JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eNeonatal Review

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NUTRITIONAL MANAGEMENT OF LOW BIRTH WEIGHT PRETERM INFANTS

In this Issue...

Achieving the goal of optimal nutritional management of low birth weight preterm infants requires finding a balance between meeting recommended nutrient intake to ensure growth and preventing morbidities such as necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP).

In this issue we review recent literature investigating:

- NEC and standardized feeding protocols
- Human milk variety and fortification
- The effects of human milk on growth
- The lipid needs of preterm infants

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the variability in macronutrient content of human milk and its impact on growth of preterm infants.
- Evaluate the potential benefits of human milk fortification and supplementation.
- Discuss the lipid needs of very low weight preterm infants.

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IN THIS ISSUE

COMMENTARY

Consideration of the goals for nutritional management of low birth weight preterm infants includes not only meeting the recommended intake of nutrients, but also ensuring that growth, neurodevelopment, and long-term health outcomes are optimized. Achieving these goals requires an understanding of the intrauterine growth rate to be targeted and of the nutrient requirements of extremely premature infants. The tension between the goals of optimizing growth outcomes with the prevention of necrotizing enterocolitis (NEC) or treatment of morbidities such as bronchopulmonary dysplasia (BPD) can be a difficult balance.

The association between growth, nutrition, and neurodevelopmental outcomes in premature infants has been well described, primarily through observational studies. Provision of maternal milk is associated with decreased in-hospital morbidity in premature infants, including lower rates of NEC, late-onset sepsis, BPD, and severe retinopathy of prematurity[1,2] as well as with improved neurodevelopment at 18 and 30 months corrected age.[3,4] Despite these tremendous benefits of human milk, observational studies have also shown that premature infants fed human milk have lower growth rates than infants fed term or preterm infant formula. Human milk – whether maternal or donor – provides insufficient quantities of protein, sodium, phosphorus, calcium and other nutrients to meet the estimated needs of the preterm infant.

Standardized feeding guidelines for preterm infants improve growth outcomes, decrease duration of parenteral nutrition, and decrease time to reach full enteral nutrition. As the research by Gephart and colleagues (reviewed in this issue) notes, feeding protocols also reduce the incidence of NEC. An intriguing finding is the fact that the use of any standardized feeding protocol – regardless of the specific details such as the rate of feeding advancement – is better than having no protocol at all. Not surprisingly, there have been no randomized controlled trials of different feeding protocols or regimens.

Every NICU should develop efforts to not only encourage but also actively support mothers in their efforts to initiate and maintain a supply of human milk. The composition of preterm milk is inherently different than term milk. As highlighted by Groh-Wargo, the composition of human milk is highly variable, and the nutrient content cannot be assumed to be identical in all mothers. Although the use of donor human milk is a reasonable alternative if mother's milk is not available, donor human milk is typically pooled from women who not only delivered at term but also who are many months into lactation. The lower protein and energy content of donor human milk must be considered in the development of fortification strategies to optimize growth.

While human milk is the indisputably optimal source of nutrition for premature infants, it is clear that fortification is needed to meet recommended macronutrient intake and improve growth outcomes. The growing number of studies evaluating the composition of pooled donor milk challenges the common assumption that all human milk contains 20 kcal/oz. In addition, these analyses demonstrating much lower than anticipated concentrations of protein in pooled donor milk should prompt a change in the mindset of how we use commercial human milk fortifiers (HMF). For example, the manufacturers of commercial HMF assume a static protein content of 1.4–1.6 g/dL in human milk and do not account for the natural decrease in protein over time with lactation. Clearly these assumptions for the macronutrient content of human milk do not apply when donor human milk is used, and our recipes and strategies for fortification must be updated if reasonable growth outcomes are to be achieved. Delays in fortification of human milk further compound the issue of suboptimal protein and energy intake with unfortified donor milk.

Improved growth outcomes were recently found in a large cohort of VLBW infants who were managed with a strategy to optimize early nutritional support according to recent recommendations.[5] Based on these findings, recommendations to begin fortification of human milk before enteral intake reaches 100 mL/kg/day have been made. In the standardized feeding protocol synthesized by Gephart et al, fortification of human milk is delayed until the infant is tolerating 100 mL/kg/day. With advancement in enteral volume of 10-20 mL/kg/day, fortification may not take place until the infant is 10-14 days of age. In the prospective observational study conducted by Hair et al that evaluated an exclusive human milk diet, fortification was introduced when the infant was receiving 60 mL/kg/day

of enteral nutrition. On the other hand, the approach used by Colaizy and colleagues in Iowa occurs much sooner (at 25 mL/d) and minimizes protein and energy deficits that can easily accrue with a delay in human milk fortification. The pilot study conducted by Tillman et al demonstrates the feasibility of fortification at the time of the very first enteral feed. Further studies are needed to determine the optimal strategy for fortification of human milk. Indeed, a fortifier that can deliver more protein and energy without diluting the volume of human milk is ideal.

Lapillonne et al provide an excellent summary of the role that long-chain polyunsaturated fatty acids (LCPUFA) play in normal growth, neurodevelopment, and health. The mean level of docosahexanoic acid (DHA) in donor human milk is significantly less than in maternal milk or preterm infant formula (and the content is highly variable from different milk banks).[6] In addition, nonnutritive components of human milk such as bile salt-stimulated lipase (which improves the bioavailability of LCPUFAs) are inactivated by pasteurization, raising other considerations for differences in nutritional properties between donor and maternal human milk.

Studies such as those conducted by Rochow et al have shown that it is possible to individualize fortification to meet the nutritional needs of premature infants. However, this process is labor-intensive, and near- and midinfrared milk analyzers have not yet been approved by the FDA for clinical use.

Nutritional strategies to optimize outcomes in premature infants include human milk, careful monitoring of growth (weight, length, and head circumference), a combined strategy of early parenteral and enteral nutrition to ensure adequate protein and energy delivery to minimize deficits, and standardized feeding guidelines. Given the inherent differences in the composition of donor and preterm human milk, further studies are needed to identify fortification strategies that account for variations in the composition of maternal and donor human milk to achieve the best growth outcomes possible for premature infants while minimizing the risk of morbidities such as NEC.

References

1. Heller CD, O'Shea M, Yao Q, et al; NICHD Neonatal Research Network. Human milk intake and retinopathy of prematurity in extremely low birth weight infants. *Pediatrics*. 2007;120(1):1-9.
2. Meinzen-Derr J, Poindexter B, Wrage L, Morrow AL, Stoll B, Donovan EF. Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *J Perinatol*. 2009; 29(1):57-62.
3. Vohr BR, Poindexter BB, Dusick AM, et al; National Institute of Child Health and Human Development National Research Network. Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics*. 2007; 120(4):e953-e959.
4. Vohr BR, Poindexter BB, Dusick AM, et al; NICHD Neonatal Research Network. Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics*. 2006;118(1):e115-e123.
5. Christensen RD, Gordon PV, Besner GE. Can we cut the incidence of necrotizing enterocolitis in half--today? *Fetal Pediatr Pathol*. 2010;29(4): 185-98.
6. Senterre T,Rigo J. Optimizing early nutritional support based on recent recommendations in VLBW infants and postnatal growth restriction. *J Pediatr Gastroenterol Nutr*. 2011;53(5):536-542.

back to top

FEEDING PROTOCOLS TO PREVENT NEC IN PREMATURE INFANTS

Gephart SM, Hanson CK. Preventing necrotizing enterocolitis with standardized feeding protocols. *Adv Neonatal Care*. 2013;13(1):48-54.

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The goal of optimizing growth outcomes of extremely premature infants is often tempered by the fear of necrotizing enterocolitis (NEC). Although NEC is a multifactorial disease process with many nonmodifiable risk factors (ie, prematurity and low birth weight), many recent quality improvement efforts to reduce NEC have focused on the practices of human milk feeding and standardized feeding protocols.

The overall objective of this evidence-based practice brief was to evaluate whether there is sufficient evidence to support the use of standardized feeding protocols, with the goal of decreasing the incidence of NEC by 50%.

The authors included the following five criteria in their consideration of standardized feeding protocols for premature infants:

1. When to start and how to determine readiness
2. How to advance the feeding through a systematic writing of a feeding schedule that replaces the daily writing of feeding orders
3. How to handle intolerance to feeding
4. When and how to fortify feedings
5. When to stop feeding

In a meta-analysis of studies that reported the incidence of NEC before and after implementing a standardized feeding protocol, the pooled risk ratio was 0.13 (95% CI 0.03-0.50) for infants less than 2500 g —meaning that the use of a standardized feeding protocol was associated with an overall reduction in NEC of up to 85%. However, it is important to note that no randomized controlled trials were identified for inclusion in the meta-analysis.

Another interesting finding highlighted by these authors is the observation that providing active support to encourage use of the mother's own milk doubles the likelihood that a mother will provide breast milk during the NICU stay.

The authors also reviewed the approach to managing feeding intolerance in each of the published standardized feeding protocols. A threshold of gastric residual volumes of 30%-50% of the previous feeding has been reported as a reasonable point to evaluate the infant and potentially hold enteral feeding. This particular evaluation did not include any protocols that do not routinely assess gastric residuals.

back to top

HUMAN MILK VARIABILITY AND TARGETED FORTIFICATION

Groh-Wargo S, Valentic J, Khaira S, Super DM, Collin M. Considering human milk variability in the nutritional management of low-birth-weight infants. *Infant Child Adolesc Nutr*. 2014;6(5):301-302.

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Although human milk (HM) is the undisputed gold standard source of infant nutrition,[1] unfortified human milk provides insufficient quantities of a number of key nutrients to meet the estimated needs of the preterm infant. Multicomponent fortification of HM is associated with short-term improvements in weight gain, linear growth, and head circumference in preterm infants. In addition, poor bone mineralization, rickets, and fractures have been described in preterm infants receiving unfortified HM.

In this brief research report, Groh-Wargo and colleagues evaluated the variability of fat, lactose, and total protein and calculated energy content of 24-hour pooled samples of HM provided by mothers of low-birth-weight infants using a midinfrared milk analyzer.

The investigators evaluated a total of 151 samples of HM from 17 mothers who delivered infants at a mean gestational age of 29 weeks. Milk samples were obtained between two

and six weeks after delivery. After analyzing nutrient content, the average coefficients of variation for weeks 2 - 6 were calculated within each mother and between mothers for each macronutrient. The investigators found statistically significant differences in variability between mothers versus within a mother for all macronutrients analyzed ($P < .05$), including a 25% coefficient of variation for bioavailable protein between mothers.

Given the tremendous variability in macronutrient content of HM between the mothers in this study, it is obvious that a one-size-fits-all approach to the content of HM may significantly under- or overestimate the actual intake of macronutrients and energy by a given infant. The authors contend that the variability in HM between mothers in this small study supports the rationale for an individualized approach to fortification of HM to optimally meet the needs of premature infants.

In this report, samples were pooled over a 24-hour period, thus the results do not address the issue of variability within a mother's own milk supply over the course of a day. Although some NICUs instruct mothers to pool milk collected over a day, others do not routinely do so.

Reference

1. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126(3):443-456.

back to top

HUMAN MILK CREAM SUPPLEMENTATION

Hair AB, Blanco CL, Moreira AG, et al. Randomized trial of human milk cream as a supplement to standard fortification of an exclusive human milk-based diet in infants 750-1250 g birth weight. *J Pediatr*. 2014;165:915-20.

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While human milk (HM) feeding has been associated with substantial benefits to the health and development of premature infants, studies evaluating the macronutrient composition of HM have found high variability in fat, protein, and energy/caloric content. Adding a pasteurized donor HM-derived cream supplement to an infant's diet may help improve overall caloric intake without substantially altering the total feeding volume given to the infant. This study was an unmasked, randomized clinical trial designed to demonstrate the noninferiority of a HM cream supplement to standard fortified HM.

The study population included 78 infants with birth weight between 750 g-1250 g. Infants were randomized to receive a human milk cream supplement or control. The energy content of human milk to be fed to the infant was measured daily using a near-infrared milk analyzer.

The primary outcome was weight gain (g/kg/day) until 36 weeks postmenstrual age. Infants randomized to receive the human milk cream supplement were found to have an average weight gain of 14 g/kg/day versus 12.4 g/kg/day in the control infants. The investigators also found a difference of 0.2 cm/week in length gain velocity in infants randomized to the group receiving the human milk cream supplement.

The current growth velocity guideline for preterm infants is 15 g/kg/day. However, for extreme preterm infants this number likely underestimates the weight gain velocity necessary to achieve optimal growth and long-term outcomes in this population. With data from the large ELGAN study cohort (n = 1187), Martin and colleagues[1] found a high incidence of postnatal growth failure (defined as weight less < 10th percentile for gestational age), despite achieving a mean weight gain of 15 g/kg/day. Thus in the current study, the weight gain velocity in the HM cream supplement group in this RCT may still reflect suboptimal growth.

Reference

1. Martin CR, Brown YF, Ehrenkranz RA, et al. Nutritional practices and growth velocity in the first month of life in extremely premature infants. *Pediatrics*. 2009;124:649–657.

back to top

TARGETED BREAST MILK FORTIFICATION

Rochow N, Fusch G, Choi A, et al. Target Fortification of breast milk with fat, protein, and carbohydrates for preterm infants. *J Pediatr*. 2013;163:1001-1007.

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Although not yet approved by the FDA for clinical use, many investigators have used near-infrared spectroscopy to analyze the composition of human milk in efforts to optimize nutritional intake of preterm infants.

In this study, the investigators analyzed batches of human milk every 12 hours for fat, protein, and carbohydrate content. Each of the 650 individual samples of human milk that were analyzed required at least one macronutrient adjustment to meet published guidelines established by the European Society for Pediatric Gastroenterology, Hepatology and Nutrition.

Infants whose diets were adjusted with target fortification had growth rates that were linearly correlated to the feeding volume received.

It is important to note that most studies investigating target fortification have only evaluated the addition of protein and have not focused on fat and carbohydrate supplementation. Clearly the effort required both to analyze and adjust fortification every 12 hours is beyond the scope of clinical feasibility in most NICUs, but this study demonstrates an important proof of concept that improving postnatal growth is possible when the infant's diet meets recommended guidelines for macronutrient intake.

back to top

GROWTH OF PRETERM INFANTS FED HUMAN MILK

Hair AB, Hawthorne KM, Chetta KE, Abrams SA. Human milk feeding supports adequate growth in infants ≤ 1250 grams birth weight. *BMC Research Notes*. 2013;6:459.

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In this single center, prospective observational cohort study, 104 premature infants (birth weight ≤ 1250 g) were provided with an exclusive human milk-based diet until 34 weeks postmenstrual age. Donor human milk-derived fortifier was added once the infant was receiving 60 mL/kg of enteral nutrition and was then advanced to provide an additional 6-8 kilocalories per ounce.

In comparison to a historical cohort, improved weight gain and linear growth was found in the cohort that received early fortification, with only 43% of these infants demonstrating extrauterine growth restriction. Weight gain velocity was significantly affected by the day of fortification of human milk and by the day that the infant reached full enteral feeds.

In most NICUs, fortification of human milk is typically delayed until the infant is receiving close to full enteral volume. These investigators have demonstrated that with early fortification of human milk and advancements in fortification beyond the typical four additional kcal/oz that adequate growth can be achieved, even with an exclusive human milk diet.

back to top

HUMAN MILK & SUBOPTIMAL GROWTH

Colaizy TT, Carlson S, Saftlas AF, Morriss FH. Growth in VLBW infants fed predominantly fortified maternal and donor human milk diets: a retrospective cohort study. *BMC Pediatrics*. 2012;12:124.

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Despite a number of well-known and characterized advantages of human milk for premature infants, provision of human milk – whether maternal or donor – is also associated with suboptimal growth.

This was a single-center, retrospective cohort study to evaluate in-hospital growth in 171 premature infants (birth weight ≤ 1250 g and median gestational age 27 weeks) who received mostly human milk. The study was performed in a NICU with high use of human milk (97% of infants in this cohort) and a robust nutritional database, which enabled the investigators to calculate the proportion of total enteral intake during hospitalization from maternal and donor human milk. Human milk intake for each infant was categorized into four groups: < 25% of diet, 25-50% of diet, 51-75% of diet, and > 75% of diet.

Growth (weight and occipitofrontal circumference) was assessed using the Fenton growth curves, and z-scores (based on postmenstrual age) for these anthropometric measurements were calculated. The primary study outcome was the change in weight z-score from birth through discharge, stratified by the amount of human milk that the infant received.

The feeding protocol in this NICU included early total parenteral nutrition (TPN -started on the day of birth) and introduction of low volume enteral feedings between day of life 0 - 2. Human milk fortifier was added when infants were tolerating 25-40 mL of milk per day (approximately 30-45 mL/kg/day based on an average birth weight of 889 g in this cohort). Initial fortification was to 24 kcal/oz (prepared according to manufacturer's directions), with additional fortification to 27 kcal/oz in most infants in order to meet recommended targets for protein and energy intake in this population.

At the time of hospital discharge, 34% of this cohort was small for gestational age, much lower than the incidence of postnatal growth restriction reported in other large cohort studies1 and likely reflecting a more aggressive approach to fortification of human milk at this center. Infants receiving the highest volume of human milk intake (> 75% of enteral intake) had a greater negative change in weight z-score from birth to discharge compared to infants receiving a lesser percentage of diet from human milk. In addition, infants receiving greater than 75% donor milk had higher rates of postnatal growth failure at the time of discharge than those fed maternal or mixed milk diets, with 56% of these infants having weight less than the 10th percentile.

Reference

1. American Academy of Pediatrics. Section On Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129(3): p. e827-e841.

back to top

EARLY USE OF FORTIFIED HUMAN MILK

Tillman S, Brandon DH, Silva SG. Evaluation of human milk fortification from the time of the first feeding: effects on infants of less than 31 weeks gestational age. *J Perinatol*. 2012;32:525-531.

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Postnatal growth failure is a common complication of prematurity and is associated with poor neurodevelopmental outcomes. Recognizing that variability in the composition of human milk and in approaches to fortification of human milk affect postnatal growth outcomes, this investigation looked to determine whether early fortification (from time of the first enteral feeding) of human milk improves weight gain and bone mineral status in premature infants.

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NEWSLETTER ARCHIVE

This retrospective study compared infants before (n = 42) and after (n = 53) a change in the standard practice for timing of human milk fortification was implemented in their NICU. Their standard practice was to fortify human milk once infants were tolerating approximately 85 mL/kg/day, which was on average at 24 days of age. In 2000, the entire NICU adopted an early fortification strategy that included fortification of human milk (to 24 kcal/oz per manufacturer's directions) beginning with the first enteral feeding.

Two groups of infants were evaluated – those cared for in the year before versus those cared for in the year after the change in practice related to fortification was adopted. The investigators included in the analysis infants born at less than 31 weeks gestation who received an exclusive human milk diet (maternal and/or donor) until 34 weeks postmenstrual age.

In this small cohort of 95 infants, the investigators found no differences in weight gain between the early and delayed fortification groups. There was, however, a difference in alkaline phosphatase values between the two groups, with the delayed fortification group having a higher percentage of infants with alkaline phosphatase values above 500. The investigators found no differences in safety outcomes such as feeding intolerance or NEC, although they acknowledge the limitation of having insufficient power to adequately address these events. Rather than being conclusive, this retrospective study supports the feasibility of providing fortified human milk from the very first enteral feeding. Further studies are clearly needed to evaluate the best fortification strategy and to further evaluate the safety of such approaches.

back to top

LIPIDS AND PRETERM NUTRITION – FACTS ON FATS

Lapillonne, A, Groh-Wargo S, Gonzalez CH, Uauy R. Lipid Needs of Preterm Infants: Updated Recommendations. *J Pediatr*. 2013;162:S37-S47.

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Although the quantity of macronutrient intake necessary to meet the needs of preterm infants has been the focus of many studies, less attention has been given to the quality of macronutrient intake. In this review, Lapillonne and colleagues provide updated recommendations related to provision of long-chain polyunsaturated fatty acids (LCPUFAs) to preterm infants, and describe opportunities for research to address knowledge gaps and further refine these recommendations.

LCPUFAs are routinely added to preterm infant formula and to some commercially available human milk fortifiers. The amount of LCPUFAs added to infant formula has been based on replicating the levels in term human milk. However, given that fetal fat accretion is highest in the third trimester, this standard may not be appropriate for infants born prematurely. The authors review evidence that although standard doses of LCPUFA supplementation have not shown improved neurodevelopment in preterm infants, improved neurologic outcomes have been demonstrated with higher doses of DHA.

The authors summarize differences in LCPUFA levels between term and preterm milk; they also outline how pasteurization and storage of human milk may alter the quantity and quality of fat composition, potentially contributing to suboptimal growth in premature infants. This review is an excellent summary of the lipid needs of preterm infants and highlights areas where additional studies are needed to evaluate LCPUFA supplements – whether through enriched fortifiers or through supplements given to the mother.

back to top

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evidence-based recommendations on recognizing and treating GERD in neonates.

- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
- Current neonatal nutritional management practices may be enhanced to optimize and meet the specific needs of low birth weight preterm infants.
- Clinicians who treat neonates are uncertain of optimal strategies for prevention and early recognition and treatment of necrotizing enterocolitis.

RESPIRATORY-RELATED ISSUES

- Clinicians may be unfamiliar with some of the newest evidence-based approaches for treating neonatal persistent pulmonary hypertension.
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The target audience (clinicians) for this initiative includes neonatologists, respiratory therapists, neonatal nurses, nurse practitioners, and other members of the NICU team.

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NURSE POST-TEST

Respiratory Therapists
Visit this page to confirm that your state will accept the CE Credits gained through this program.