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Targeted Fortification of Donor Breast Milk in Preterm Infants

A. Study Purpose and Rationale:

Breast milk is the preferred method of nutrition for all infants, including preterm infants. When mom's breastmilk is not available, donor milk is preferred to formula for preterm and very low birth weight infants due to decreased risk of complications such as necrotizing enterocolitis and sepsis[1]. However, human milk alone is insufficient to provide calories and macronutrients needed for appropriate postnatal growth. For that reason, standard practice is to fortify human milk in the NICU with products such as bovine derived human milk fortifier. However, standard fortification assume that all human milk has the same number of calories, fats, protein, and carbohydrates when in fact there is significant variation in the nutritional content from different women and overtime [2]. As a result, approximately >50% of very low birth weight (VLBW) infants in the NICU experience postnatal growth failure[2,3]. This is significant due to the association between poor growth and adverse neurodevelopmental outcomes.

Donor milk, specifically, has been shown to frequently be lower in calorie than the assumed 20 kcal/oz with reduced protein levels even with fortification. This is thought to be due, in part, to the processing and pasteurization of donor human milk[4]. As a result, infants fed primarily donor milk often have slower weight gain as compared to infants fed mother's own milk[5,6].

Several studies have looked to evaluate the benefits of targeted breast milk fortification using human milk analyzers to achieve goal nutritional content. Results of these trials have shown to improve postnatal growth among preterm and VLBW infants without increased gastrointestinal morbidity or intolerances[8,9,10]. However, the feasibility of large scale targeted fortification of mothers milk is limited by cost and personnel. Targeted donor milk fortification, however, may provide the opportunity to have an even greater impact on the relatively smaller number of infants for whom mother's own milk is unavailable. To our knowledge, no studies have been done to evaluate targeted donor breast milk fortification alone.

The aim of this project is the reduce the rates of postnatal growth restriction among preterm infants fed donor milk using targeted donor milk fortification. We hope to achieve this using the FDA approved MIRIS milk analyzer to more accurately measure the true nutritional content of donor breast milk and provide appropriate fortification to meet the nutritional needs of preterm and very low birth weight infants. We hypothesize that infants provided targeted fortification will have better growth outcomes (weight, length, and head circumference) at 34 weeks corrected gestational age (CGA) as compared to infants fed donor milk with standard fortification practices.

B. Study Design:

This project is a prospective, non-blinded, randomized controlled trial of infants born at </= 30 weeks gestational age (GA), birth weight of </= 1500 gm, whose mothers' consent to donor breast milk. Exclusion criteria includes infants with complex congenital heart disease, GI malformations such as omphalocele and gastroschisis, and infants born at <3rd percentile for gestational age. Eligible infants receiving donor breast milk will be randomized to receive targeted fortification vs. standard fortification. Multiples will be randomized to the same group. Infants will be stratified by birth weight (1,000-1,500gm, 750-1,000gm, and 500-750 gm) to have equal number of each birth weight category in the intervention and control group. Patients will be recruited prior to the initiation of fortified milk, generally around 1 week of life. Mothers who speak Spanish will be enrolled with the aid of a Spanish interpreter and consent form that has been accurately translated in Spanish.

Pooled donor milk at NYP is provided by the New York Milk Bank. Two samples of donor milk from each batch will be defrosted for analysis. Analysis will be done using the MIRIS Human Milk Analyzer according to manufacturer's recommendations. Each batch will be labeled with a unique color label. A note will be placed in the experimental patient's chart with the recipe for the particular batch of donor milk using HMF with additives such as poly-carb, liquid protein, or microlipids. For infants in the experimental arm, protein will be targeted such that the infant will receive 4 g/kg/day of protein, and fat will be targeted to achieve total kcals of 80 kcal/100 ml AND at least 4.8 and at most 6.6 g/k/day of fat. Infants in the control arm will receive 4 packets of HMF/100ml for an estimated calorie content of 24kcal/oz. As is our standard practice, patients in the control group receiving standard fortification will be offered additional fortification in response to poor growth, at the discretion of the medical team. The patients will remain on fortified donor breast milk as per their assigned group until 34 weeks CGA and >1800gm.

C. Statistical Procedures

Primary outcomes will be weight gain (g/kg/day) and growth parameters (weight, length, head circumference) at the time of full fortification and 34 weeks CGA. Secondary outcomes will include feeding intolerance, NEC, BPD, ROP and NICU length of stay. Growth parameters will be collected weekly by bedside nurses, while secondary outcomes will be collected through chart review.

Statistical analyses will be conducted using the student t-test for continuous variables and fisher exact test for categorical variables. In order to detect a differential growth rate of 1.8g/kg/day with 80% power and alpha <0.05 a total of 22 infants are needed in both groups. Because many infants ultimately do not require donor milk, closer to 60 infants will need to be recruited to achieve these final numbers. Infants feeding >20% mothers' milk during the study period will not be included in the final analysis.

D. **Study Procedures:** None
E. **Study Drugs:** Similac Human Milk Fortifier, poly-carb, liquid protein, or microlipids
F. **Medical Devices:** Miris Human Milk Analyzer, FDA approved
G. **Study Questionnaires:** None
H. **Study Subjects:** Infants admitted to the CHONY NICU between October 2022-October 2023 with a birth weight of </=1500 gm and GA </=30 weeks for whom mother's have consented to Donor Breast Milk will be approached for enrollment in our study. Infants will be excluded if they have any complex congenital heart disease, GI malformations such as omphalocele and gastroschisis, or are born small for gestational age (<3rd percentile).
I. **Informed consent:** Informed consent by the infant's parents will be required prior to enrollment and will be completed in the patient's preferred language (Spanish/English).
J. **Confidentiality:** This is a non-blinded trial. All members of the research team and patient's care team will be aware of which infants are in the treatment and control groups. Parents are welcome to know to which fortification group their child has been assigned as well as any growth or laboratory information that has been collected. Paper consent forms and any other paper work will be stored in a locked drawer separate from the data. All collected data will be stored on a CUMC drive that is only accessible to members of the research team.
K. **Potential Risks:** The primary difference of this study as compared to standard of care, is to proactively add additional liquid protein, microlipids, and/or carbohydrates to donor milk +HMF rather than waiting to add these elements in response to poor growth. Some of the potential risks of adding additional fortification includes providing hyperosmolar milk and providing too many calories. Hyperosmolar milk increases the risk for feeding intolerance and necrotizing enterocolitis. However, the risk of hyperosmolarity is very unlikely as we will be directly measuring the macronutrient content of the milk and adding fortification to meet recommended values of macronutrients, specifically protein, according to the ESPGHAN 2014 recommendations. Following these recommendations will also help to avoid the risk of over-feeding. We will also be working closely with our nutrition team in creating the fortification recipes with multiple checks to ensure the recipes are appropriate prior to publishing in the patient charts.
L. **Potential Benefits:** The potential benefit of enrolling in this study is that infants receiving targeted donor milk fortification may have improved growth as compared to infants receiving standard fortification. Because post-natal growth restriction has been associated with poorer neurodevelopmental outcomes, improved growth may have a beneficial impact on long term cognitive outcomes. This study may also help to inform future fortification practices for donor breast milk in our NICU.
M. **Alternatives:** Participation in this study is voluntary at the discretion of the parents. If parents do not wish to participate in the study their baby will receive standard donor milk fortification as per CHONY NICU protocols.
N. **Research at External Sites:** Not Applicable

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