Applying New Learnings on Human Milk Composition to Clinical Practice in the NICU

Presented by
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Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

With Michaela Berroya, RNC, MSN Ed, and Jennifer Fowler, MS, RDN, LDN

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Learning Objectives

By participating in this education, you will better:

- Understand the typical nutrient profile of preterm, term, and donor human milk
- Assimilate new learnings from human milk research on the nutrient composition of human milk, including its variability, dynamicity, and factors that influence its components
- Provide improved growth and nutrition-related outcomes to premature infants, leveraging the variety of human milk fortification strategies available

Nutritional Needs of Preterm Infants

Supporting Growth and Development Through Nutrition

The **American Academy of Pediatrics** recommends that preterm nutrition should "provide nutrients **to approximate the rate of growth and composition of weight gain for a normal fetus** of the same postmenstrual age and to maintain normal concentrations of blood and tissue nutrients."[1]

Benefits of achieving recommended growth rates in preterm infants:[1]–[3]

- Improved short- and long-term neurodevelopmental outcomes
- Reduced rate of school difficulties (ie, need for special educational accommodations, lower than average grades)
- Improved short- and long-term body composition scores

[1]. Kleinman RE, Greer FR, eds. *Pediatric Nutrition, 8th ed.* American Academy of Pediatrics; 2020. [2]. Guellec I et al. *J Pediatr.* 2016;175:93-99.e1. [3]. Ramel S et al. *J Pediatr.* 2016;173:108-115.

Preterm Infant Growth Benefits: Preventing Morbidity

Preterm infants with growth faltering are at elevated risk for...

- Late-onset sepsis[1]
- Necrotizing enterocolitis (NEC)[1]
- Bronchopulmonary dysplasia[1]
- Retinopathy of prematurity[2]
- Suboptimal neurodevelopment[3]

[1]. Guellec I et al. *J Pediatr.* 2016;175:93-99.e1. [2]. Hellström A et al. *Acta Paediatr.* 2010;99(4):502-508. [3]. Ehrenkranz RA et al. *Pediatrics*. 2006;117(4):1253-1261.

Preterm Infant Growth Benefits: Neurodevelopment

From 1 week of age to term, for every **z-score improvement** in…

Cognitive testing at **18 months** corrected age showed…

	Weight gain[1]	**BMI**[1]	**Head growth**[1]
MDI score	↑2.4	↑1.7	↑1.4
PDI score	↑2.7	↑2.5	↑2.5

Neurodevelopmental benefits of postnatal growth in preterm infants carry through **childhood**[2],[3] and into **early adulthood**[4]

MDI, Mental Developmental Index; PDI, Psychomotor Development Index.

[1]. Belfort MB et al. *Pediatrics*. 2011;128(4):e899-e906. [2]. Claas MJ et al. *Early Hum Dev.* 2011;87(7):495-507. [3]. Isaacs EB et al. *J Pediatr.* 2009;155(2):229-234. [4]. Sammallahti S et al. *J Pediatr*. 2014;165(6):1109-1115.e3.

Most Recent Enteral Nutrition Recommendations for Preterm Infants

Nutrient	2021 Koletzko Guidelines[1] per kg/d	2022 ESPGHAN Guidelines[a],[2] per kg/d
Fluid, mL	135–200	150–180 (135–200)
Energy, kcal	110–130	115–140 (–160)
Protein, g	3.5–4.5	3.5–4.0 (−4.5)
Carbohydrate, g	11–13	11–15 (−17)
Fat, g	4.5–8.0	4.8–8.1
Sodium, mg	69–115 (−184)	69–115 (−184)
Potassium, mg	78–195	90–180
Chloride, mg	107–178 (−284)	106–177 (−284)
Calcium, mg	120–220	120–200
Phosphorus, mg	70–120	68–115
Iron, mg	2–3	2–3 (−6)
Zinc, mg	2–3	2–3

a. Parentheses indicate ranges or upper intakes that may be needed for certain neonates.

[1]. Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed*. Karger; 2021. [2]. Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.

Changes in ESPGHAN Guidelines: 2010→2022[1],[2]

- Tighter target range for fluid intake
- Changes to **macronutrients**:
  - Lower upper intake for protein
  - Higher upper intake for fat
  - Wider target range for carbohydrates
- Higher target ranges for **micronutrients**:
  - Potassium
  - Calcium
  - Phosphorous
  - Zinc

Nutrient	2010[1] per kg/d	2022[2] per kg/d
Fluid, mL	135–200	150–180
Macronutrients		
Protein, g	3.5–4.5	3.5–4.0
Fat, g	4.8–6.6	4.8–8.1
Carbohydrate, g	11.6–13.2	11–15 (−17)
Micronutrients		
Potassium, mg	66–133	90–180
Calcium, mg	120–140	120–200
Phosphorus, mg	59–90	68–115
Zinc, mg	1.1–2	2–3

ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition.

[1]. Agostoni C et al. *J Pediatr Gastroenterol Nutr.* 2010;50(1):85-91. [2]. Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.

Changes in Koletzko Guidelines: 2014→2021[1],[2]

- Wider range, including increased upper intake, for **fat**
- Tighter range for **carbohydrates**
- Changes to **micronutrients**:
  - Calcium
  - Iron
  - Zinc

Nutrient	2014[1] per kg/d	2021[2] per kg/d
Macronutrients		
Fat, g	4.8–6.6	4.55–8.1
Carbohydrate, g	11.6–13.2	11–13
Micronutrients		
Calcium, mg	120–200	120–220
Iron, mg	2–3	1–3[a]
Zinc, mg	1.4–2.5	2–3

[a]. Weight dependent: 2-3 mg/kg/d for <1500 g; 2 mg/kg/d for 1500-2000 g; and 1-2 mg/kg/d for 2000-2500 g

[1]. Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines*. Karger; 2014. [2]. Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed*. Karger; 2021.

Human Milk and Preterm Infant Feeding

Exclusive Human Milk Feeding for the First 6 Months of Life: a "Public Health Imperative"[1]

World Health Organization

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

National Association of Neonatal Nurses

Department of Health & Human Services • USA

ESPGHAN

USDA

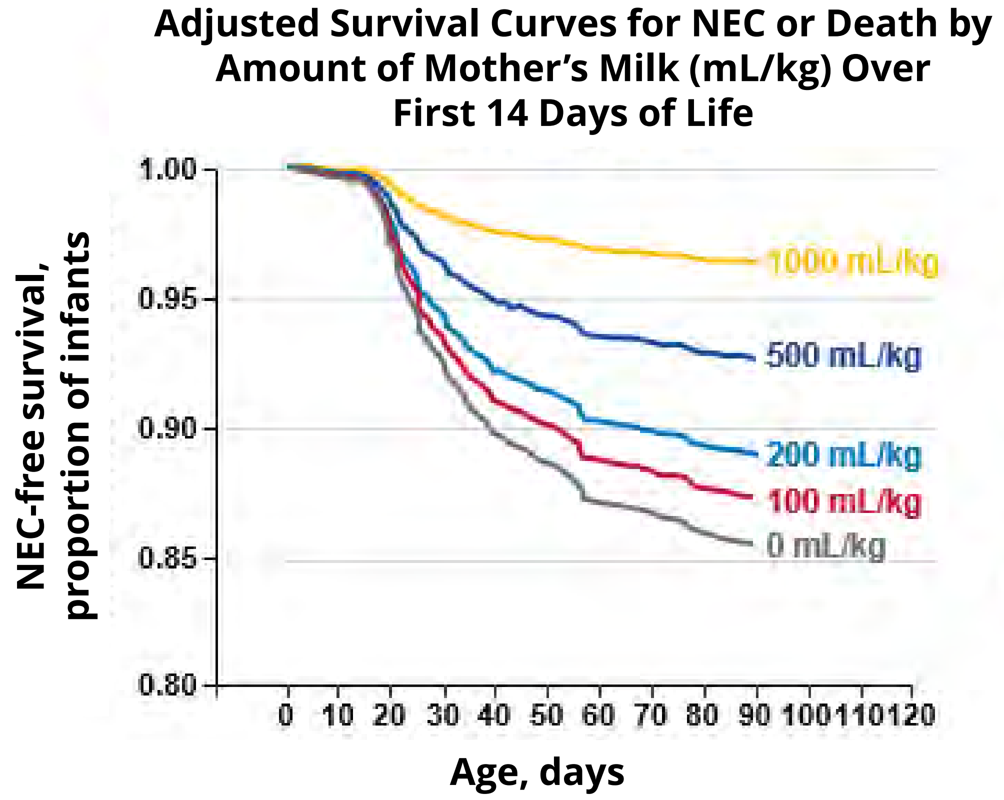
ACOG

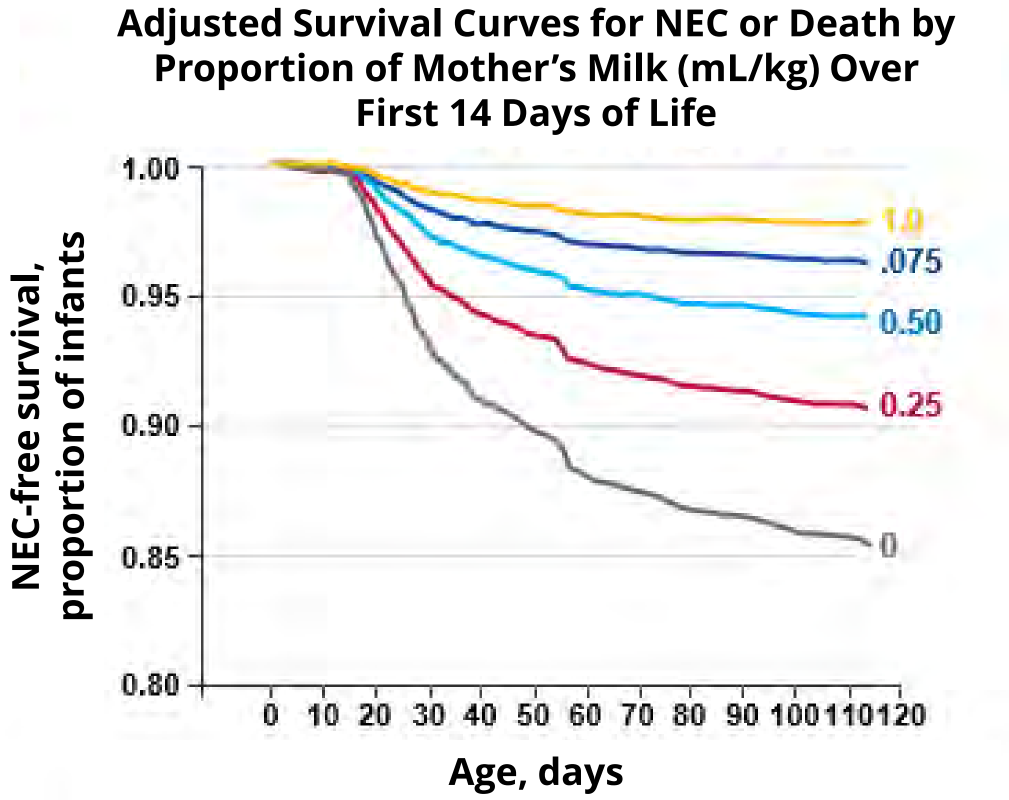
eat right. Academy of Nutrition and Dietetics

Maternal, infant, and public health organizations recommend **exclusive breastfeeding** or **use of human milk** for virtually all infants—including preterm infants—for the first 6 months of life[1]–[8]

[1]. Meek JY et al. *Pediatrics*. 2022;150(1):e2022057988. [2]. World Health Organization (WHO). WHO Recommendations on Maternal and Newborn Care for a Positive Postnatal Experience. March 30, 2022. Accessed February 9, 2023. https://www.who.int/publications/i/item/9789240045989. [3]. American College of Obstetricians and Gynecologists (ACOG) Committee on Obstetric Practice; Breastfeeding Expert Work Group. *Obstet Gynecol*. 2016;127(2):e86-e92. [4]. US Department of Agriculture (USDA). Dietary Guidelines for Americans, 2020-2025. December 2020. Accessed February 9, 2023. www.DietaryGuidelines.gov. [5]. US Department of Health & Human Services. The Surgeon General's Call to Action to Support Breastfeeding. Office of the Surgeon General; 2011. [6]. Agostoni C et al. *J Pediatr Gastroenterol Nutr*. 2009;49(1):112-125. [7]. Lessen R, Kavanagh K. *J Acad Nutr Diet*. 2015;115(3):444-449. [8]. Spatz DL, Edwards TM. *Adv Neonatal Care*. 2016;16(4):254.

Human Milk and Risk of NEC or Death in Preterm Infants





Mother's own milk feeding in preterm infants is associated with a dose-dependent reduction in risk of NEC or death.

Meinzen-Derr J et al. *J Perinatol*. 2009;29(1):57-62. Adapted from figure 1 and 2.

Human Milk and the Unique Nutritional Needs of Preterm Infants

Despite clear advantages of human milk for preterm infants, several challenges remain:[1],[2]

- Rapid growth rate of preterm infants (twice the rate of term infants) and high metabolic demands
- Suboptimal gestational nutrient accretion and deficient nutrient stores
- Weight-appropriate human milk feeding volumes insufficient to meet nutritional needs due to fluid restrictions
- Variability of human milk composition

[1]. Hay WW, Jr. *Pediatr Gastroenterol Hepatol Nutr*. 2018;21(4):234-247. [2]. Kleinman RE, Greer FR, eds. *Pediatric Nutrition, 8th ed*. American Academy of Pediatrics; 2020.

Factors Influencing Human Milk Composition

Maternal[1]–[3]

- Prepregnancy BMI
- Age
- Race/ethnicity
- Parity
- Geographic location
- Diet
- Genetics

Perinatal[1],[3]

- Lactation stage
- Infant gestational age
- Milk volume
- Mode of delivery
- Infant sex

Environmental[4]

- Pasteurization or heat treatment
- Storage temperature
- Thawing procedures
- Pooling practices

[1]. Han SM et al. *J Nutr.* 2021;151(6):1383-1393. [2]. McGuire MK et al. *Am J Clin Nutr.* 2017;105(5):1086-1100. [3]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. [4]. Kleinman RE, Greer FR, eds. *Pediatric Nutrition, 8th ed*. American Academy of Pediatrics; 2020.

Maternal Supplementation & Human Milk Composition

- Quality and quantity of maternal **fatty acid intake** influence human milk composition, particularly for PUFAs (eg, LA, ALA, DHA) [1]
  - Omega-3 and DHA supplementation during pregnancy and lactation can increase DHA levels in human milk
- **Vitamin B** supplementation can rapidly increase human milk concentrations[1]
- **Choline** requirements are high for fetal (and thus preterm infant) development and can be supplemented via maternal diet [2]
- Mixed evidence for the benefits of **vitamin A** and **vitamin D** supplementation; effects for vitamin D driven by dosing schedule [3]
- **Zinc** and **iron** supplementation do not meaningfully change human milk concentrations [1]

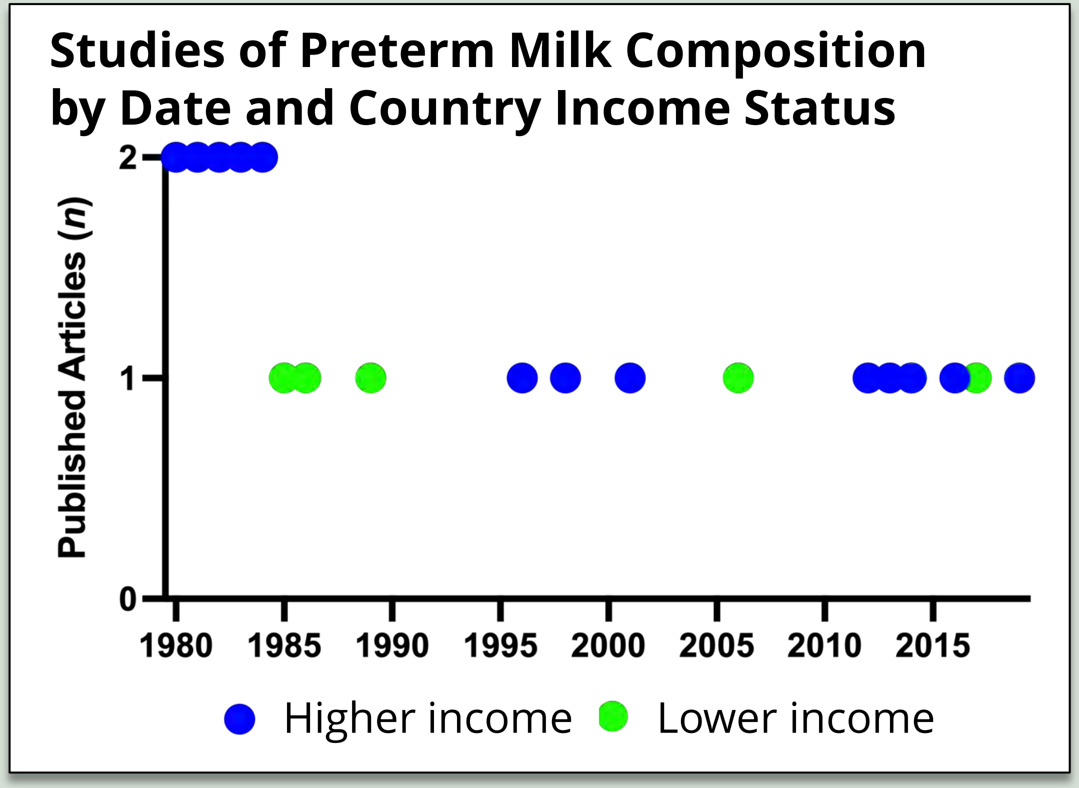
PUFA, polyunsaturated fatty acids; LA, linoleic acid; ALA, α-linolenic acid; DHA, docosahexaenoic acid.

[1]. Samuel TM et al. *Front Nutr.* 2020;7:576133. [2]. Mun JG et al. *Nutrients*. 2019;11(5):1125. [3]. Keikha M et al. *Int Breastfeed J.* 2021;16(1):1.

Preterm Human Milk Composition: Challenges and Limitations of the Literature

In a review of 27 articles with original data on composition of preterm milk, several literature deficits were identified:

- All US studies (n = 7) published prior to 1984
- Under-representation of Black women
- Under-representation of deliveries <28 weeks' gestation



Gates A et al. *Nutr Clin Pract.* 2021;36(6):1163-1172. Figure not in print article.

Preterm Human Milk Composition: Challenges and Limitations of the Literature

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- Under-representation of Black women
- Under-representation of deliveries <28 weeks' gestation

Noted preterm milk composition trends by lactation stage:

- Sharp increase in **caloric density** over initial 1–2 weeks
- 2-fold increase in **fat** concentration in first 2 weeks
- Enrichment of **protein** in early preterm milk
- Stable **carbohydrate** levels over first 30 days
- Declining levels of **sodium** and **chloride** over first 30 days

Gates A et al. *Nutr Clin Pract.* 2021;36(6):1163-1172.

Prospective, Longitudinal Study of Preterm Human Milk Composition: Design and Baseline Demographics

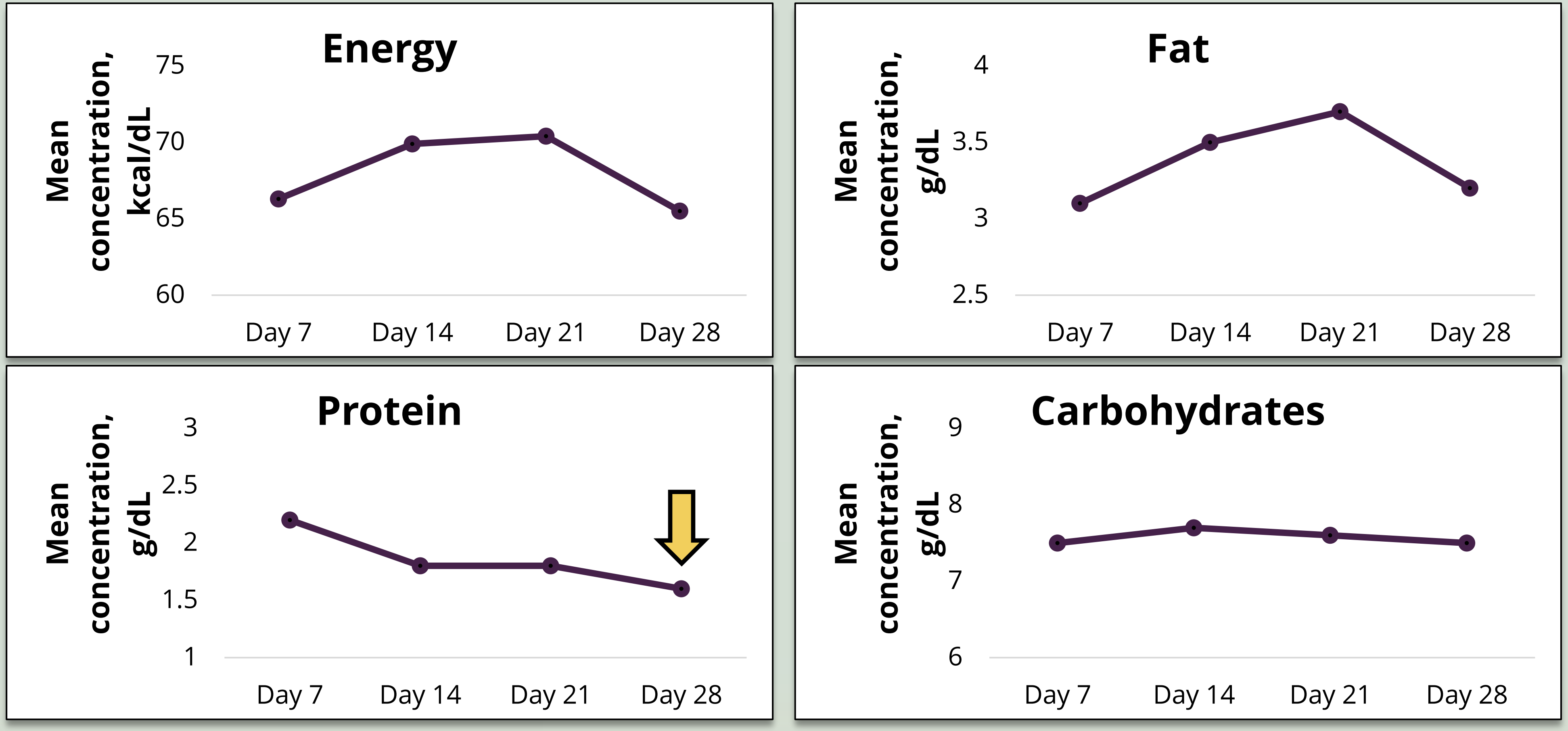
- Women who delivered ≤33 weeks' gestation (N = 38)
- Pooled 24-hour milk samples from days 7, 14, 21, and 28
- Assessed macro- and micronutrient composition

	Mean ± SD or N (%)	Range
Maternal age, y	27 ± 5.1	18–37
EGA, wk	**28 ± 3**	**23–33**
EGA <28 wk	**16 (42)**	
Infant birth weight, g	1098 ± 347.3	545–2130
Male infant sex	20 (53)	
Race		
Black	**25 (66)**	
White	13 (34)	

EGA, estimated gestational age; SD, standard deviation.

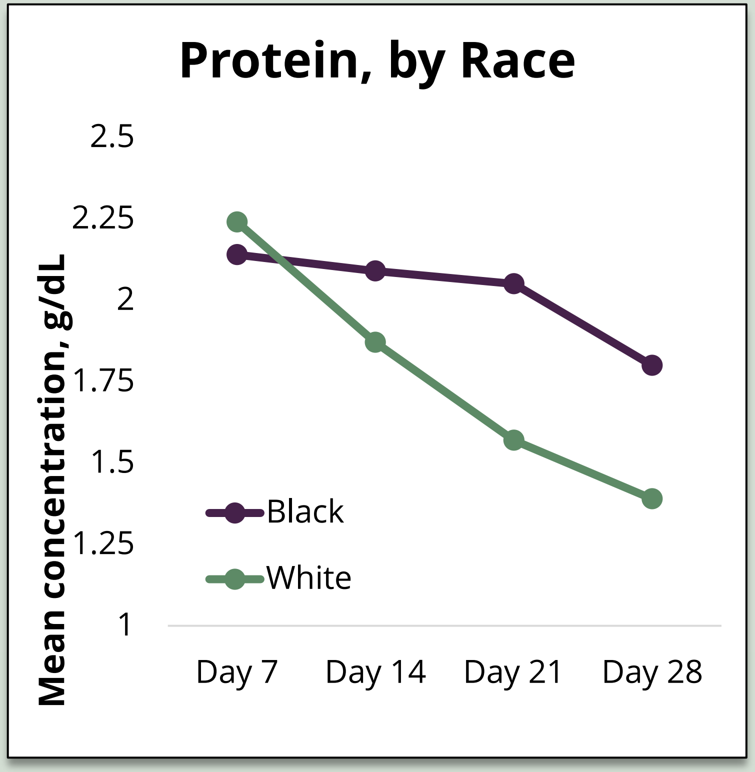
Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728.

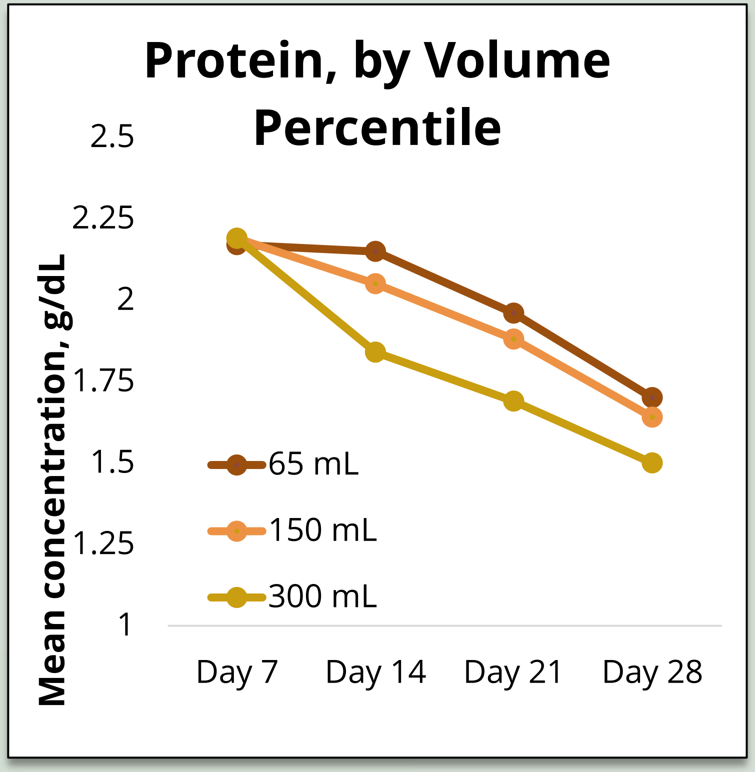
Prospective, Longitudinal Study of Preterm Human Milk Composition: Macronutrients by Lactation Stage

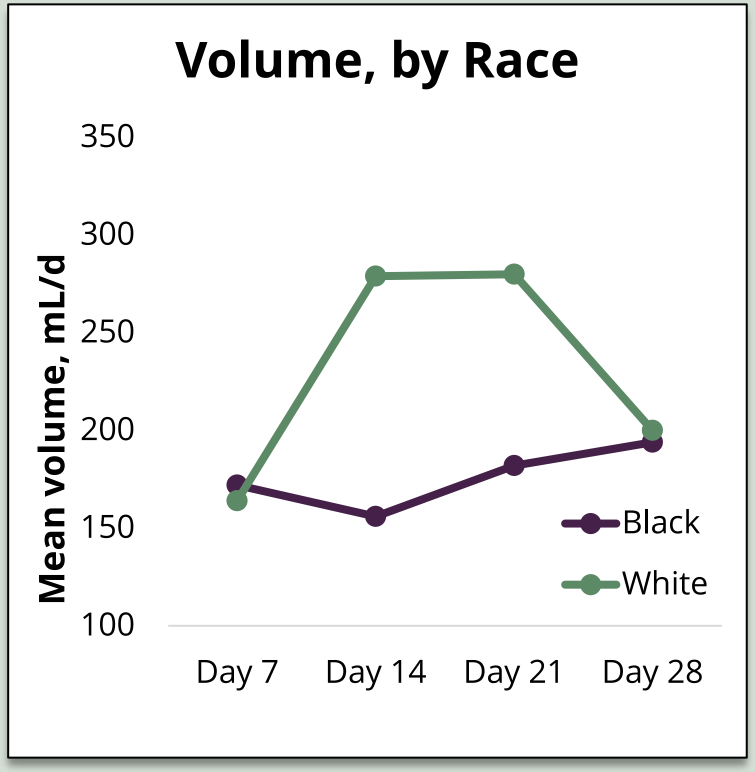


Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. Adapted from figure 2.

Prospective, Longitudinal Study of Preterm Human Milk Composition: Race, Protein, and Volume

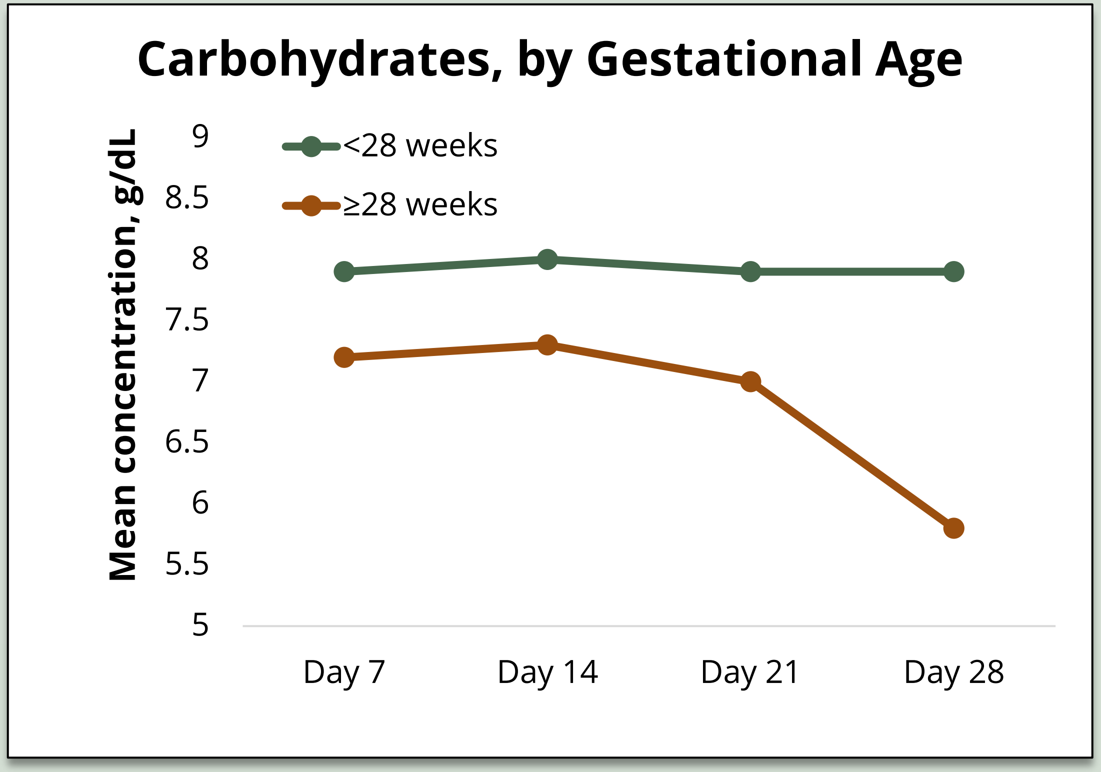


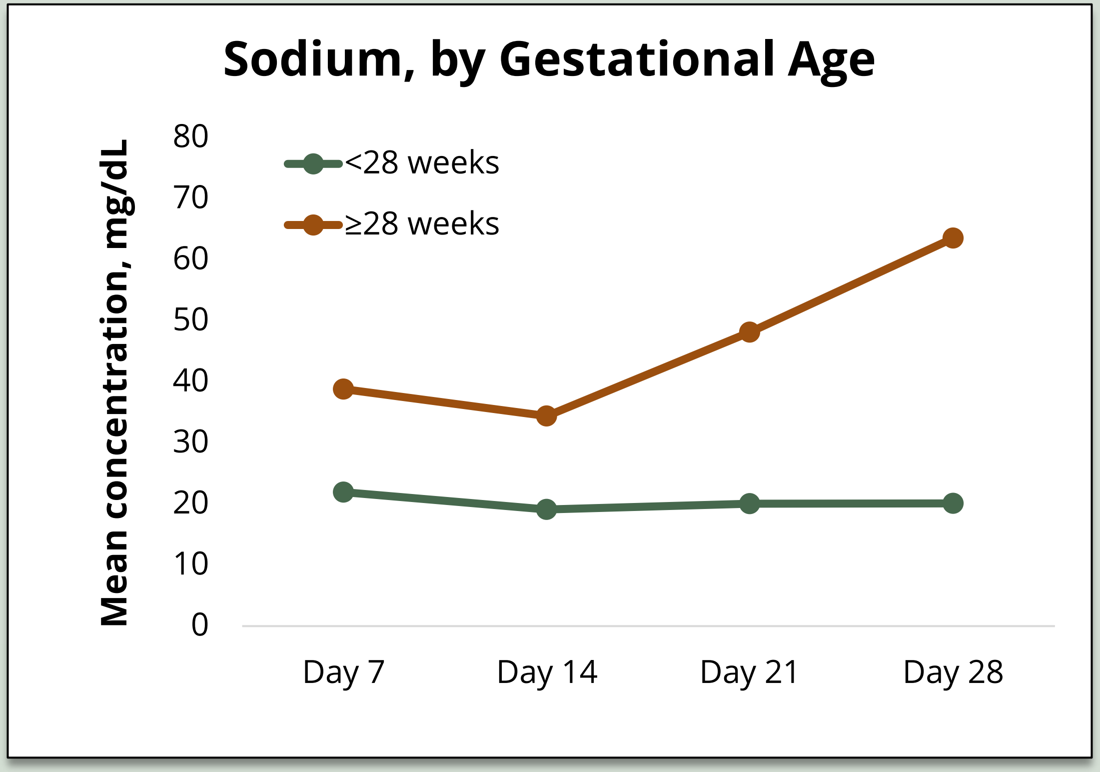




Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. Adapted from figure 2.

Prospective, Longitudinal Study of Preterm Human Milk Composition: Gestational Age





Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. Adapted from figures 2 and 3.

Variation in Mother's Own Milk Composition for Preterm vs Term Infants

Nutrient	Preterm milk[1] per 100 mL	Term milk[2] per 100 mL
Energy, kcal	66–70	65–70
Protein, g	1.6–2.2	0.9–1.2
Carbohydrate, g	7.5–7.7	6.7–7.8
Fat, g	3.1–3.7	3.2–3.6
Sodium, mg	29–36	15–26
Potassium, mg	50–64	40–55
Chloride, mg	58–70	40–50
Calcium, mg	21–24	20–25
Phosphorus, mg	13–15	12–16
Iron, mg	0.09[2]	0.03–0.09
Zinc, mg	0.3–0.5	0.1–0.3

[1]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. [2]. Kim SY, Yi DY. *Clin Exp Pediatr.* 2020;63(8):301-309.

Prospective, Longitudinal Study of Preterm Human Milk Composition: Key Takeaways

- Preterm human milk is **dynamic** in the first month of lactation
  - Relatively stable nutrients: energy, fat, carbohydrates
  - Dynamic nutrients: protein (↓), sodium (↓↑; volume dependent), zinc (↓)
- Other factors that influence the composition of preterm human milk:
  - **Maternal race/ethnicity** (protein content)
  - **Gestational age** (carbohydrate and sodium content)

Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728.

Donor Milk Overview

What About Donor Milk?

- Guidelines recommend the use of donor milk when mother's own milk is unavailable, **particularly in the first few days of life**[1]–[3]
- Donor milk characteristics:[3]
  - Primarily expressed by mothers of **term infants**
  - Primarily collected in **later stages** of lactation
  - Represents "excess" milk supply
  - **Pooled** from multiple mothers
  - **Pasteurized** to destroy microbes

[1]. AAP Committee on Nutrition et al. *Pediatrics.* 2017;139(1):e20163440. [2]. Arslanoglu S et al. *J Pediatr Gastroenterol Nutr.* 2013;57(4):535-542. [3]. Koletzko B et al, eds. In: Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed*. Karger; 2021.

Donor Milk Pasteurization: Effects on Milk Composition

Changes in bioactive components[1]–[3]

- Complete loss of certain **enzymes** and maternal **cell populations (eg, neutrophils, stem cells)**
- Reduced activity level or concentration of other **enzymes**, **cytokines**, **growth factors**, **immunoglobulins**, and **hormones**

Changes in macronutrient composition[4]

- Reduced **caloric density**
- Reduced levels of **lipids** and **long-chain polyunsaturated fatty acids**

Changes in micronutrient composition[1]

- Reduced **ascorbic acid** and **vitamin B6**

[1]. Peila C et al. *Nutrients*. 2016;8(8):477. [2]. Hård AL et al. *Acta Paediatr.* 2019;108(6):998-1007. [3]. Kleinman RE, Greer FR, eds. *Pediatric Nutrition, 8th ed*. American Academy of Pediatrics; 2020. [4]. Koletzko B et al, eds. In: Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed*. Karger; 2021.

Target-Pooled Donor Milk

- **Target-pooling** is the process of strategically combining milk from multiple donors to achieve specific nutritional composition (usually caloric density)[1]
  - Used by many donor milk banks
- In 1 study of target-pooled donor milk, samples contained sufficient energy (18.70 kcal/oz) but still **did not meet protein goals** (0.91 g/dL)[2]
  - Using target-pooled donor milk, infants fed >50% donor milk still had worse growth than those fed <50% donor milk

[1]. Sun R et al. *Serv Sci.* 2022;14(1):13-34. [2]. Fu TT et al. *Nutrients*. 2019;11(8):1884.

Effects of Donor Milk Processing, Handling, and Feeding on Macronutrient Composition

The various processing, handling, and feeding practices used with donor milk result in changes to macronutrient concentrations, primarily related to protein and fat.

Donor Milk Processing, Handling, & Feeding Practices

Mean ± SD concentrations (g/dL)	Raw	Pasteurized	Thawed	Feeding schedule (bolus vs continuous)	
	Fat	**Fat**	**Fat**	**Fat (Bolus)**	**Fat (CI)**
	2.17 ± 1.46	2.05 ± 1.46	2.00 ± 1.45	1.88 ± 1.22	1.00 ± 0.99
	Protein	**Protein**	**Protein**	**Protein (Bolus)**	**Protein (CI)**
	1.03 ± 0.39	0.99 ± 0.42	0.97 ± 0.41	0.94 ± 0.38	0.89 ± 0.41

Overall Changes

Fat
↓1.17 g/dL
(↓59%)

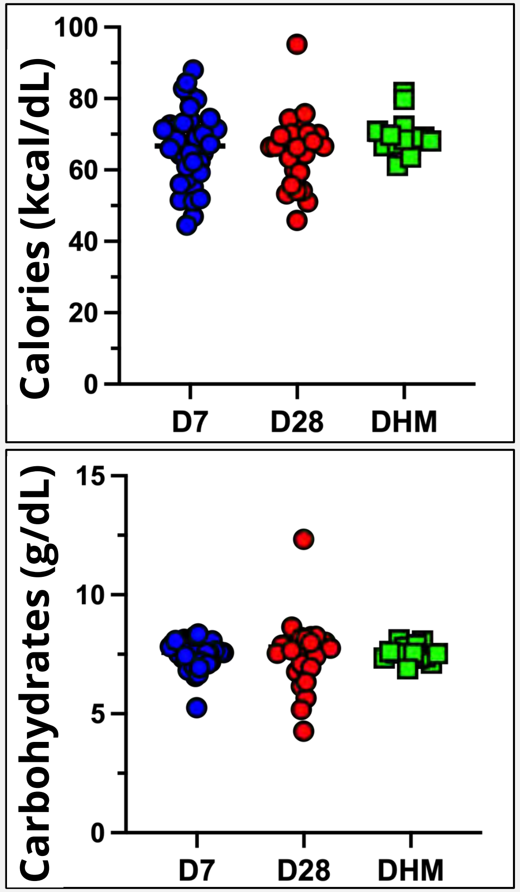
Protein
↓0.14 g/dL
(↓14%)

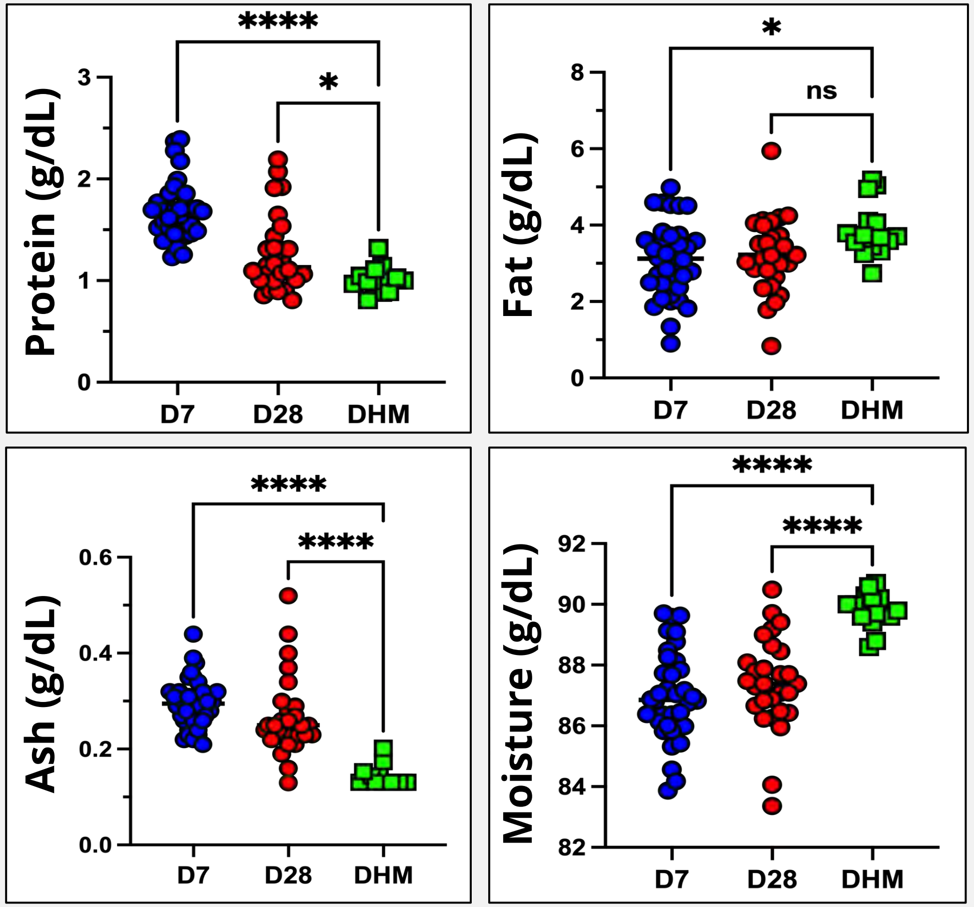
CI, continuous infusion.

Donor Milk vs Preterm Milk

Preterm vs Donor Milk: Macronutrient Content

No significant difference in **calorie** or **carbohydrate** content between preterm and donor milk





Higher protein and **ash** content with preterm milk

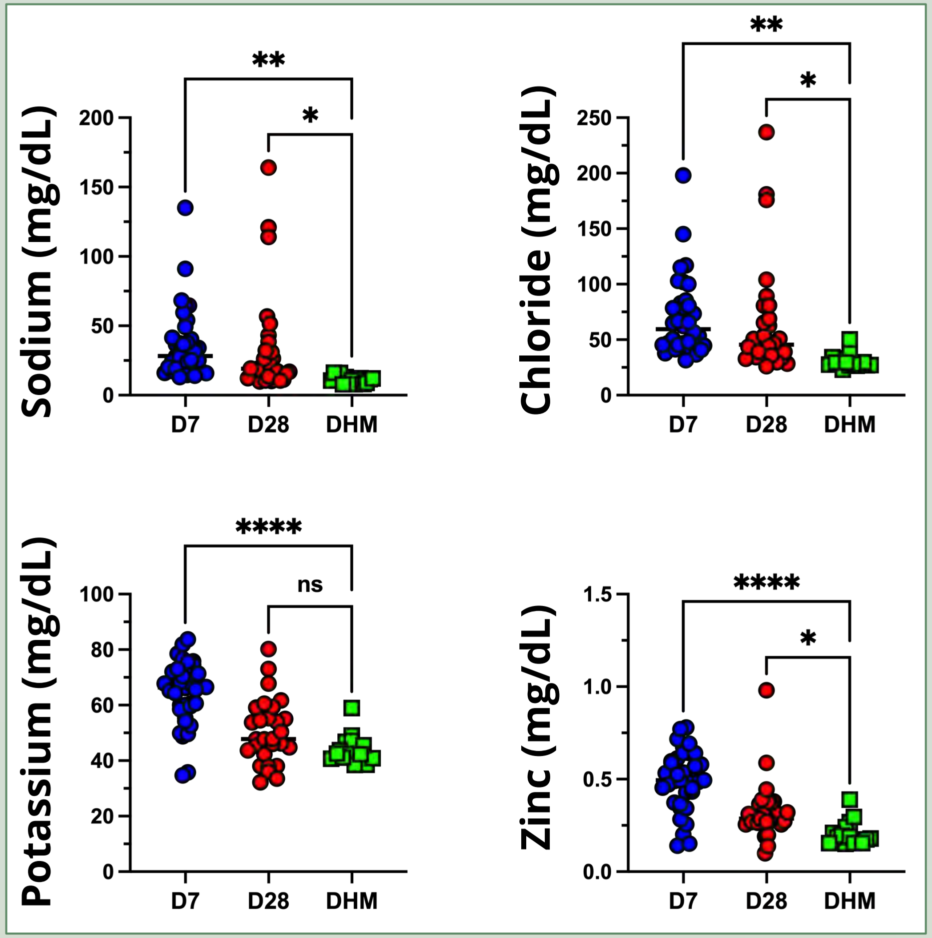
Lower moisture content with preterm milk

Lower fat content with day-7 preterm milk

*P < .05, **P < .01, ***P < .001, ****P < .0001
D7, day 7 of preterm milk; D28, day 28 of preterm milk; DHM, donor human milk.

Gates A, Stansfield B. Presented at PAS 2023. Abstract 361.

Preterm vs Donor Milk: Electrolyte and Mineral Content



Differences for Preterm vs Donor Milk

Significantly higher levels of **sodium**, **chloride**, **potassium** (day 7 only), and **zinc** in preterm milk

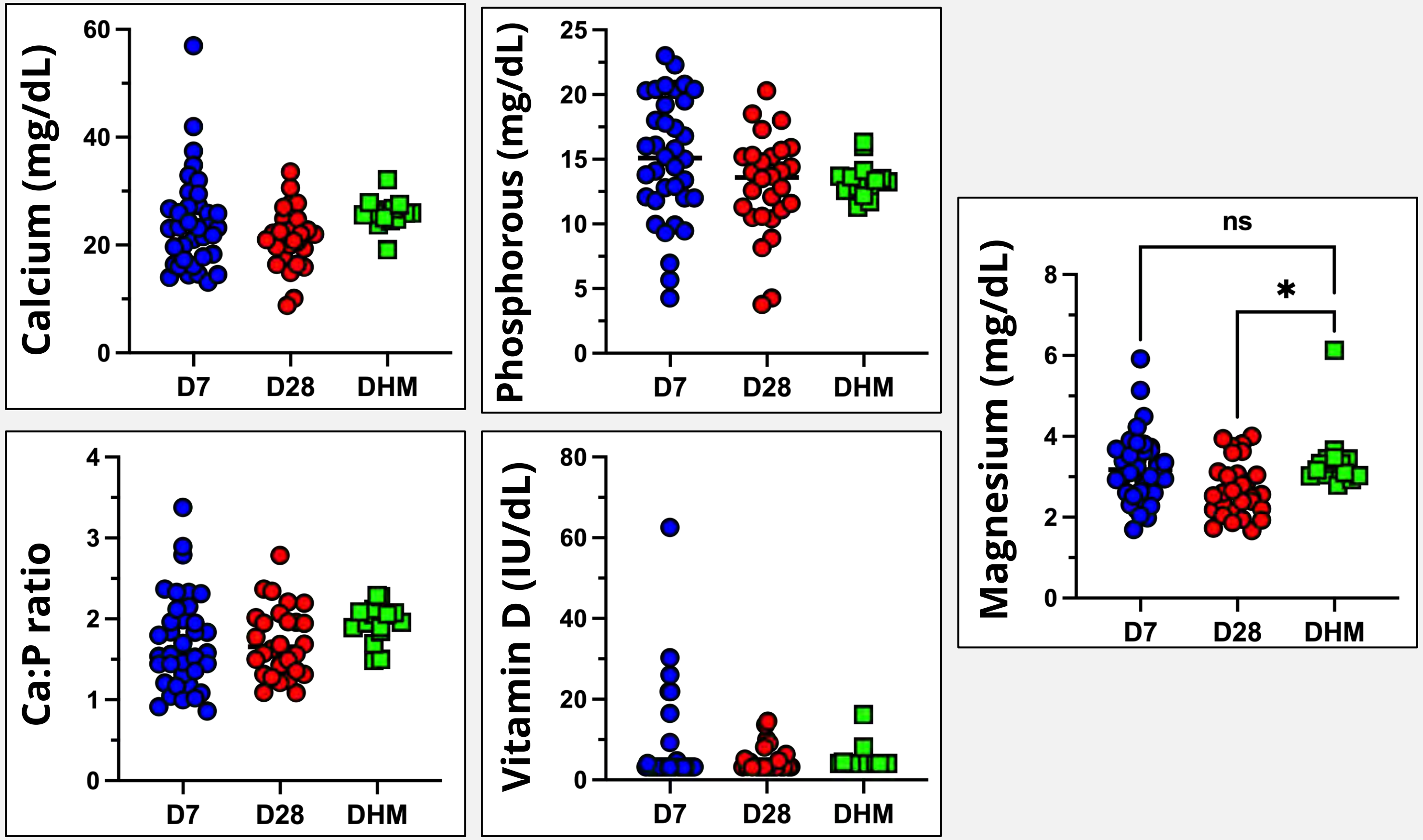
**P < .05, **P < .01, ***P < .001, ****P < .0001.*

Gates A, Stansfield B. Presented at PAS 2023. Abstract 361.

Preterm vs Donor Milk: Minerals & Vitamin D

No significant difference in **calcium**, **phosphorous**, **vitamin D**, or **Ca:P** content

Significantly **higher magnesium** concentration with day-28 preterm milk



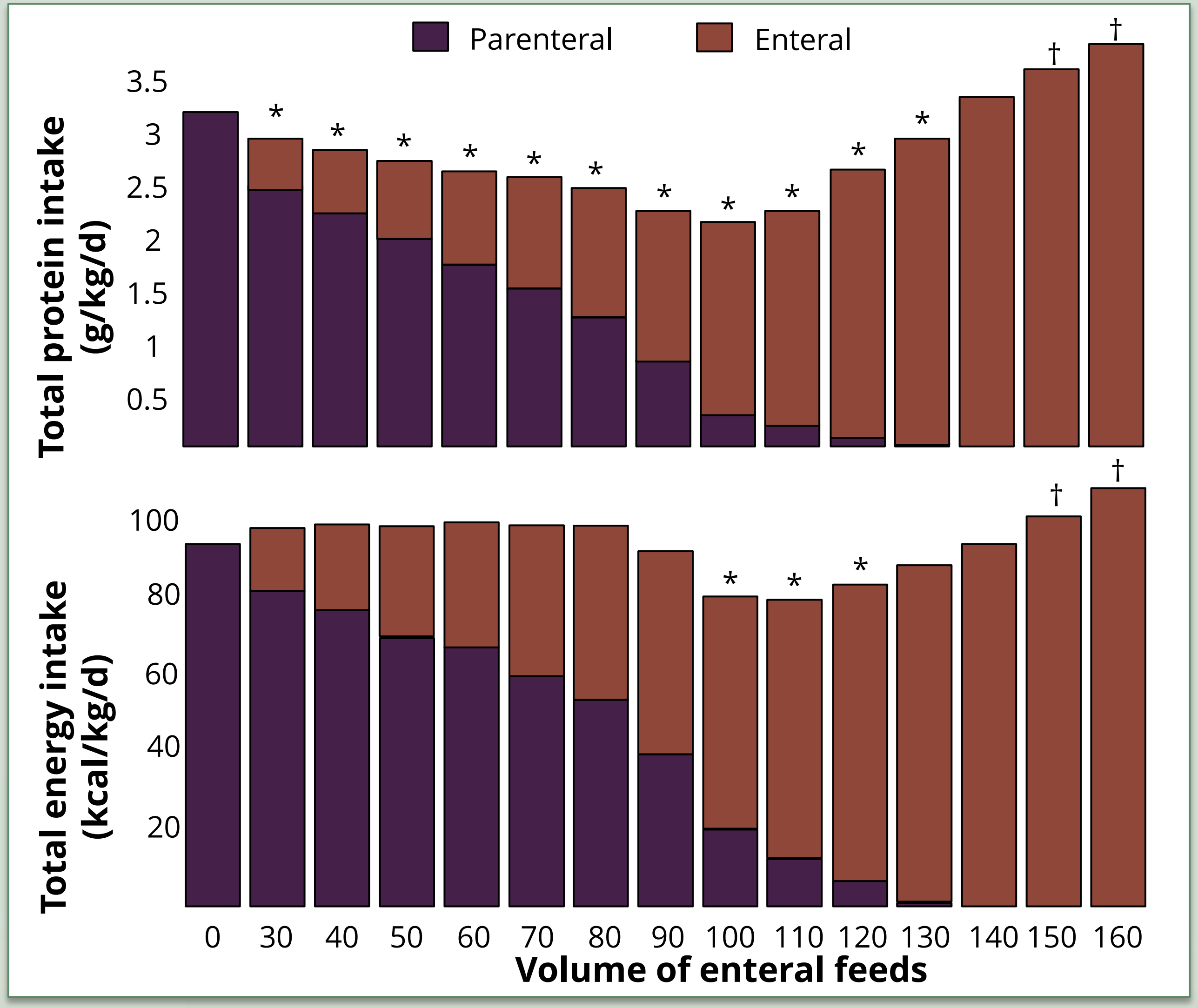
*$P < .05$

Gates A, Stansfield B. Presented at PAS 2023. Abstract 28.

Goals of Fortification and Fortification Strategies

Nutrition During the Parenteral-to-Enteral Transition

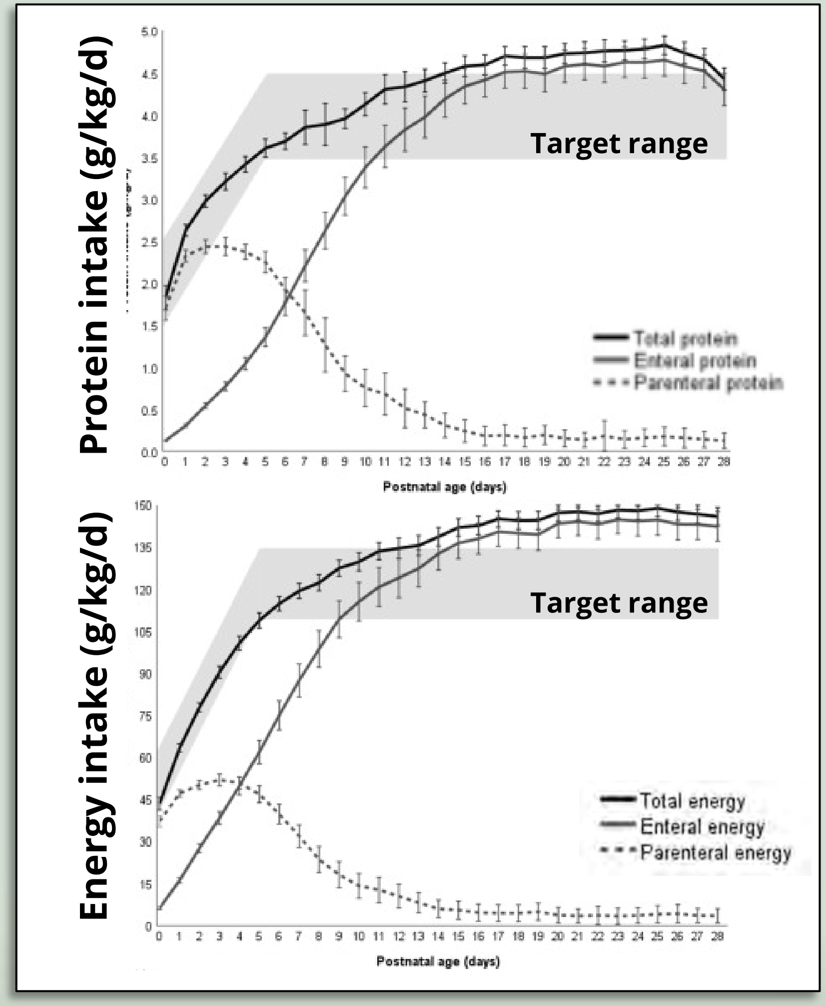
- The transition from parenteral to enteral nutrition is associated with…
  - **Decreased protein** intake
  - **Slowed growth** velocity
- Ensuring adequate nutrient delivery for preterm infants at all time points and especially during transition is important for optimizing growth



* Significantly lower vs baseline parenteral intakes ($P < .05$). † Significantly higher vs baseline parenteral intakes ($P < .05$).

Standardized Feeding Protocols to Improve Nutritional Adequacy & Preterm Infant Growth During Transition

- Secondary analysis of the **120 preterm infants** in the ImNuT RCT, which compared fatty acid supplementation strategies
- **Standardized feeding protocol:**
  - Combination of PN and human milk beginning at birth
  - Milk advanced in 12–18 mL/kg/d as tolerated
  - EN administered by GI tube
  - Fortifier added at 100–115 mL/kg/d
  - Fortification based on estimated milk composition
- Associated with **near-target nutrient intake** and **growth**



Rossholt et al. *Clin Nutr ESPEN.* 2023;53:251-259. Adapted from figure 2; used under terms of a creative commons license (CC BY 4.0).

Importance of Human Milk Fortification for Preterm Infants

Term infant formula and unfortified human milk do not meet the nutritional requirements of preterm infants[1]

In a meta-analysis of 18 trials (N = 1456), human milk fortification was associated with several growth benefits during hospitalization:[2]

- Increased **weight gain** (mean difference vs unfortified milk, 1.76 g/kg/d; 95% CI, 1.30–2.22 g/kg/d)
- Increased **body length** (0.11 cm/week; 0.0–0.15 cm/week)
- Increased **head circumference** (0.06 cm/week; 0.0–0.08 cm/week)

[1]. Kleinman RE, Greer FR, eds. *Pediatric Nutrition, 8th ed*. American Academy of Pediatrics; 2020. [2]. Brown JV et al. *Cochrane Database Syst Rev.* 2016;(5):CD000343.

Goals of Human Milk Fortification

- **Augment**—but **not replace**—human milk to meet energy needs for rapid preterm infant growth
  - Avoid displacement of mother's own milk
  - Support milk supply
  - Limit formula exposure

- Meet estimated needs of **protein** and **micronutrients** (calcium, phosphorous, magnesium, vitamins, and trace elements) with a limited volume

Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed*. Karger; 2021.

Dilemmas in Human Milk Fortification: Decision Points

Decision 1	Decision 2	Decision 3	Decision 4
Base milk?	**Fortifier type?**	**Feeding volume?**	**Duration of fortification?**
• Mother's own milk vs donor milk • Protein content differences • Effects of processing on bioactive components • Heterogeneity by gestational age and lactational stage	• Bovine human milk fortifier vs donor human milk–derived fortifier • Liquid vs powder (bovine) • Extent of research support • Cost differences	• Early (<100 mL/kg/d) vs late (≥100 mL/kg/d) fortification • Challenges meeting nutritional requirements	• Discharge vs term postmenstrual age vs beyond • Patient characteristics and clinical needs

Hair AB et al. *J Perinatol.* 2023;43(1):103-107.

Human Milk Variability & Differing Nutritional Gaps Requiring Fortification

Nutrient	Preterm milk[1] per 100 mL	Term milk[3] per 100 mL	Recommended preterm intake (Koletzko)[2] per kg/d
Energy, kcal	66–70	65–70	110–130
Protein, g	1.6–2.2	0.9–1.2	3.5–4.5
Carbohydrate, g	7.5–7.7	6.7–7.8	11–13
Fat, g	3.1–3.7	3.2–3.6	4.5–8.0
Sodium, mg	29–36	15–26	69–115
Potassium, mg	50–64	40–55	78–195
Chloride, mg	58–70	40–50	107–178
Calcium, mg	21–24	20–25	120–220
Phosphorus, mg	13–15	12–16	70–120
Iron, mg	0.09[2]	0.03–0.09	2–3
Zinc, mg	0.3–0.5	0.1–0.3	2–3

[1]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719–1728. [2]. Koletzko B et al, eds. In: Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines,* 2nd ed. Karger; 2021:430–449. [3]. Kim SY, Yi DY. *Clin Exp Pediatr.* 2020;63(8):301–309.

Randomized Controlled Trials of Early vs Delayed Fortification

Early vs Late Fortification With HMBF in VLBW (<1250 g) Infants[1]

	Early HMBF (≥40 mL/kg/d) (n = 71)	Delayed HMBF (≥100 mL/kg/d) (n = 67)
NEC, %	7.0%	4.5%
Late-onset sepsis, %	21%	28%
Retinopathy of prematurity, %	35%	46%
Duration of PN, d	20	20
Weight gain, g/kg/d	14.2	14.2

Early vs Late Fortification With BMBF in VLBW (<1250 g) Infants[2]

	Early BMBF (≥20 mL/kg/d) (n = 49)	Delayed BMBF (≥100 mL/kg/d) (n = 50)
NEC, %	4%	4%
Time to full feeds, d	20	20
Feeding intolerance, episodes	58	57
Cumulative protein intake in first 4 weeks, g/kg	98.6	89.6[a]

A meta-analysis of these 2 RCTs concluded that early fortification is not associated with feeding intolerance and has no effect on growth or NEC [3]

[a]. $P < .001$
HMBF, human milk–based fortifier; BMBF, bovine milk–based fortifier; PN, parenteral nutrition; VLBW, very low birth weight.

[1]. Sullivan S et al. *J Pediatr.* 2010;156(4):562-7.e1. [2]. Shah SD et al. *J Pediatr*. 2016;174:126-131.e1. [3]. Thanigainathan S et al. *Cochrane Database Syst Rev.* 2020;7(7):CD013392.

Methods of Fortification

Methods of Human Milk Fortification

Standard
most common & easiest

- Fixed amount of fortifier added to fixed human milk volume
- Based on manufacturer's instructions, which typically assumes starting protein and energy content of 1.5 g/dL and 20 kcal/oz, respectively

Adjustable
more cost efficient & less labor intensive than individualized

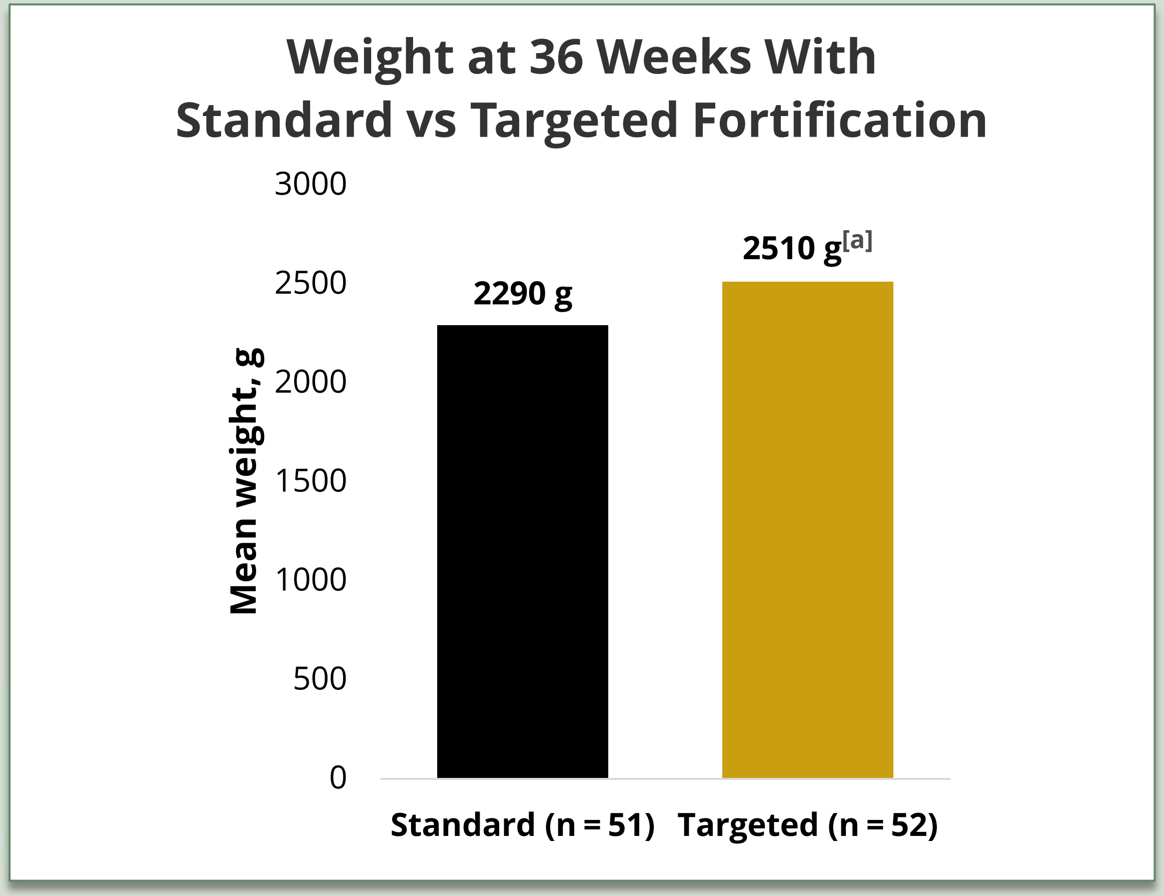
- Protein concentration is adjusted based on serial BUN measurements
- Additional protein supplementation added to standard fortification if BUN is <10 mg/dL

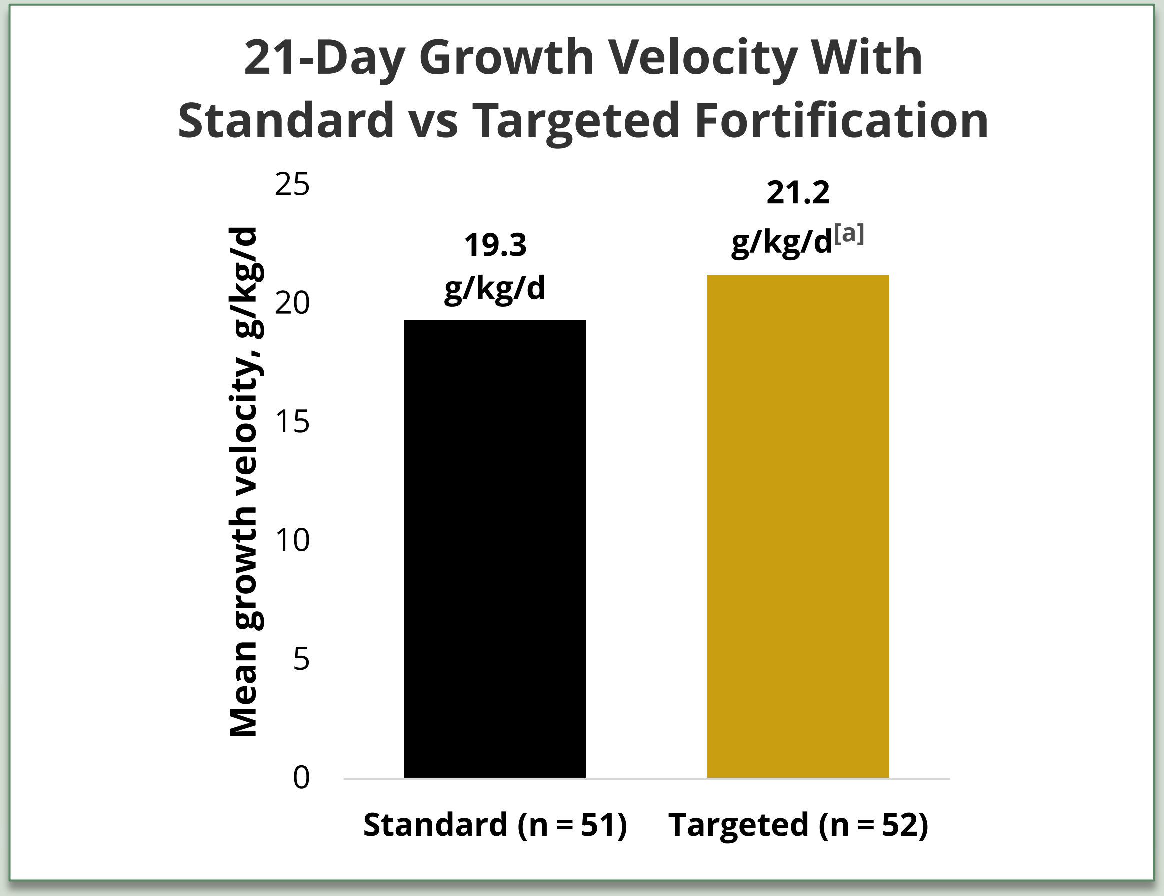
Targeted
most accurate & most costly

- Macronutrient concentrations in human milk are analyzed with a bedside human milk analyzer
- Fortification procedures are based on analysis

Bergner EM et al. *Clin Perinatol.* 2022;49(2):447-460.

Standard vs Targeted Fortification: Effects on Growth

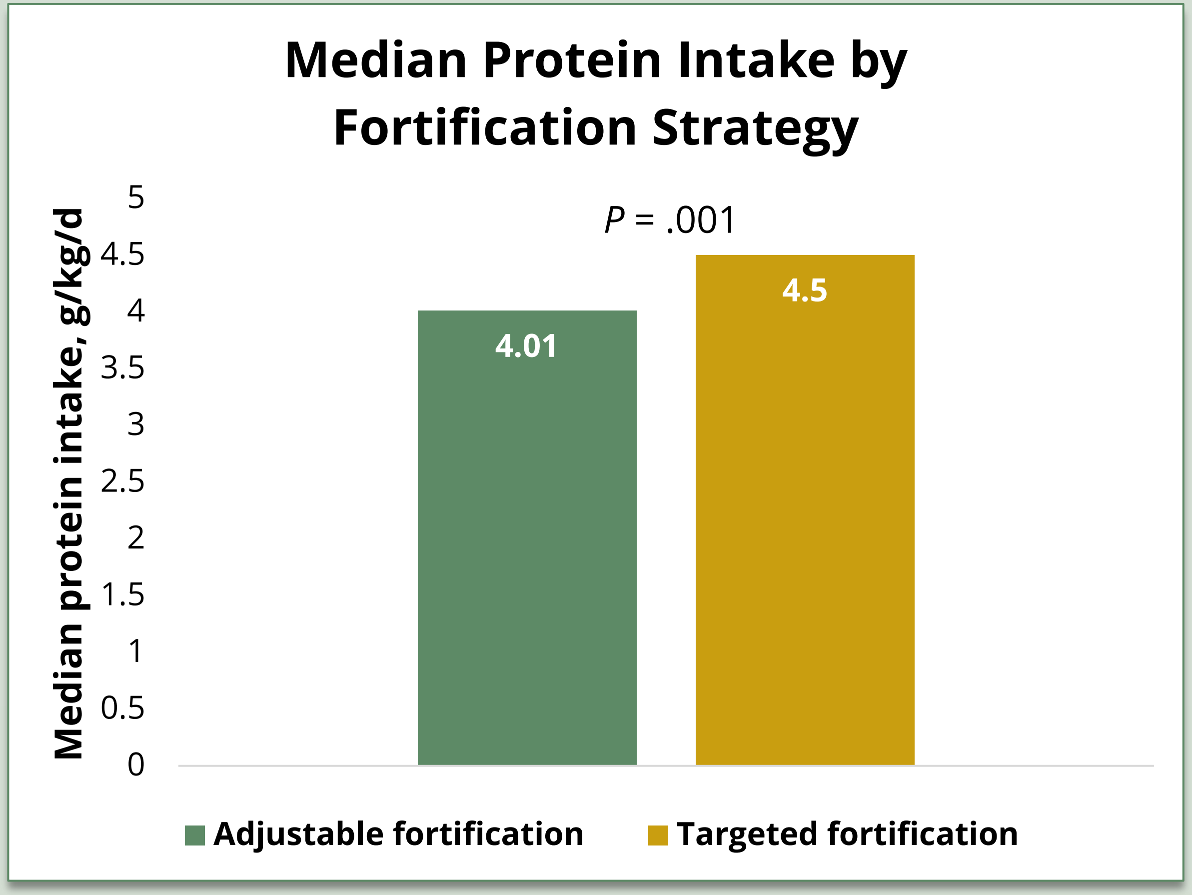


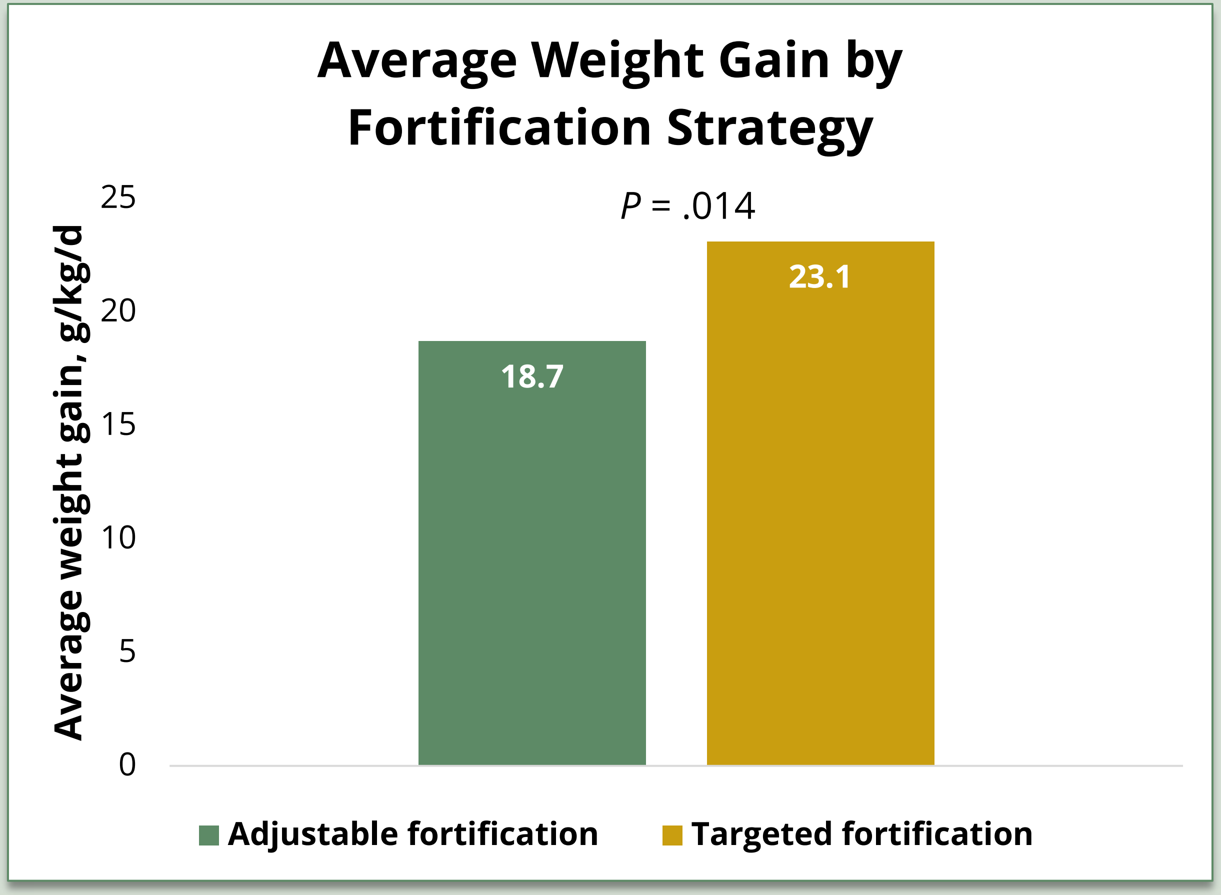


a. $P < .001$

Rochow N et al. *Clin Nutr.* 2021;40(1):54-63.

Adjustable vs Targeted Fortification[1]



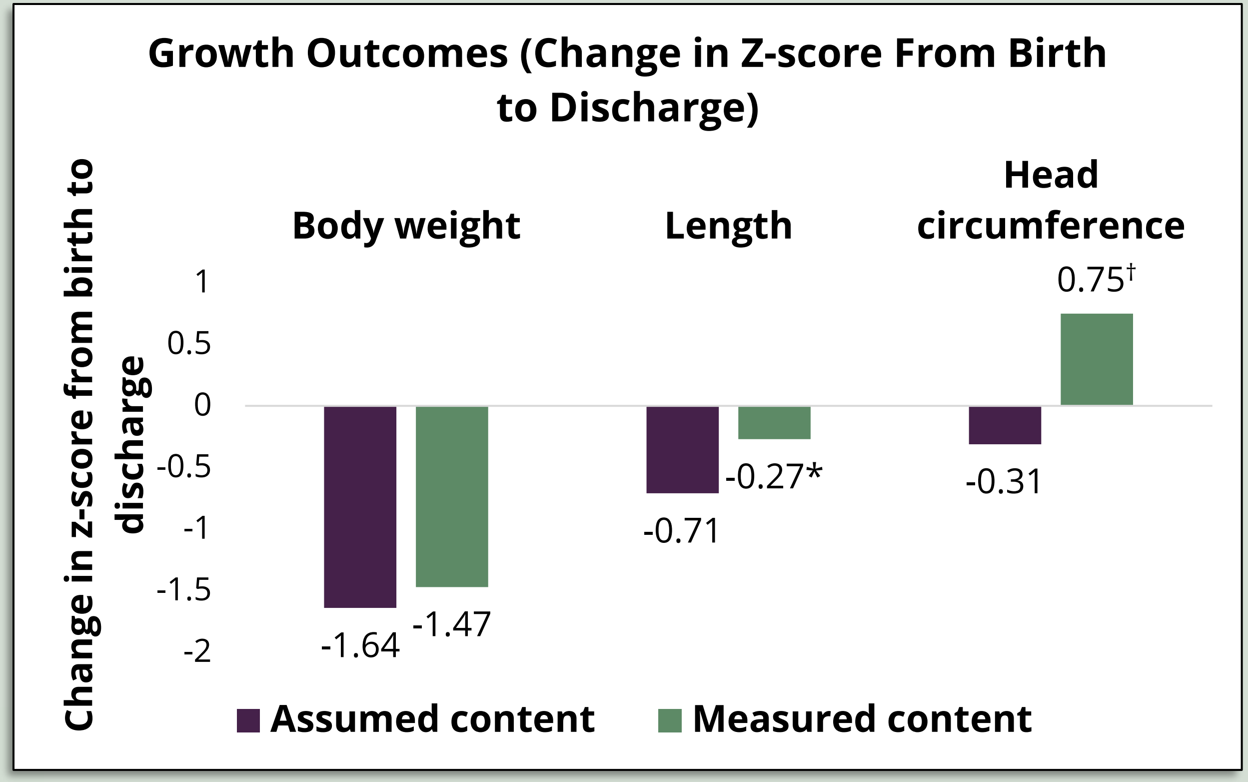


Note: ESPGHAN-recommended protein intake range is now 3.5–4.0 g/kg/d[2]

[1]. Bulut O et al. *Nutr Clin Pract.* 2020;35(2):335-343. [2]. Embleton ND et al. *J Pediatr Gastroenterol Nutr*. 2023;76(2):248-268.

Fortification Based on Assumed vs Measured Macronutrient Content

- Observational, mixed-cohort study
- Compared outcomes of preterm infants fed fortified milk based on **assumed (n=58)** vs **measured (n=57) macronutrient content**
- Protein and modular supplements were allowed in both groups
- Supplementation practices based on 2010 ESPGHAN guidelines



Infants in the milk analyzer group also had higher fat-free mass percentage after discharge.

a. **P* = .005; †*P* < .001

Clinical Trials Comparing Fortifiers

Growth With Liquid vs Powder BMBF

Acidified Liquid vs Powdered Fortifier (Enfamil) in Preterm Infants (<1250 g)[1]

Day-28 per-protocol outcomes	Powder (n = 32)	Liquid (n =24)	*P*
Mean (SE) weight, g	1662 (36)	1829 (42)	.004
Mean (SE) length, cm	41 (0.2)	42 (0.3)	.003
Mean (SE) head circumference, cm	30 (0.2)	31 (0.3)	.043

Extensively Hydrolyzed Liquid vs Powdered Intact Protein Fortifier (Similac) in Preterm Infants (<33 Weeks)[2]

Day-29 per-protocol outcomes	Powder (n = 25)	Liquid (n = 41)	*P*
Mean weight, g	1797	2039	.036
Mean length, cm	42.1	43.7	.029
Mean head circumference, cm	30.0	30.8	NS

Liquid fortifiers are safe and efficacious compared with powder fortifiers; RCTs show that those who strictly followed study protocols tended to have better growth outcomes with liquid fortifiers

[1]. Moya F et al. *Pediatrics*. 2012;130(4):e928-e935. [2]. Kim JH et al. *J Pediatr Gastroenterol Nutr.* 2015;61(6):665-671.

Fortification With Human Milk–Based Fortifier (HMBF) vs Bovine Milk–Based Fortifier (BMBF)

- RCT of VLBW infants (birth weight, 500–1250 g)
- Compared HMBF (Prolact+ H²MF) introduced at 100 or 40 mL/kg/d enteral intake with BMBF at 100 mL/kg/d enteral intake

Outcome	Delayed HMBF (≥100 mL/kg/d) (n=67)	Early HMBF (≥40 mL/kg/d) (n=71)	Delayed BMBF (≥100 mL/kg/d) (n=69)	*P*
Weight gain, g/kg/d	14.2 (11.9–15.8)	14.2 (12.3–16.3)	15.1 (12.8–17)	.13
Linear growth, cm/week	0.86 (0.72–1.08)	0.88 (0.70–1.03)	0.94 (0.72–1.16)	.35
Head growth, cm/week	0.76 (0.62–0.85)	0.75 (0.61–0.88)	0.75 (0.62–0.86)	.99
Median (IQR) time on parenteral nutrition, days	20 (14–35)	20 (12–33)	22 (14–34)	.71
Median (IQR) length of stay, days	74 (61–107)	79 (64–110)	78 (67–99)	.90
Late-onset sepsis, %	28	21	19	.39
Late-onset sepsis and/or NEC, %	33	28	30	.84

Sullivan S et al. *J Pediatr.* 2010;156:562-567.

Randomized Trial of Human Milk Cream as a Supplement to Standard Fortification

- Noninferiority RCT of preterm infants (birth weight, 750–1250 g)
- Compared supplementation with human milk cream (Prolact CR) to reach 20 kcal/oz or no supplementation in infants fed HMBF-fortified human milk (donor or mother's)

Outcome	Control (n=39)	Cream supplementation (n=39)	*P*
Mean (SD) growth outcomes			
Weight velocity, g/kg/d	12.4 (3.9)	14.0 (2.5)	.03
Length velocity, cm/wk	0.83 (0.41)	1.03 (0.33)	.02
Head circumference, cm/wk	0.84 (0.22)	0.90 (0.19)	.21
Growth velocity from time infant regained birth weight, g/kg/d	13.7 (4.0)	15.7 (2.5)	.02
Clinical outcomes, %			
NEC	0	0	-
Sepsis	7.7	10.3	1.0
Death	0	0	-

Hair AB et al. *J Pediatr.* 2014;165(5):915-920.

Comparison of Bovine vs Donor Milk–Derived Fortifier in a Randomized Controlled Trial

- Multicenter, triple-blind RCT
- Enrolled 127 VLBW (<1250 g) infants fed mother's milk supplemented with donor milk, as necessary
- Compared bovine milk–based fortifier (BMBF) with human milk–based fortifier (HMBF)

VLBW, very low birth weight.

Signs of Feeding Intolerance During Intervention [1]

	HMBF (n = 64)	BMBF (n = 61)	Adjusted *P* value
Feeding interruption (primary)	27%	33%	.45
Parental nutrition restarted	5%	2%	.33
Feedings withheld for 24 h not due to clinical procedure/breastfeeding	11%	16%	.37
Gastric residuals	41%	41%	.97
Abdominal distension	80%	85%	.41

Major Morbidity and Mortality

	HMBF	BMBF	*P* value
Mortality and morbidity index	35.9%	49.2%	.13
Late-onset sepsis	12.5%	23.0%	.12
NEC stage ≥II	4.7%	4.9%	.95
Severe ROP	1.6%	4.9%	.04

[1]. O'Connor DL et. al. *Am J Clin Nutr.* 2018;108(1):108-116.

Acidified vs Nonacidified Liquid BMBF in Preterm Infants

- Compared **acidified liquid BMBF** with **nonacidified liquid BMBF** in 164 preterm infants (≤32 weeks gestational age; birth weight, 700–1500 weeks)

- Primary outcome (weight gain to day 29)
  - No significant difference between acidified vs nonacidified fortifier: **16.4** vs **16.9 g/kg/d**

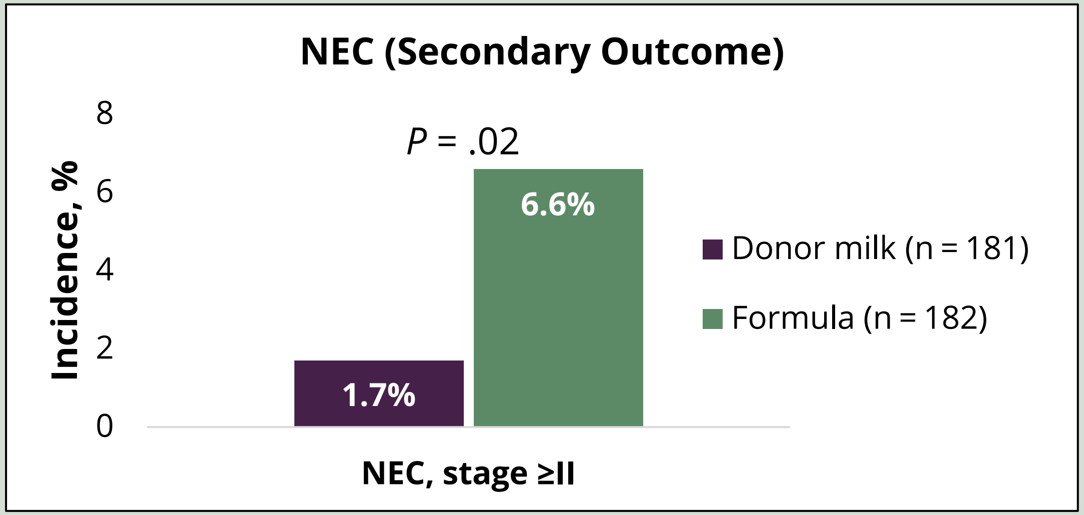
- No significant difference in length or head circumference gains

BMBF, bovine milk–based fortifier.

Schanler RJ et al. *J Pediatr.* 2018;202:31-37.e2.

DoMINO Randomized Controlled Trial: Short-term Outcomes [1]

- Multicenter, double-blind RCT
- Enrolled 363 VLBW (<1500 g) preterm infants
- Compared supplementation with either fortified donor milk[a] or preterm infant formula
- Most enteral feeds were mother's own milk for both the donor milk (58%) and formula groups (63%)



Outcome	Donor milk (n = 181)	Formula (n = 182)	*P*
Mortality and morbidity index, %	43.1	40.1	.20
Death, %	9.4	11.0	.82
Late-onset sepsis, %	24.3	19.2	.24
Severe ROP, %	3.9	4.4	.80

ROP, retinopathy of prematurity
a. Donor milk was fortified with powdered bovine fortifier and protein module to reach estimated 1.2 g/dL

[1]. O'Connor DL et al. *JAMA*. 2016;316(18):1897-1905.

Outcomes With Fortified Mother's Own Milk vs Donor Milk

- Donor milk is recommended based on evidence for **reduced risk of NEC** vs formula[1],[2]

- Recent studies comparing mother's own milk with donor human milk have shown **conflicting effects on short-term growth**[2]
  - Insufficient nutritional concentrations and inadequate donor human milk fortification practices may explain discrepancies

- Effects of donor milk on **long-term outcomes**, including growth and neurodevelopment, are under investigation[2],[3]

[1]. Quigley M et al. *Cochrane Database Syst Rev.* 2019;7(7):CD002971. [2]. Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed*. Karger; 2021. [3]. Colaizy TT et al. Presented at: Hot Topics in Neonatology 2022. National Harbor, MD; December 4-7, 2022.

Duration of Fortification

- Continuation of fortification or use of nutrient-rich formulas beyond hospital discharge **may improve growth outcomes** in very preterm infants[1],[2]
  - Can be continued until corrected age of **~6 months**
- **Options for postdischarge fortification include:**[2]
  - Bovine transitional powdered formula mixed with pumped human milk
  - Supplementing breast feeding and pumped milk with postdischarge transitional formula for a specific number of feeds
  - If resources permit, continued fortification with BMBF

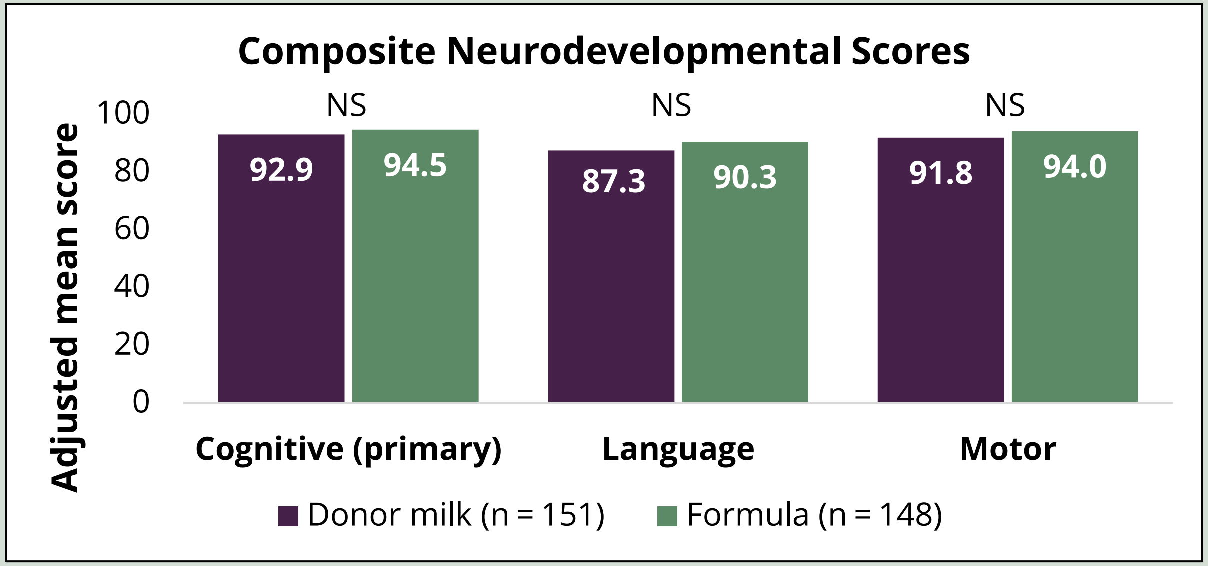
BMBF, bovine milk–based fortifier.

[1]. Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed*. Karger; 2021. [2]. Hair AB et al. *J Perinatol.* 2023;43(1):103-107.

Long-term Outcomes From Trials of Fortification

DoMINO Randomized Controlled Trial: Key Outcomes at 18 Months[1]

- Multicenter, double-blind RCT
- Enrolled 363 VLBW (<1500 g) preterm infants
- Compared supplementation with either fortified donor milk[a] or preterm infant formula
- Most enteral feeds were mother's own milk for both the donor milk (58%) and formula groups (63%)



Neuroimpairment scores <85	Donor milk	Formula	*P*
Cognitive, %	27.2	16.2	.02
Language, %	46.7	37.2	.10
Motor, %	25.5	20.4	.47

[a]. Donor milk was fortified with powdered bovine fortifier and protein module to reach estimated 1.2 g/dL

[1]. O'Connor DL et al. *JAMA*. 2016;316(18):1897-1905.

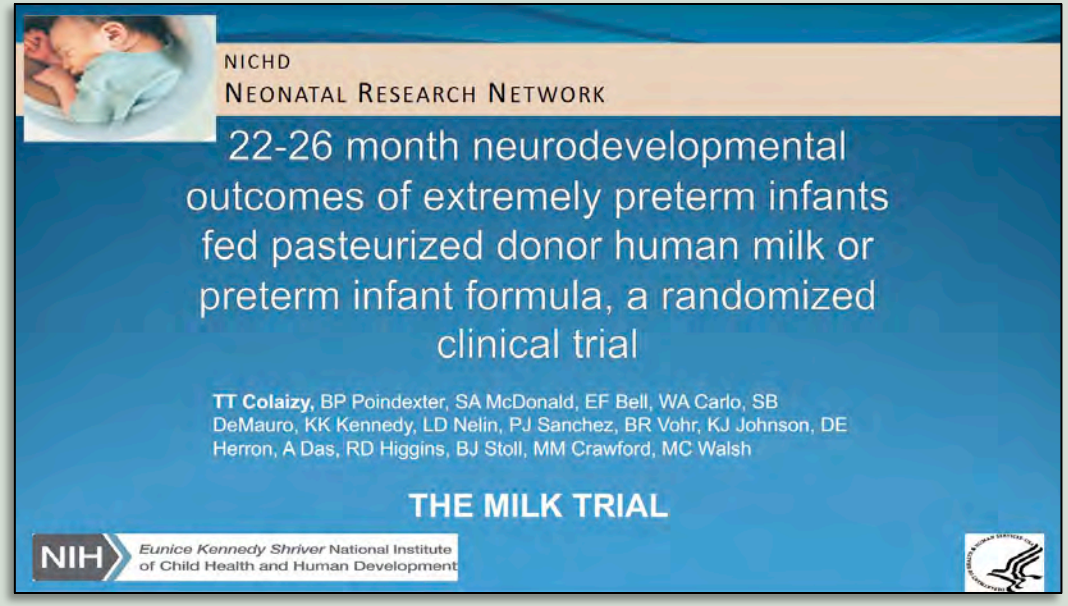
OptiMoM Trial: 5.5-Year Follow-up of DoMINO Trial Participants

Despite prior reports of slower in-hospital growth with donor milk, long-term results from the DoMINO trial do not support significant differences in long-term growth between preterm infants supplemented with formula and those supplemented with donor milk.

Unadjusted mean (95% CI)	Donor milk (n = 80)	Preterm formula (n = 78)	Adjusted *P* value
Weight, z score	-0.4 (-0.7, -0.2)	-0.5 (-0.8, -0.2)	.10
Height, z score	-0.4 (-0.7, -0.1)	-0.6 (-0.8, -0.3)	.49
BMI, z score	-0.3 (-0.6, -0.01)	-0.3 (-0.5, 0.009)	.43
Systolic blood pressure, mm Hg	101 (98, 103)	101 (99–103)	.33
Diastolic blood pressure, mm Hg	60 (58, 61)	60 (58–62)	.59

McGee M et al. *J Nutr.* 2020;150(2):331-339.

MILK Triple-Blinded Randomized Controlled Trial: Study Design



Thank you to **Tarah Colaizy, MD, MPH,** for sharing slides and data presented at the Hot Topics in Neonatology 2022 conference.

- Compared **fortified (bovine), pasteurized donor milk** with **preterm infant formula**
  - Used site-specific preterm infant feeding practices (eg, recipes, advancement, fortification)
  - Recommended protein fortification for donor milk recipes
- Randomized infants up to 21 days of age
- Conducted at 14 NICHD Neonatal Research Network centers

NICHD, National Institute of Child Health and Human Development.

MILK Trial: Participant Demographics

Infant Enrollment Criteria

- <29 weeks' gestation or <1000 g birth weight
- Admitted to center <7 days of age
- Mother providing no or minimal milk
- No severe congenital anomalies, NEC, or SIP

	Donor milk (n = 239)	Preterm formula (n = 244)	NRN, MILK trial period[a] (n = 10,717)
Mean (SD) age at randomization, days	14.4 (6.06)	14.4 (6.02)	
Mean (SD) gestational age, wk	26.0 (1.76)	26.1 (1.61)	25.9 (1.69)
Multiples, n (%)	50 (21)	48 (20)	2848 (27)
Mean (SD) maternal age, yr	27.9 (6.11)	28.2 (6.57)	28.6 (6.19)
Maternal race, n (%)			
Black	126 (54)	121 (50)	4224 (41)
White	98 (42)	108 (44)	5482 (53)
Other	11 (4.7)	14 (5.8)	706 (6.8)
Maternal education, n (%)			
Less than high school	64 (29)	57 (25)	1539 (18)
High school	82 (37)	93 (41)	2569 (30)
More than high school	74 (34)	77 (34)	4581 (53)
Public insurance, n (%)	172 (75)	184 (77)	6068 (57)
Antenatal steroids	206 (87)	203 (85)	9782 (91)

SIP, spontaneous intestinal perforation.

a. Comprehensive registry database of all infants <29 weeks within Neonatal Research Network (NRN) centers

[1]. Colaizy TT et al. Presented at: Hot Topics in Neonatology 2022. National Harbor, MD; December 4-7, 2022. [2]. ClinicalTrials.gov. Donor Milk vs. Formula in Extremely Low Birth Weight (ELBW) Infants. Results posted February 6, 2023. Accessed April 14, 2023. https://www.clinicaltrials.gov/ct2/show/results/NCT01534481?view=results.

MILK Trial: Neurodevelopmental Outcomes (Primary & Secondary)

	Donor milk	Preterm formula	Effect (95% CI)
Adjusted mean (SD) BSID score[a]			
Cognitive (primary)	80.7 (17.4)	81.1 (16.7)	-0.77 (-3.93 to 2.39)
Motor	80.3 (21.6)	80.1 (19.9)	-0.38 (-4.28 to -3.52)
Language	76.7 (19.6)	75.8 (18.6)	0.68 (-2.89 to 4.24)
Adjusted categorical BSID score, n (%)[a]			
Cognitive <85	95 (46)	106 (49)	0.96 (0.79–1.17)
Motor <85	90 (45)	102 (48)	0.96 (0.79–1.17)
Language <85	115 (57)	134 (63)	0.89 (0.77–1.04)
Moderate to severe NDI	87 (49)	96 (50)	0.99 (0.81–1.22)

No significant difference in BSID-III scores at 22–26 months corrected age with donor milk vs formula in extremely preterm infants

BSID-III, Bayley Scales of Infant Development; NDI, neurodevelopmental impairment.

a. Deaths assigned lowest BSID-III score of 54

[1]. Colaizy TT et al. Presented at: Hot Topics in Neonatology 2022. National Harbor, MD; December 4-7, 2022. [2]. ClinicalTrials.gov. Donor Milk vs. Formula in Extremely Low Birth Weight (ELBW) Infants. Results posted February 6, 2023. Accessed April 14, 2023. https://www.clinicaltrials.gov/ct2/show/results/NCT01534481?view=results.

MILK Trial: Other Outcomes (Secondary)

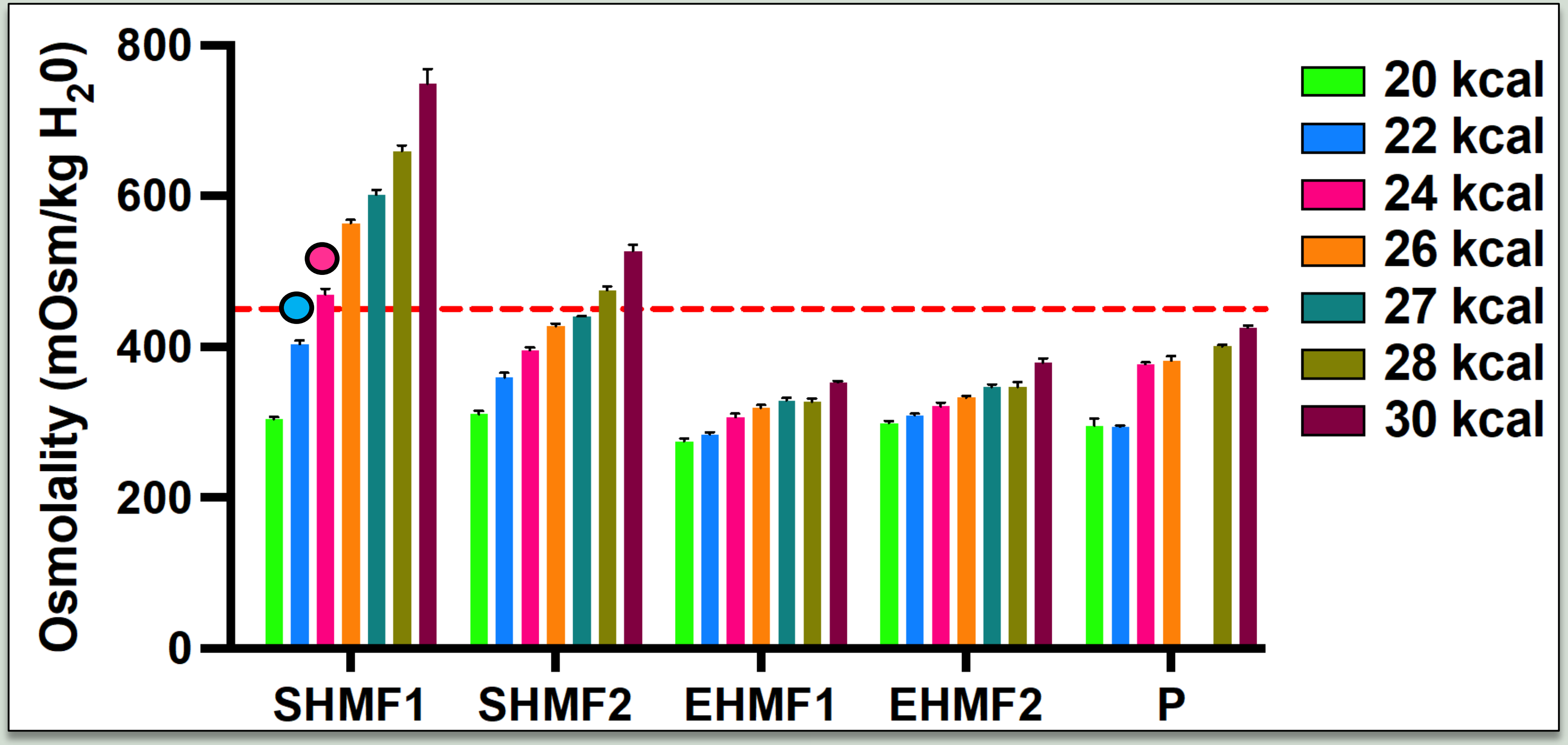
	Donor milk (n = 239)	Preterm formula (n = 244)	Adjusted effect (95% CI)
Death before discharge, n (%)	24 (10)	18 (7.4)	1.36 (0.83–2.23)
NEC, n (%)	10 (4.2)	22 (9.0)	0.45 (0.24–0.84)
NEC or death before discharge, n (%)	27 (11)	33 (14)	0.84 (0.59–1.18)
Late-onset sepsis, n (%)	47 (20)	37 (15)	1.31 (0.83–2.06)
Growth, change in z scores (Fenton) from randomization to end of study			
Weight	-0.43 (0.89)	-0.09 (0.86)	*P* < .0001
Length	-0.93 (1.12)	-0.77 (1.20)	NS
Head circumference	0.39 (1.98)	0.44 (1.34)	NS

Donor milk may be protective against NEC but is associated with nutritional risk.

[1]. Colaizy TT et al. Presented at: Hot Topics in Neonatology 2022. National Harbor, MD; December 4-7, 2022. [2]. ClinicalTrials.gov. Donor Milk vs. Formula in Extremely Low Birth Weight (ELBW) Infants. Results posted February 6, 2023. Accessed April 14, 2023. https://www.clinicaltrials.gov/ct2/show/results/NCT01534481?view=results

Unanswered Questions and Ongoing Research

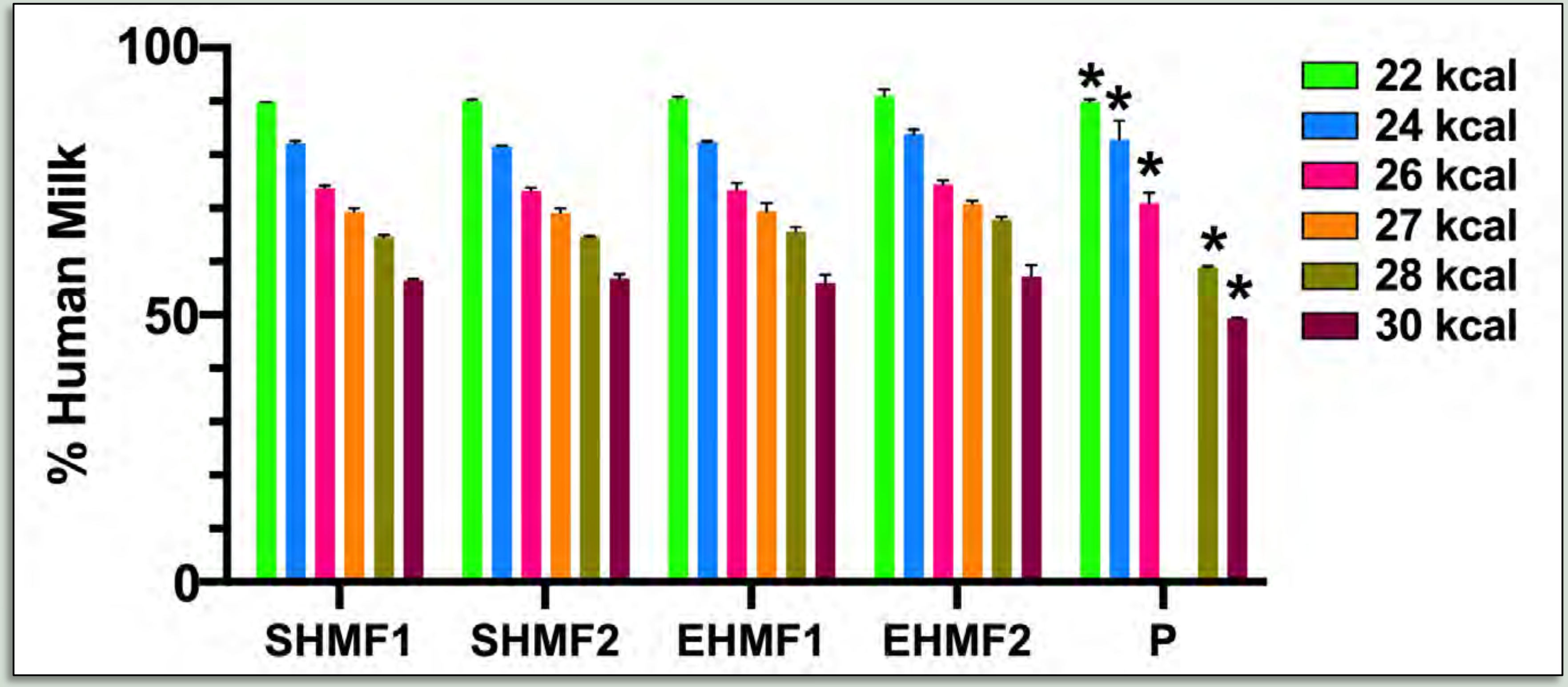
Variable Osmolality by Fortifier Type & Target Caloric Density



SHMF1, Similac® Human Milk Fortifier Extensively Hydrolyzed Liquid; SHMF2 , Similac® Human Milk Fortifier Concentrated Liquid; EHMF1 , Enfamil® Liquid Human Milk Fortifier Standard Protein; EHMF2 ,Enfamil® Liquid Human Milk Fortifier High Protein; EHMF3, Enfamil® Human Milk Fortifier Powder, P, Prolact CR; Prolact +4, +6, +8, +10 H^2MF.

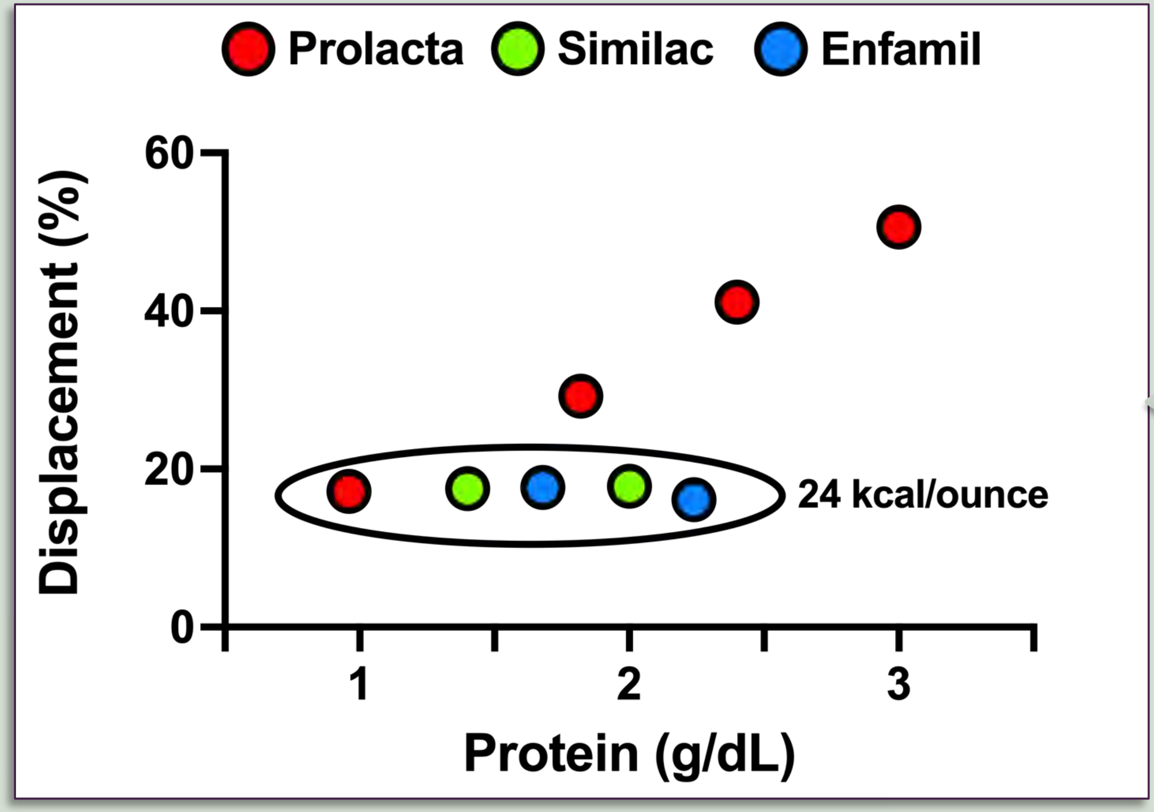
Pineda D, Stansfield B. Presented at PAS 2023. Abstract 71.

Variable Displacement by Fortifier Type & Target Caloric Density



SHMF1, Similac® Human Milk Fortifier Extensively Hydrolyzed Liquid; SHMF2 , Similac® Human Milk Fortifier Concentrated Liquid; EHMF1 , Enfamil® Liquid Human Milk Fortifier Standard Protein; EHMF2 ,Enfamil® Liquid Human Milk Fortifier High Protein; EHMF3, Enfamil® Human Milk Fortifier Powder, P, Prolact CR, Prolact +2, +4, +6, +8, +10 at 22, 24, 26, 28, and 30 kcal/oz, respectively.
Data are mean ± SD.
* *P* < .0001

Effects of Liquid Human Milk Fortifier Protein on Displacement



BMBFs provide more protein at equivalent caloric density (and with less displacement) of HMBF

BMBF, bovine milk–based fortifier; HMBF, human milk–based fortifier.

Pineda D, Stansfield B. Unpublished as of April 30, 2023.

Ongoing Questions: Micronutrient Supplementation

- **Wide reference ranges** for many micronutrients are based on a variety of factors:
  - Inter- and intra-individual **variation** in requirements
  - **Limited high-quality evidence** for intake levels that optimize functional outcomes
  - **Variable dietary absorption** and retention rates, which can be impacted by use of diuretics and other medications

- High-quality RCTs are needed to refine micronutrient supplementation practices

Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.

Emerging Data: Enteral Zinc Supplementation

- In a meta-analysis of 8 RCTs that enrolled 742 preterm infants, **growth benefits of zinc supplementation** included:[1]
  - Increased weight gain
  - Increased linear growth
  - Higher motor development scores
- In a separate meta-analysis of 5 RCTs and quasi-RCTs that enrolled. 482 preterm infants, **morbidity and mortality benefits** of zinc supplementation included:[2]
  - Moderately decreased all-cause mortality
  - No effect on NEC or other common comorbidities

[1]. Alshaikh B et al. *J Perinatol*. 2022;42(4):430-439. [2]. Staub E et al. *Cochrane Database Syst Rev.* 2021;3(3):CD012797.

Emerging Data: Enteral Iron Supplementation

- Iron is critically important for neurodevelopment, but excess iron supplementation can lead to iron overload[1],[2]
- In a **meta-analysis of 8 trials that enrolled 1093 preterm or low–birth weight infants**, researchers concluded iron supplementation was associated with:[1]
  - Improved linear growth
  - Reduced anemia
  - Minimal effect on NEC or infection
- In a post hoc analysis of a randomized trial of 692 preterm infants enrolled in the PENUT study, higher iron dose (IQR, 2.1–5.8mg/kg/d)[a] was associated with improved cognition at 2 years of age[2]

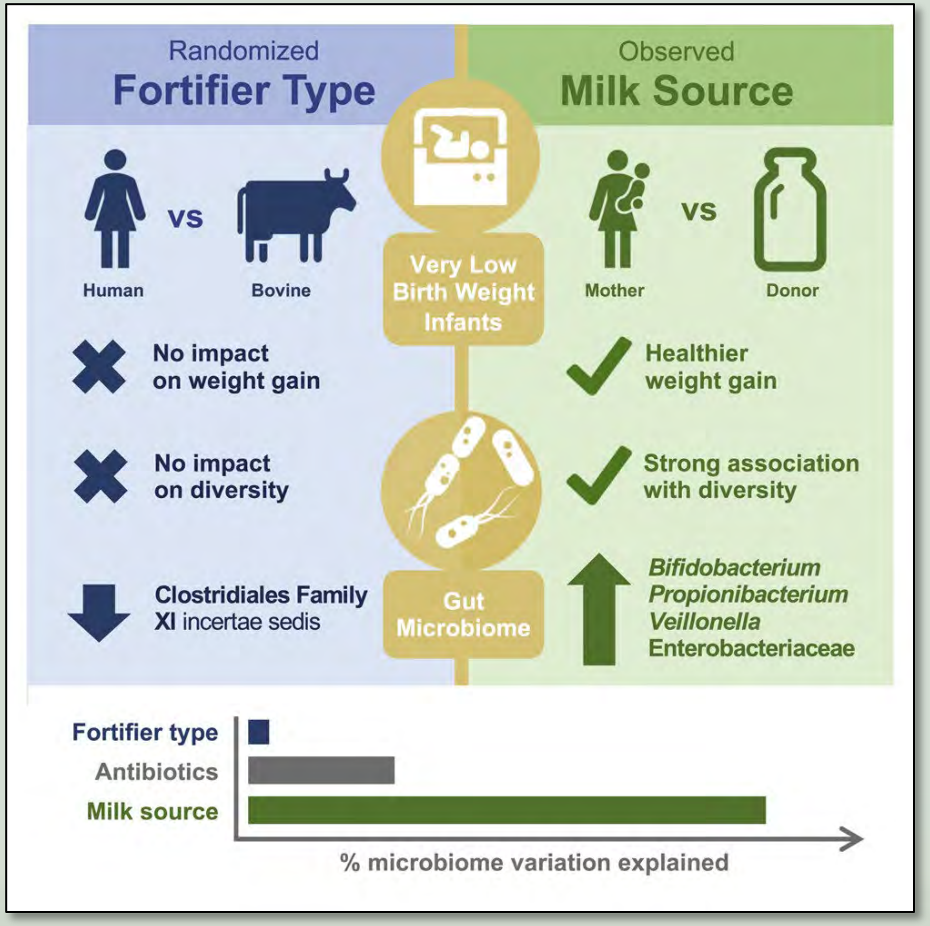
a. ESPGHAN-recommended iron intake is 2–3 mg/kg/d.

[1]. Manapurath RM et al. *Pediatrics*. 2022;150(Suppl 1):e2022057092I. [2]. German KR et al. *J Pediatr.* 2021;238:102-109.e8.

Interaction Between Preterm Infant Feeds & the Microbiome

- Effects of fortifier type and base milk on preterm infant microbiome are poorly defined[1]
- Fortifier type (bovine vs human) does **not** appear to affect microbiome diversity[2],[3]
- However, base milk type was **strongly** associated with microbiome diversity, with greater microbial diversity in infants fed mother's own milk

Summary of Outcomes From an RCT of 30 Preterm Infants [2]



[1]. Granger CL et al. *Acta Paediatr.* 2021;110(2):450-457. [2]. Kumbhare SV et al. *Cell Rep Med.* 2022;3(9):100712. [3]. Embleton ND et al. *JAMA Netw Open.* 2023;6(3):e231165. Image courtesy of Kumbhare SV et al. Cell Rep Med. 2022;3(9):100712. CC BY-NC-ND 4.0.

Key Takeaways

Key Takeaways: Optimizing Human Milk

- **Preterm mother's own milk is dynamic:**
  - Protein-rich through first week → SEQUENTIAL FEEDING
  - Higher protein, sodium, and zinc than donor human milk through the first month
  - Consider sodium supplementation after first week (particularly donor human milk)
  - Recognize that gestational age and race may influence mother's own milk composition
- **Pooling mother's own milk (24-h collection) may provide more even distribution of nutrients**

Key Takeaways: Optimizing Human Milk

- **Donor human milk is…**
  - Pooled and pasteurized
  - Lower in protein, sodium, and zinc relative to mother's own milk
- Know your donor milk bank's pooling practices and whether they have an analyzer
- Supplement with protein

Preterm mother's own milk

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Donor human milk

Pay careful attention to growth in infants fed donor milk, even with fortification and protein supplementation

Key Takeaways: Optimizing Human Milk

Fortification considerations for day-28 mother's own milk:

- Consider displacement if mother's own milk is primary
- Osmolality may contribute to feeding intolerance (?)
- Additional protein based on gestational age and lactational stage
- Human milk can meet caloric needs, but not protein, sodium, calcium, iron, and zinc requirements
  - Consider zinc supplementation for infants on long-term diuretics