven molecular pathways (genomics) and oral feeding behavior in extremely-very preterm infants highlights progress towards evidence-based individualized care of the preterm infant.

The Mizuno research team has a decade of experience developing and refining the human milk bank at Koto Toyosu Hospital at Showa University in Japan. This report emphasizes the urgent need to better understand the usage of donor human milk (DHM) in the NICU as there is only one human milk bank in Japan. Six key policy elements designed into their database are described which promote the efficient operation of the human milk bank, including accessibility from the NICU, streamlined input process, reliability and continuity, anonymity, database search functionality, and overall efficient administration. Collectively, these database elements serve to promote the operation of the human milk bank and contribute positively to perinatal outcomes nationwide. Moreover, these authors point out that globally it is rare to build a database aimed at understanding the background and prognosis of all children supplied with DHM.

Based on molecular assays, the Maron research team has shown in a randomized controlled trial that RNASeq analytics of genes present in neonatal saliva provides a near real-time window into ongoing development of molecular pathways and neural subsystems involved in feeding, hunger, and satiation. This innovative approach to study patterns of gene expression has the potential to identify biological networks, including sex-specific pathways associated with pneumotactile stimulation of the infant’s oral sensorium and the transition to oral feeding success. This is an exciting outcome as inclusion of RNA-sequencing (RNASeq) analytics provides the NICU-based care team with evidence-based markers for specifying individualized care and target treatment strategies based upon an infant’s sex and individual gene expression profile.

The sensory, motor, and cognitive experiences within the home environment, including nutrition and sleep, impacts child development. The Zimmerman laboratory shows us that the home environment is dynamic, and changes significantly over the first year of life. Research is limited on how the home environment influences and promotes word production and vocabulary building among children and adults. Thus, one of the goals of this study was to quantify the relation between select home environment variables and the quantity of vocalizations and/or word productions. This study also mapped the occurrence of conversational turns produced by parents and their infants, between 3 and 12 months of age. For example, at 3 months, learning materials in the home were found to be related to adult words. The changing dynamics of the home environment between 3 and 12 months

was correlated with sex dependent changes in vocalization production rates. Male children produced fewer vocalizations, whereas female children produced more vocalizations. The authors recommend that future research consider a longitudinal, repeated measures design and a larger, more diverse participant pool.

Research in the McGrattan laboratory considers swallowing deficits in infants and systematically examines the effect of clinical variables on thickness (viscosity) of two popular anti-reflux formulas used in the U.S., including Enfamil A.R.™ and Similac Spit-Up®, which are available in ready-to-feed and powder formulations. A major consideration raised by the authors is the effect of clinical conditions [e.g., time since mixing, caloric density, and refrigeration] which can alter the viscosity of these anti-reflux formulas. Enfamil A.R.™ is a valid semi-thick liquid option in its ready to feed formulation, whereas the viscosity of the powder formulation to attain a slightly thick designation is dependent on its caloric density. For example, over thickening may hinder an infant's ability to sustain nutritional needs, whereas a formula with undesirably low viscosity (insufficient thickening) may increase the risk of aspiration. Thus, it is important for clinicians to monitor these variables related to the preparation of anti-reflux formulas to ensure the desired treatment effect.

The Pados' laboratory shows that gestational age (GA) is an important factor when evaluating and monitoring gastroesophageal reflux (GER). Infants born prior to 32 weeks gestation tend to experience more symptoms of GER compared to infants born at later gestation. Preterm infants who manifest GER experience longer lengths of hospitalization and increased medical costs. For these preterm infants, there is a worsening of symptoms over the first 6 months of life. GER symptoms also are associated with feeding difficulties, which may negatively influence the infant's growth and development. Knowledge of the patterns of GER evolution in infants (<32 weeks GA) will aid in the creation of targeted management strategies. A primary question is why full-term infants improve in terms of GER symptoms, but preterm infants with GER do not. These observations suggest the presence of a critical sensorimotor period to begin GER management strategies in preterm infants. Continued study is needed to elucidate the underlying mechanisms and progression of GER symptoms in preterm infants. Follow-up outcome data are needed beyond 6 months of life to better understand how GER symptoms resolve or change as the aerodigestive tract in children grow and modify their diets to include solid food.

The Lau laboratory teaches us that the NICU environment poses a moderate to highly stressful experience for mothers. Support is needed to assist mothers (families) during their infants' hospitalization. Mothers whose premature babies are admitted to the NICU encounter numerous stressors and uncertainties, including decisions regarding the need for medical interventions (e.g., surgery), and the realization that their new baby will remain in an isolette surrounded by the sounds and lights of physiological monitors and breathing support devices, including a myriad of connections via tubes, electrical leads and sensors, cannulations, and the busy flow of care team professionals. Mothers are not only encumbered with their infant's fragility but must deal with their own personal trials surrounding a perceived inability to fill their maternal role during this challenging time (8). The promise of mother-infant bonding is interrupted, which may impact the relationship

between the child and mother. Mediational modeling is proposed by the authors to improve our understanding of the overall impact that multiple stressors can have on NICU mothers and improve treatment approaches.

Frequency domain analytics implemented by the Barlow laboratory represents the first study of its kind to characterize ororhythmic compression pressure dynamics during NNS burst evolution in extreme-very premature infants. Machine learning longitudinal cluster analyses of spectral density metrics revealed three significantly distinct membership classes of NNS compression pressure growth patterns. Linear mixed modeling was subsequently used to examine the effects of GA, postmenstrual age (PMA), sex, patient type [bronchopulmonary dysplasia (BPD), non-BPD], and oral pneumotactile treatment to identify the phenotypes of NNS production in the frequency domain. NNS features which are relatively invariant *vs.* other features which are modifiable by sensory experience are expected to inform effective treatment strategies in this fragile population.

In spite of significant advances in perinatal medicine during the past few decades, the review compiled by the Wang laboratory suggests that extremely preterm infants (EPIs) are at increased risk of mortality and morbidity. Advances in perinatal care have yielded increased survival rates for EPIs, however these most fragile infants remain at high risk of morbidity and mortality. The authors suggest that proactive management strategies need to be implemented during the perinatal period to mitigate the mortality and impairment rates among EPIs. Large meta-analyses and/or large-sample, randomized controlled trials are needed to assess the efficacy and safety of innovative management strategies applied to preterm infants in the NICU.

Clinical study of neonatal feeding and neurodevelopmental issues among preterm and in children who were born prematurely is likely to benefit from collaborations with scientists who bring primary expertise in computer science, bioinformatics, genomics, molecular biology, statistics, neuroscience, and biomechanics. Some of this work has already led to the development of predictive models and digital signal processing tools which utilize time and frequency domain features extracted from NNS pressure patterns to predict oromotor development and feeding readiness in extreme and very preterm infants (9). Machine learning, hierarchical feature cluster, and relevant AI models which utilize oral feeding metrics, neural correlates of ororhythmogenesis [e.g., functional near-infrared spectroscopy (fNIRS)], and genomics as inputs to the modeling process will not only improve individualized care for at-risk preterm infants in the NICU setting, but also provide a window into neurodevelopmental outcomes related to cognition, sensory processing, sensorimotor control of movement, and speech-language function.

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Conflicts of Interest:

The author has completed the ICMJE uniform disclosure form (available at https://pm.amegroups.com/article/view/10.21037/pm-24-18/coif). The series “Neonatal Feeding and Developmental Issues” was commissioned by the editorial office without any funding or sponsorship. S.M.B. served as the unpaid Guest Editor of the series and

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