

Variations in the Nutritional Content of Human Milk



Pediatric Nutrition
CONTINUING EDUCATION FOR CLINICIANS

Presented by
Brian Stansfield, MD



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Mead Johnson Nutrition.

Faculty Presenter

Brian Stansfield, MD

Associate Professor
and Vice Chair of Research
Department of Pediatrics
Member, Vascular Biology Center
Medical College of Georgia
Augusta University
Augusta, Georgia, USA



Dr. Stansfield on service. Photo courtesy of Brian Stansfield, MD.



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Brian Stansfield, MD

Research Consultant

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Learning Objectives



Discern what is known or not known about the nutritional composition of human milk



State general nutritional expectations associated with mother's own milk and donor milk



Apply critical assessment to the planned feeding strategy for a preterm infant



Human Milk for Preterm Infants



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

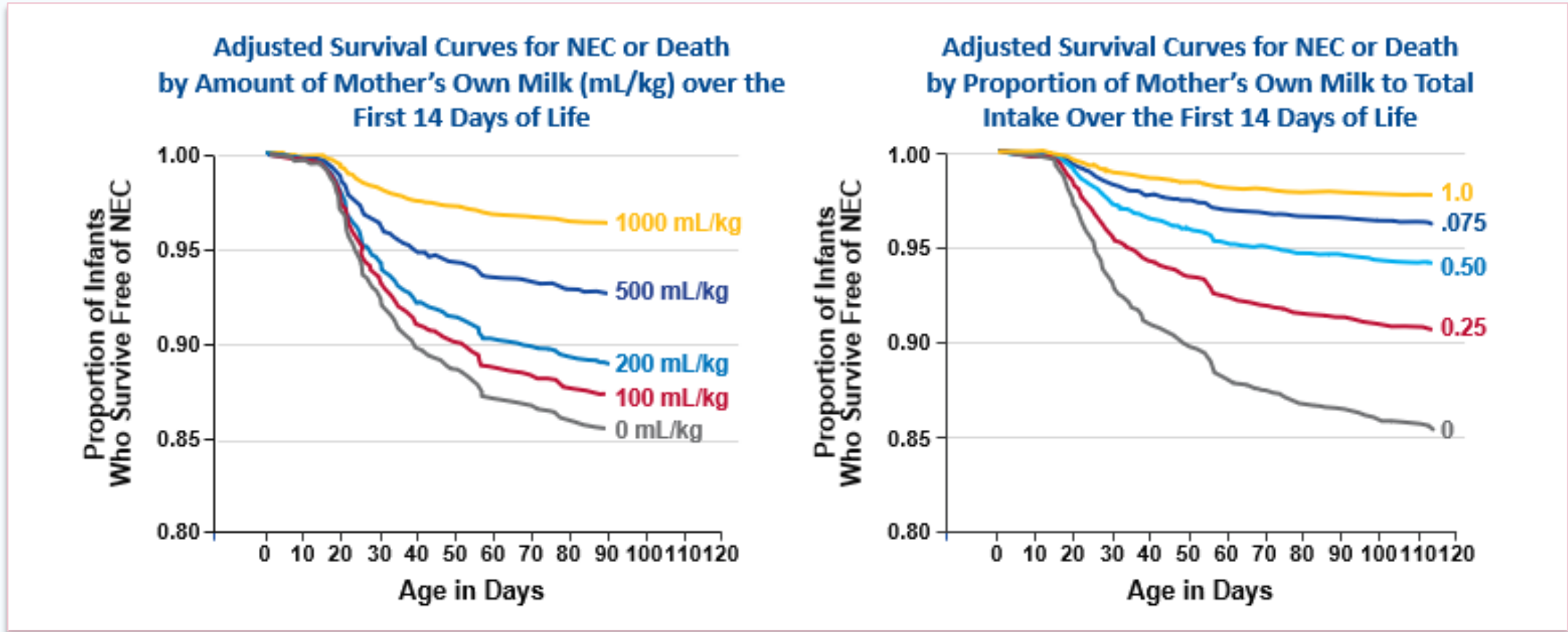


Maternal, infant, and public health organizations recommend **exclusive breastfeeding** or **use of human milk** for virtually all infants—including preterm infants—for the first 6 months of life [1]–[6]

[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

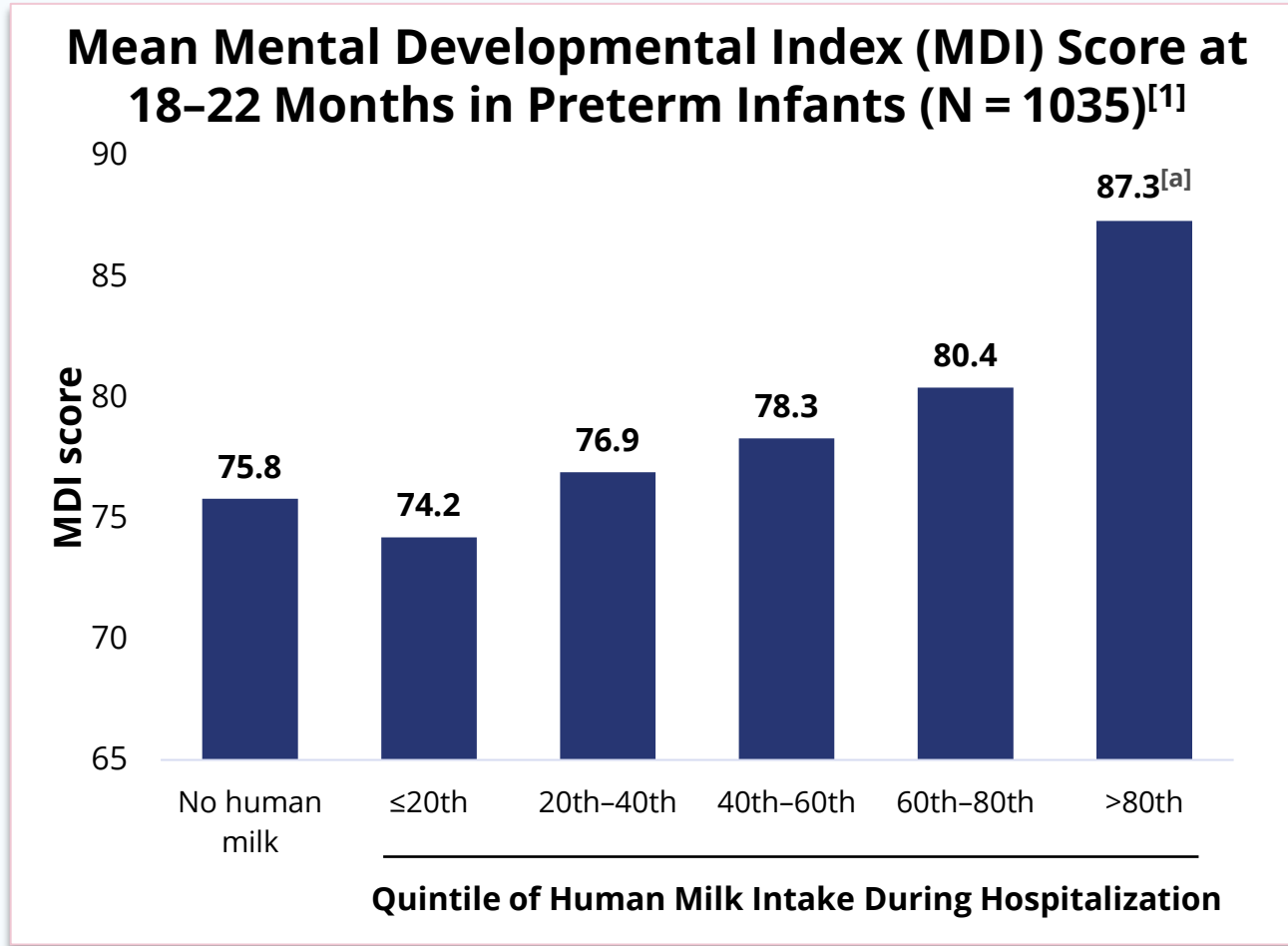


NEC, necrotizing enterocolitis.

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



Human Milk and Neurodevelopment in Preterm Infants



a. $P < .01$ vs no human milk

At 22 months of age, higher levels of human milk intake during hospitalization was associated with better neurodevelopmental outcomes.^[1]





In cohort studies, the neurodevelopmental benefits of human milk for hospitalized preterm infants persisted for up to **8 years of age**.^{[2],[3]}

[1]. Vohr BR et al. *Pediatrics*. 2006;118(1):e115-e123. [2]. Horwood LJ et al. *Arch Dis Child Fetal Neonatal Ed*. 2001;84(1):F23-F27. [3]. Belfort MB et al. *JAMA Netw Open*. 2022;5(7):e2221608.



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
-  Variability of human milk composition



Adequate Growth and Preterm Infant Outcomes



Preterm Infant Growth Benefits: Preventing Morbidity

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



Late-onset sepsis^[1]



Necrotizing enterocolitis^[1]



Bronchopulmonary dysplasia^[1]



Retinopathy of prematurity^[2]

[1]. Guellec I et al. *J Pediatr*. 2016;175:93-99.e1. [2]. Hellström A et al. *Acta Paediatr*. 2010;99(4):502-508.



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



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]

↑2.4
MDI score

↑2.7
PDI score

BMI ^[1]

↑1.7
MDI score

↑2.5
PDI score

Head growth ^[1]

↑1.4
MDI score

↑2.5
PDI score

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 M] 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.



Risk Factors for Preterm Infant Growth Faltering

- Lower birth weight or younger gestational age
- Male sex
- Comorbidities and their treatments (eg, mechanical ventilation, steroids, diuretics, and catecholamines, all of which are catabolic)
- Intrauterine growth restriction
- Insufficient nutritional intake

Modifiable risk factor for preventing growth faltering



Composition of Human Milk



Factors Influencing Human Milk Composition

Maternal [1]-[3]

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

Perinatal [1],[3]

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

Environmental [4]

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

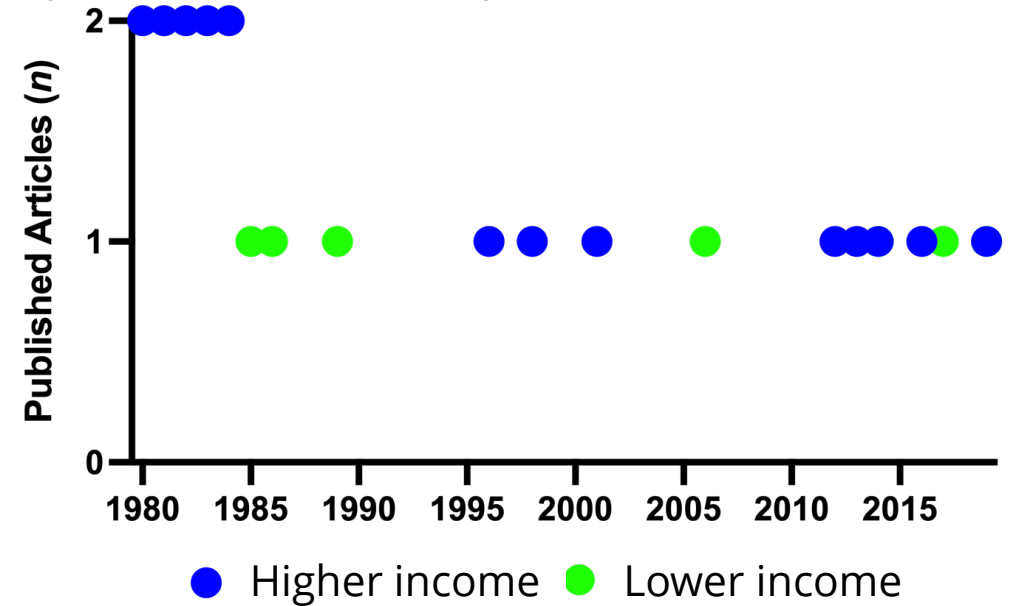


Preterm Human Milk Composition: Challenges and Limitations of the Literature

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
- Underrepresentation of Black women
- Underrepresentation of deliveries <28 weeks gestation

Studies of Preterm Milk Composition by Date and Country Income Status



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

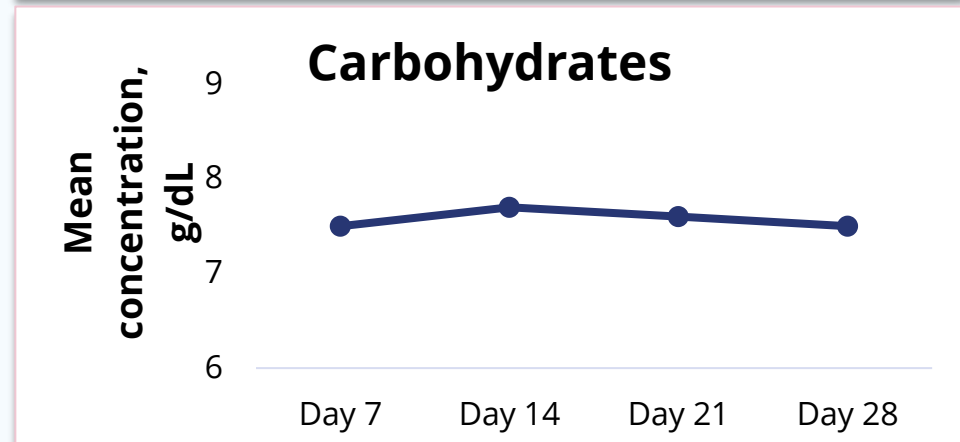
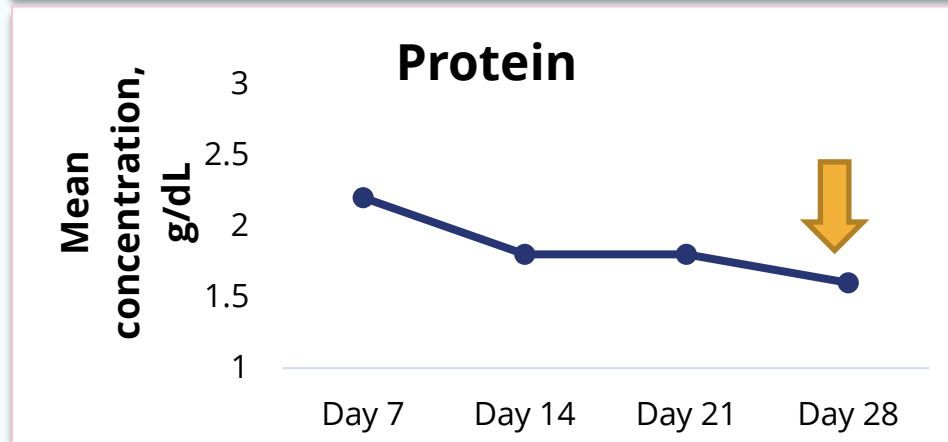
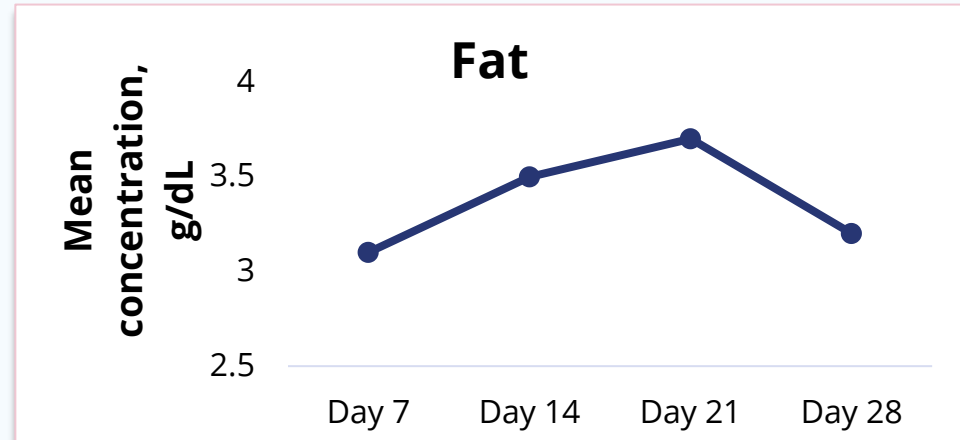
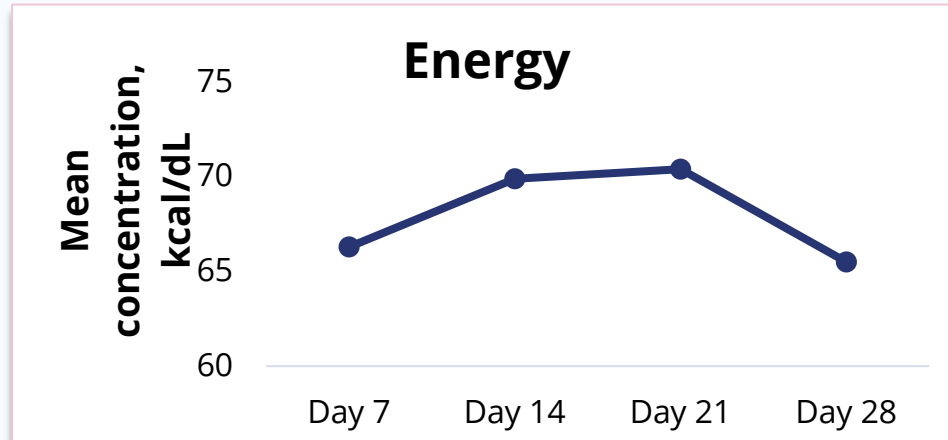
- Women who delivered ≤ 33 weeks gestation (N = 38)
- Pooled 24-hour milk samples from days 7, 14, 21, and 28
- Assessed macro- and micronutrient composition

	Mean \pm SD or N (%)	Range
Maternal age, y	27 \pm 5.1	18–37
EGA, wk	28.2 \pm 2.8	22.9–33.0
EGA <28 wk	16 (42)	
Infant birth weight, g	1098 \pm 347.3	545–2130
Male infant sex	20 (53)	
Race		
Black	25 (66)	
White	13 (34)	

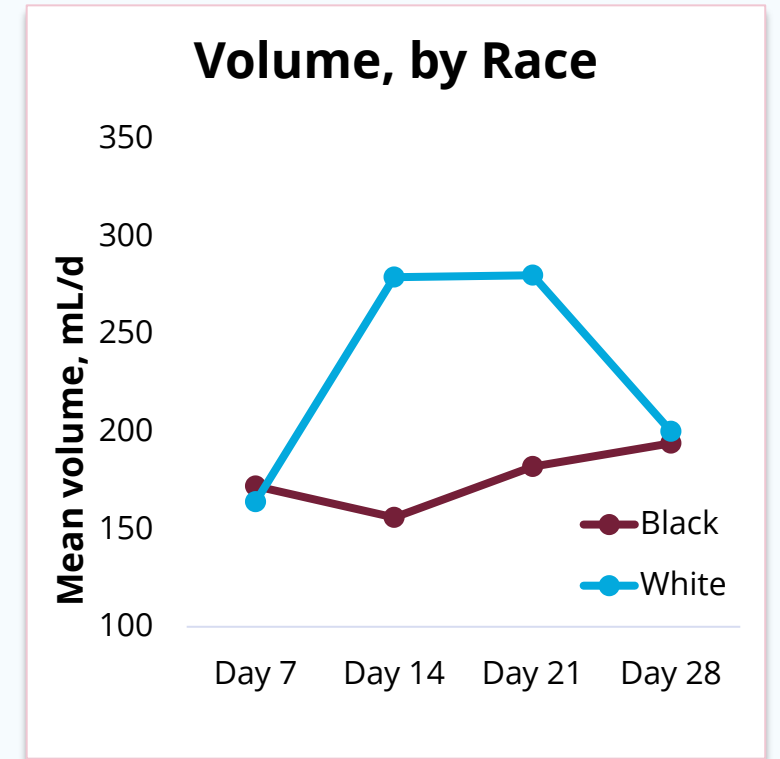
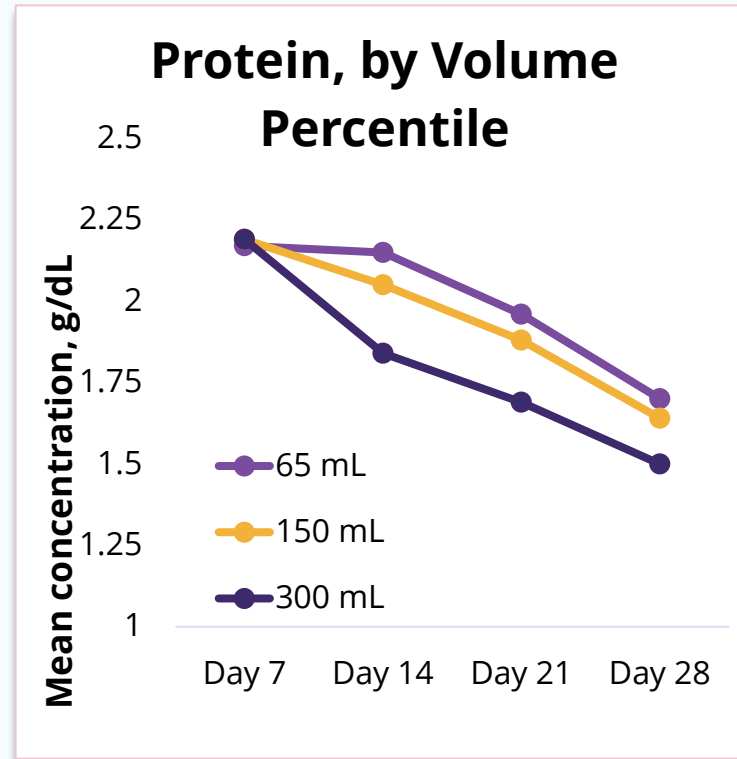
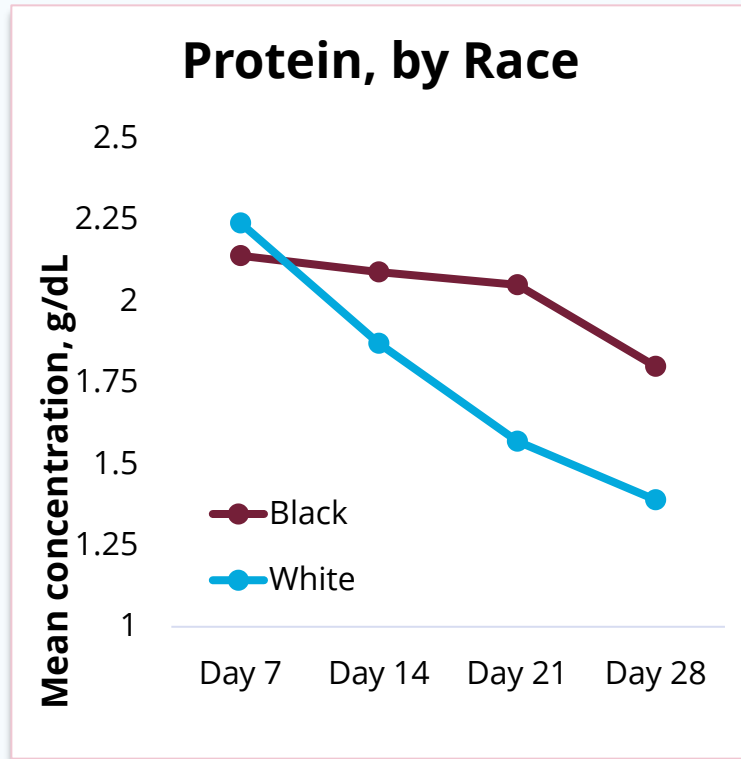
EGA, estimated gestational age; SD, standard deviation.



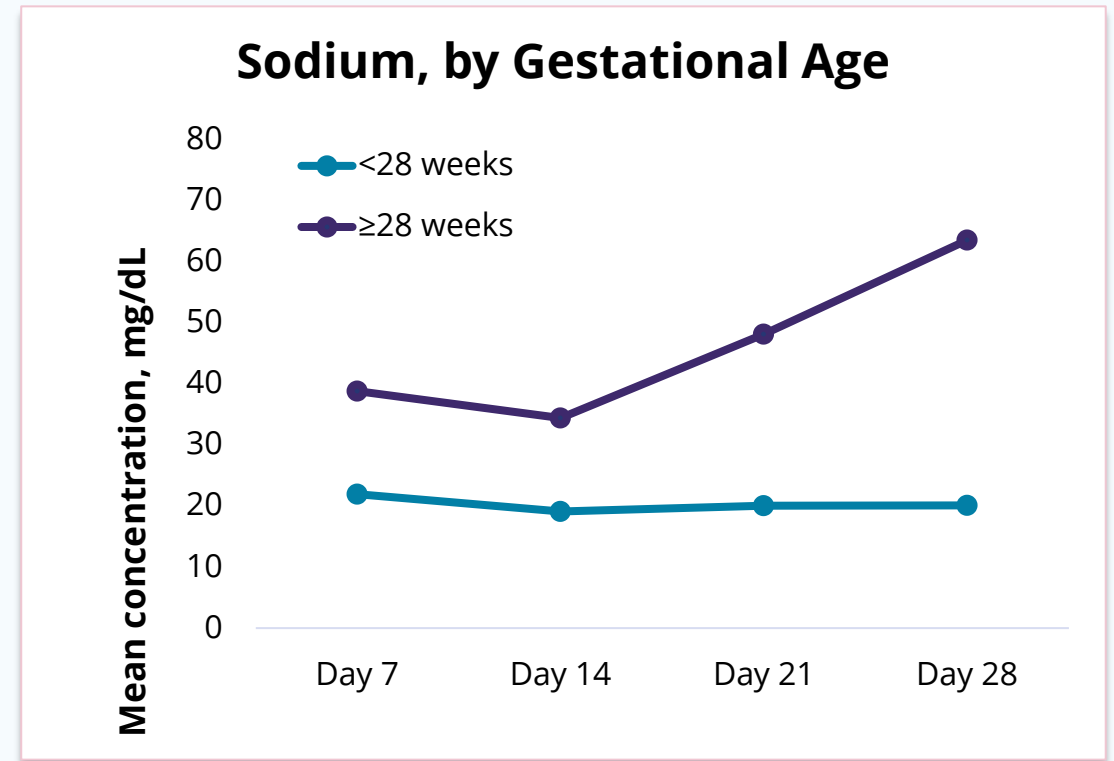
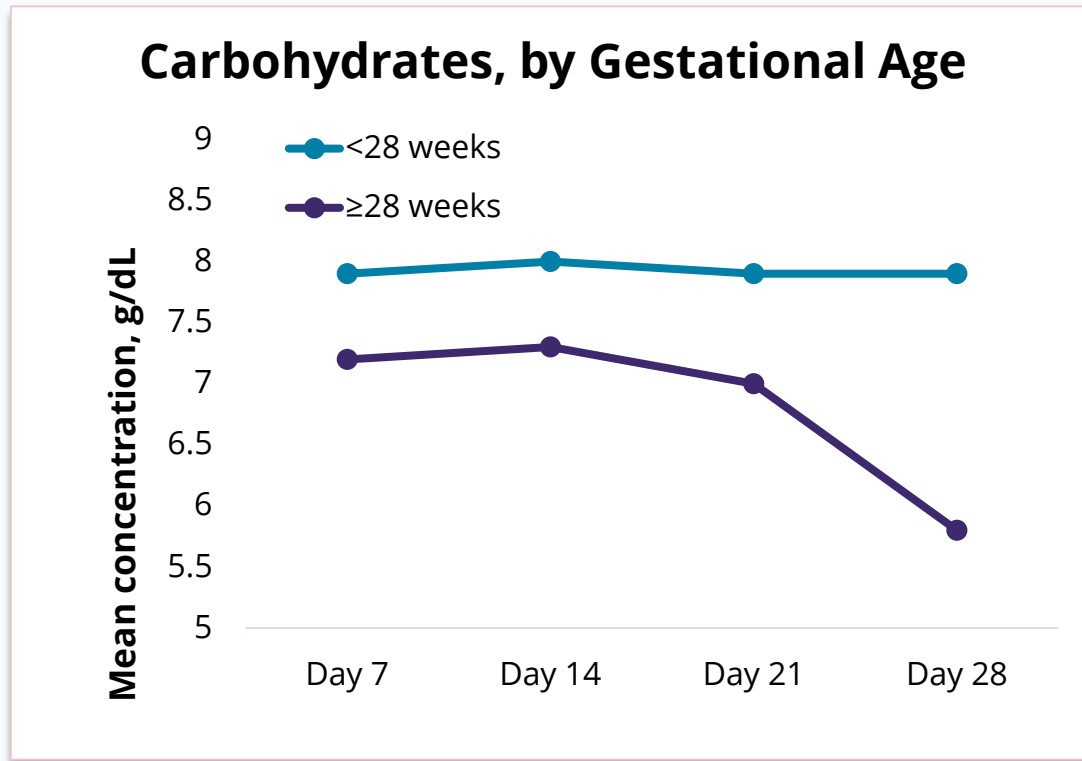
Prospective, Longitudinal Study of Preterm Human Milk Composition: Macronutrients by Lactation Stage



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



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



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

Nutrient	Preterm milk^[1] (per 100 mL)	Term milk^[3] (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]. 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.



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)



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



Differences in Growth With Mother's Own Milk vs Donor Milk

- Donor milk is recommended based on evidence for **reduced risk of necrotizing enterocolitis** 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
- Its effects on **long-term outcomes**, including growth and neurodevelopment, are uncertain ^[2]



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]

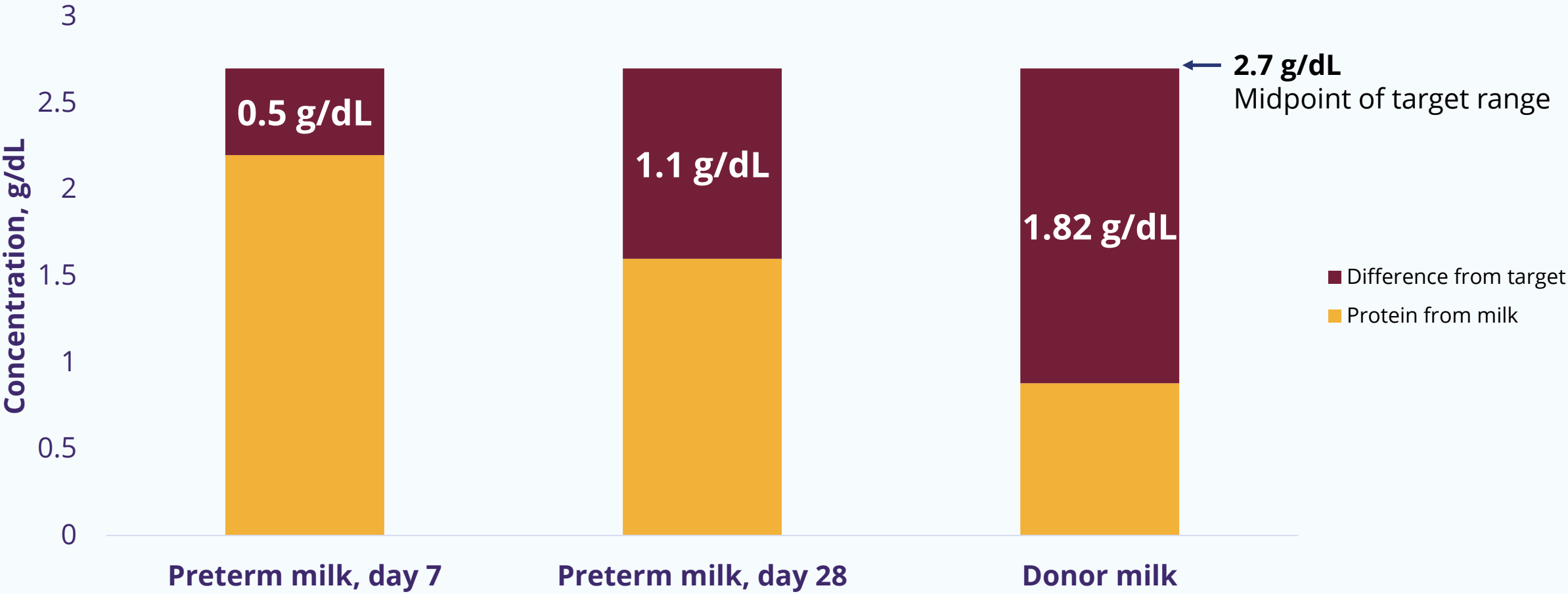
- Reduced **caloric density**
- Reduced levels of **lipids** and **long-chain polyunsaturated fatty acids**

Changes in micronutrient composition^[1]

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



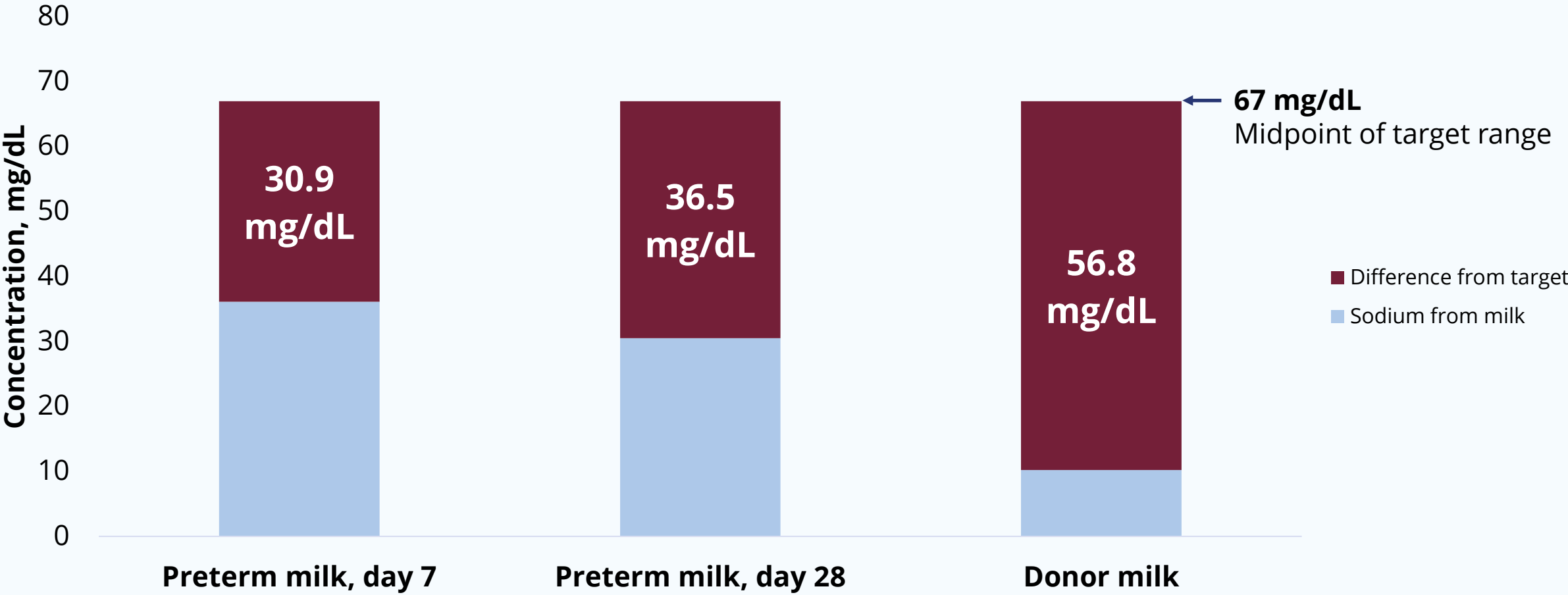
Differences in Protein Between Preterm Mother's Own Milk^[1] and Donor Milk^[2]



[1]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. [2]. Piemontese P et al. *BMC Pediatr.* 2019;19(1):58.



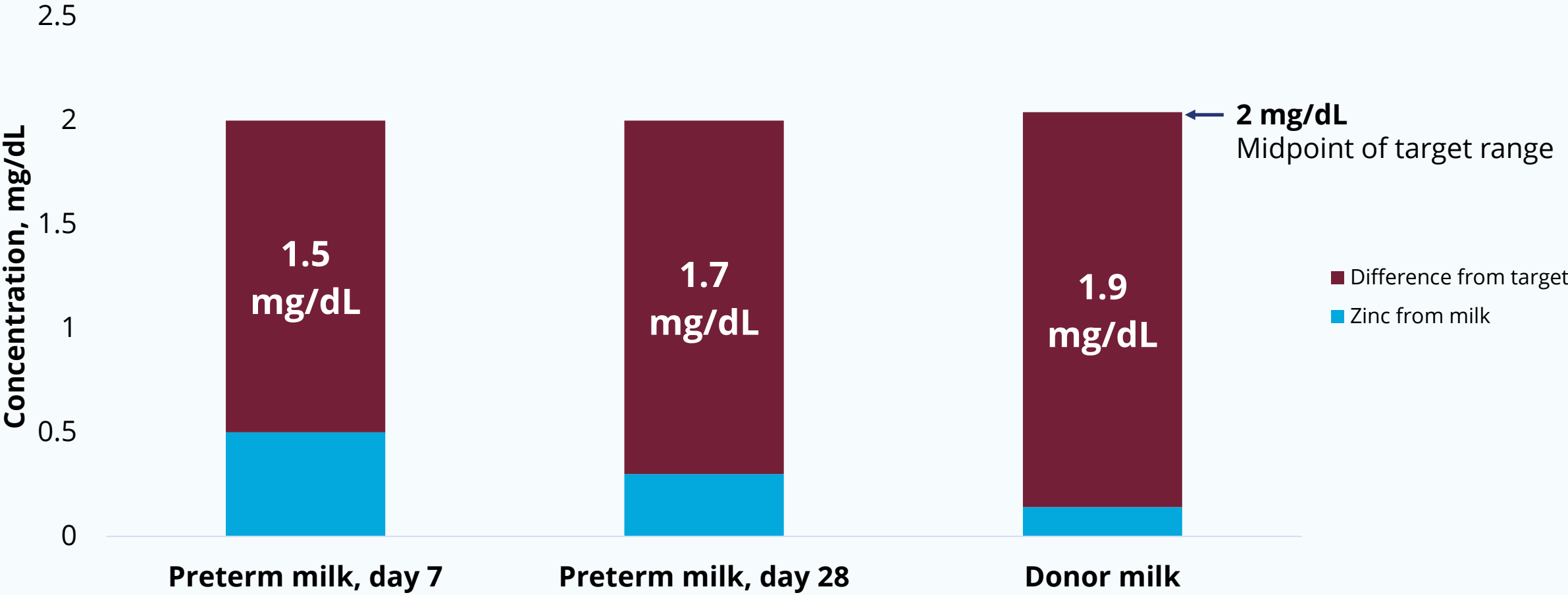
Differences in Sodium Between Preterm Mother's Own Milk^[1] and Donor Milk^[2]



[1]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. [2]. Perrin MT et al. *J Pediatr.* 2022;244:219-223.e1.



Differences in Zinc Between Preterm Mother's Own Milk ^[1] and Donor Milk ^[2]



[1]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. [2]. Young BE et al. *J Pediatr.* 2019;214:54-59.



★ Key Takeaway:

All Human Milk Requires Fortification to Meet Recommended Intakes, But Milk Variability Can Influence Fortification Needs

Nutrient	Preterm milk ^[1] (per 100 mL)	Term milk ^[3] (per 100 mL)	Recommended preterm intake ^[2] (per kg/day)
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.



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)



Best Practices for Human Milk Fortification in Preterm Infants



Volume of Unfortified Milk Needed to Meet Nutritional Requirements

Recommended preterm feeding volume:
135–200 mL/kg/day^[4]

Nutrient	Preterm milk ^[1] (per 100 mL)	Term milk ^[3] (per 100 mL)	Recommended preterm intake ^[2] (per kg/day)
Energy, kcal	66–70	65–70	110–130
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MOM, mother's own milk; DHM, donor human milk.



[1]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. [2]. Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed.* Karger; 2021. [3]. Kim SY, Yi DY. *Clin Exp Pediatr.* 2020;63(8):301-309. [4]. Arslanoglu S et al. *Front Pediatr.* 2019;7:76.

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				MOM	DHM
Energy, kcal	66–70	65–70	110–130		
Protein, g	1.6–2.2	0.9–1.2	3.5–4.5	220 mL	390 mL
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		
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Zinc, mg	0.3–0.5	0.1–0.3	2–3

Volume (per kg/d)

MOM DHM
220 mL 390 mL

240 mL 465 mL

MOM, mother's own milk; DHM, donor human milk.



[1]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. [2]. Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed.* Karger; 2021. [3]. Kim SY, Yi DY. *Clin Exp Pediatr.* 2020;63(8):301-309. [4]. Arslanoglu S et al. *Front Pediatr.* 2019;7:76.

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Fat, g	3.1–3.7	3.2–3.6	4.5–8.0		
Sodium, mg	29 –36	15 –26	69 –115	240 mL	465 mL
Potassium, mg	50–64	40–55	78–195		
Chloride, mg	58–70	40–50	107–178		
Calcium, mg	21 –24	20 –25	120 –220	570 mL	600 mL
Phosphorus, mg	13 –15	12 –16	70 –120	540 mL	580 mL
Iron, mg	0.09 ^[2]	0.03 –0.09	2 –3	>2000 mL	>6000 mL
Zinc, mg	0.3 –0.5	0.1 –0.3	2 –3	670 mL	2000 mL

MOM, mother's own milk; DHM, donor human milk.



[1]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728. [2]. Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed.* Karger; 2021. [3]. Kim SY, Yi DY. *Clin Exp Pediatr.* 2020;63(8):301-309. [4]. Arslanoglu S et al. *Front Pediatr.* 2019;7:76.

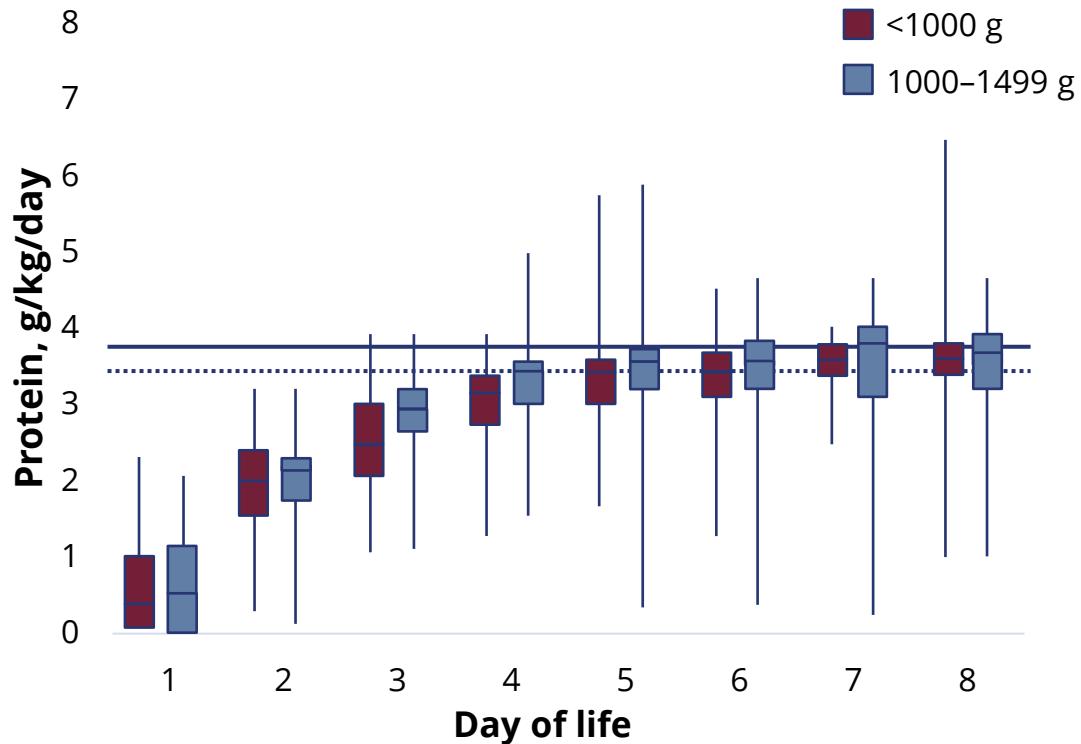
Goals of Human Milk Fortification

- 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
- Provide optimal levels of protein and micronutrients (calcium, phosphorous, magnesium, vitamins, and trace elements) with a limited volume

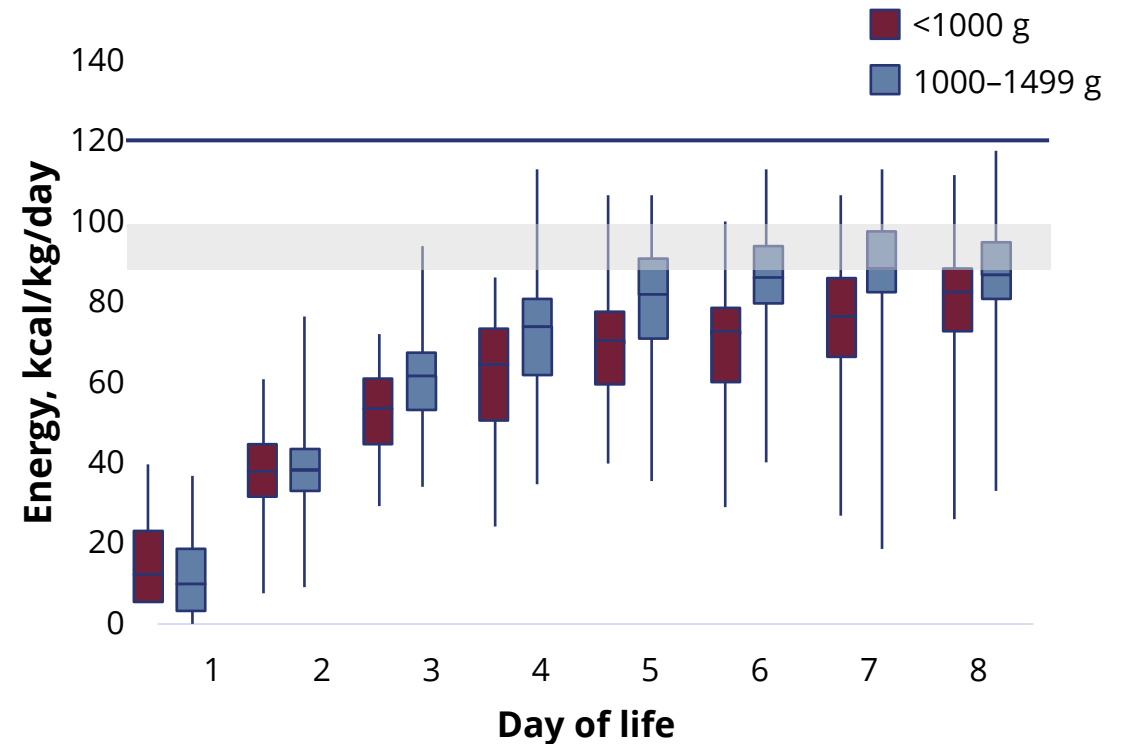


Nutritional Fortification in NICUs: Frequently Inadequate to Meet Target Intakes

First Week Protein Intake by Birth Weight Group



First Week Energy Intake by Birth Weight Group



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 level 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



Standard Fortification of Human Milk

Standard fortification practices have some limitations:

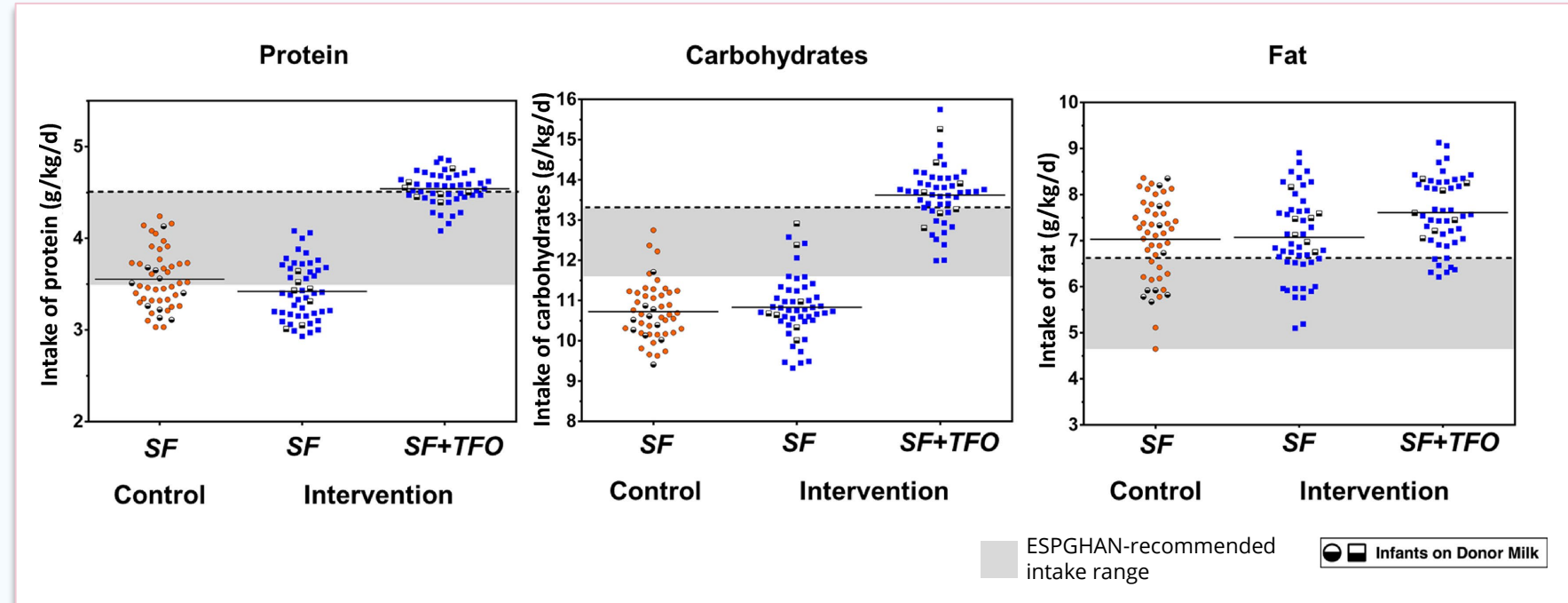
- No accounting for variability in human milk composition over time
- May not always meet nutritional requirements of preterm infants
- Often fail to meet protein requirements

Observational studies have shown that preterm infants fed human milk fortified using standard practices tend to have **slower growth** than those fed preterm formula ^{[1],[2]}



Standard vs Targeted Fortification: Effects on Nutritional Composition

Double-blind randomized controlled trial of infants <30 weeks, comparing standard vs targeted fortification (N = 103) [1]



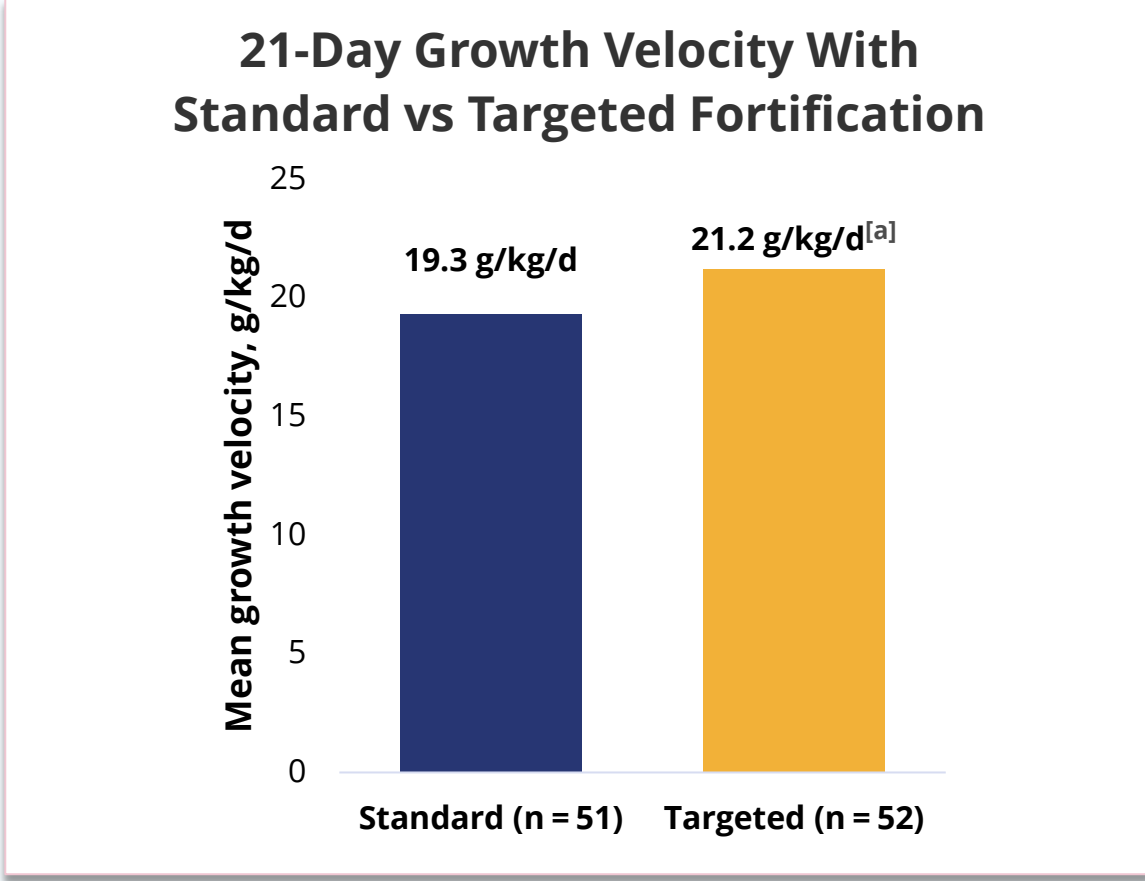
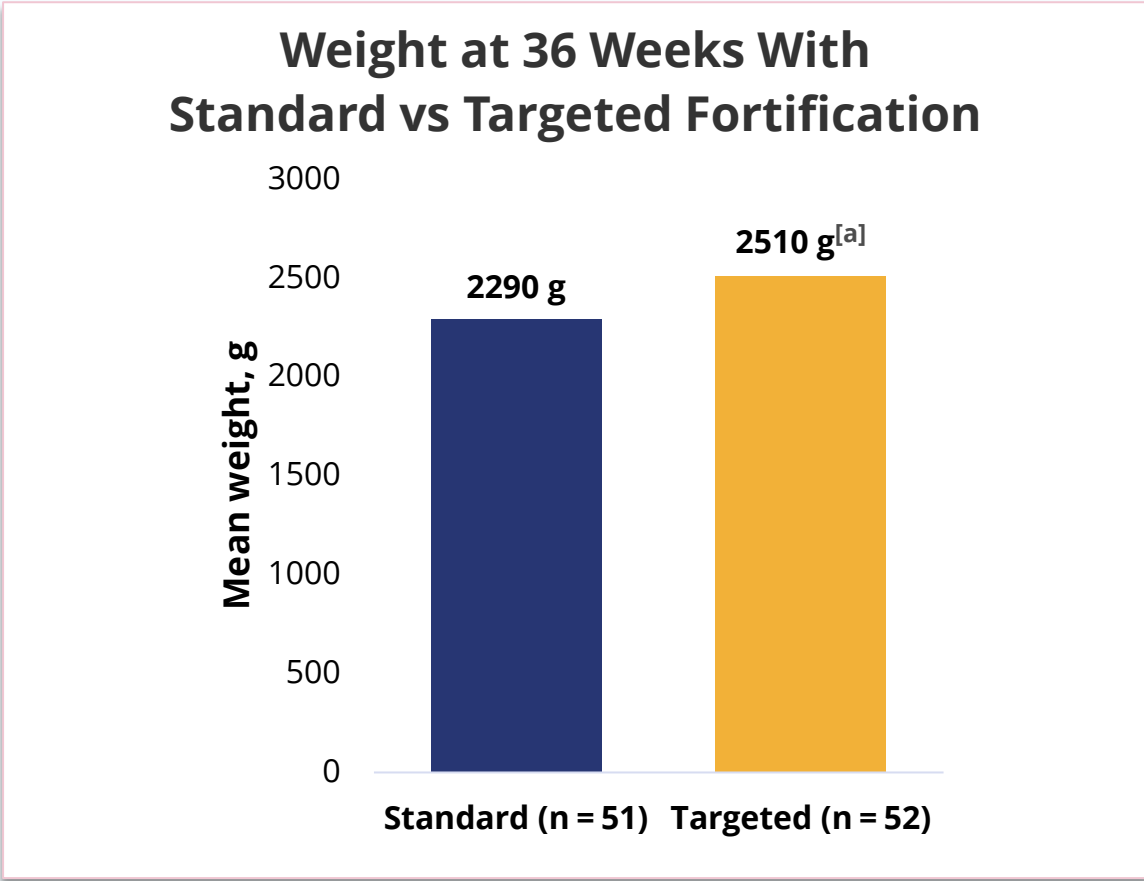
Note: In 2023, ESPGHAN updated the recommended intake range for protein to 3.5–4.0 g/kg/d [2]

SF, standard fortification; TFO, target fortification.

[1]. Rochow N et al. *Clin Nutr.* 2021;40(1):54-63. Figure 3 reprinted with permission from Elsevier. [2]. Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.



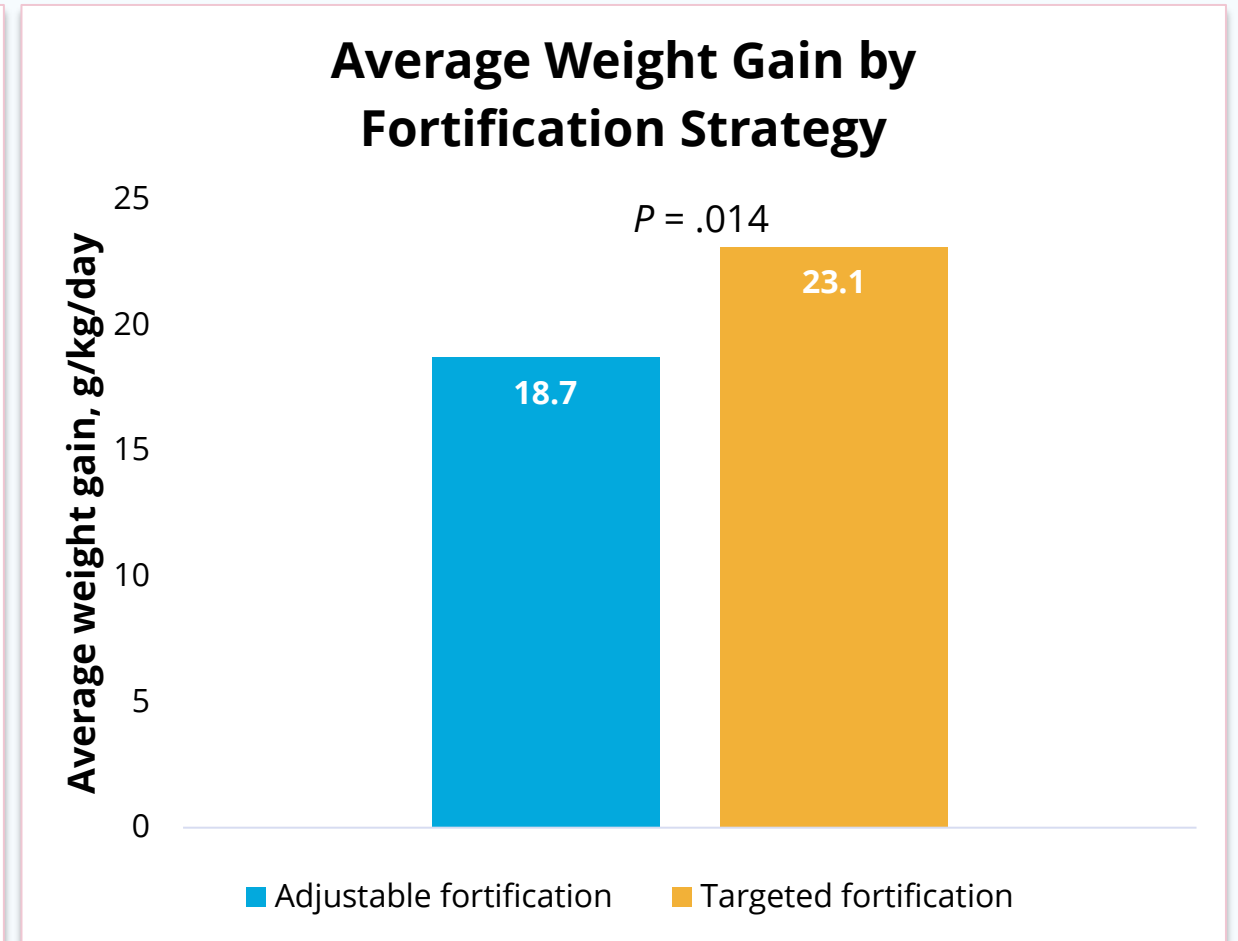
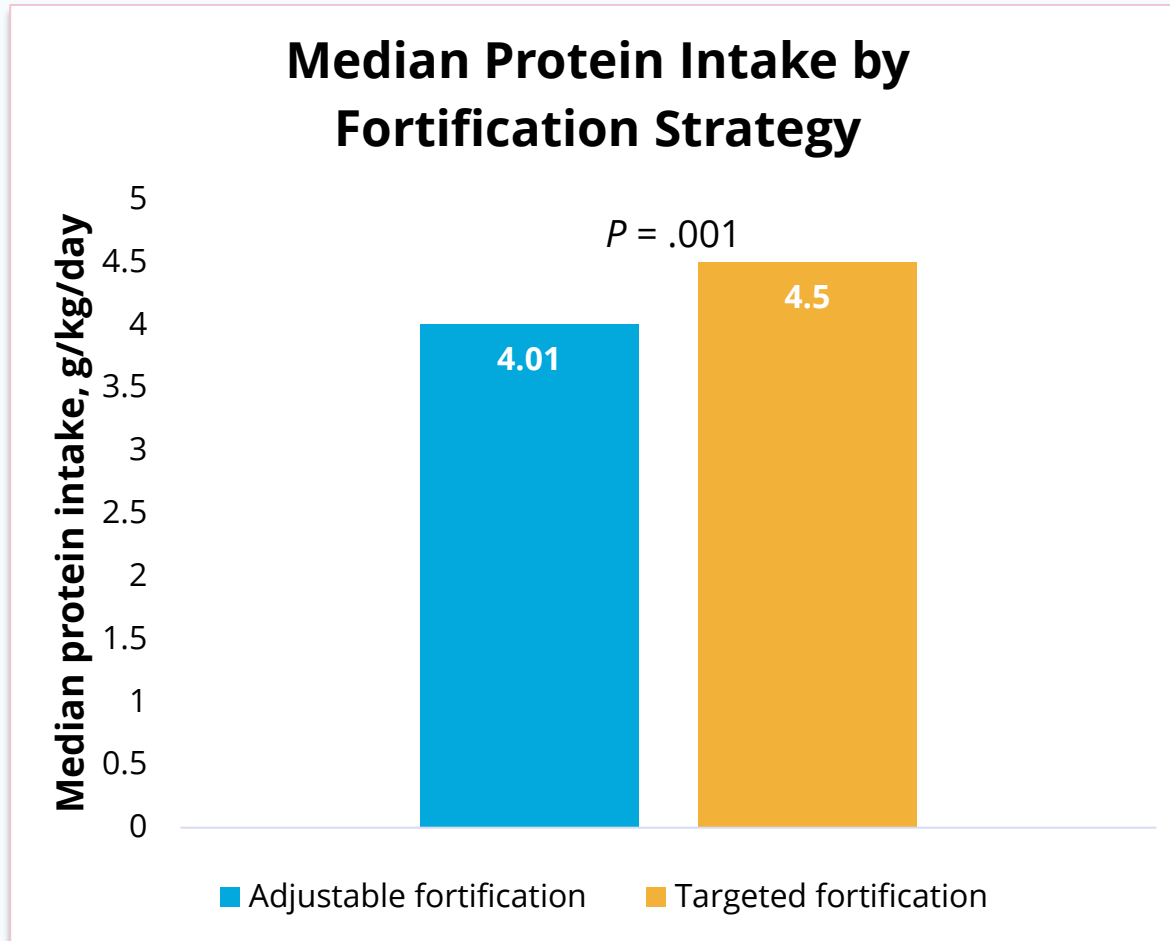
Standard vs Targeted Fortification: Effects on Growth



a. $P < .001$



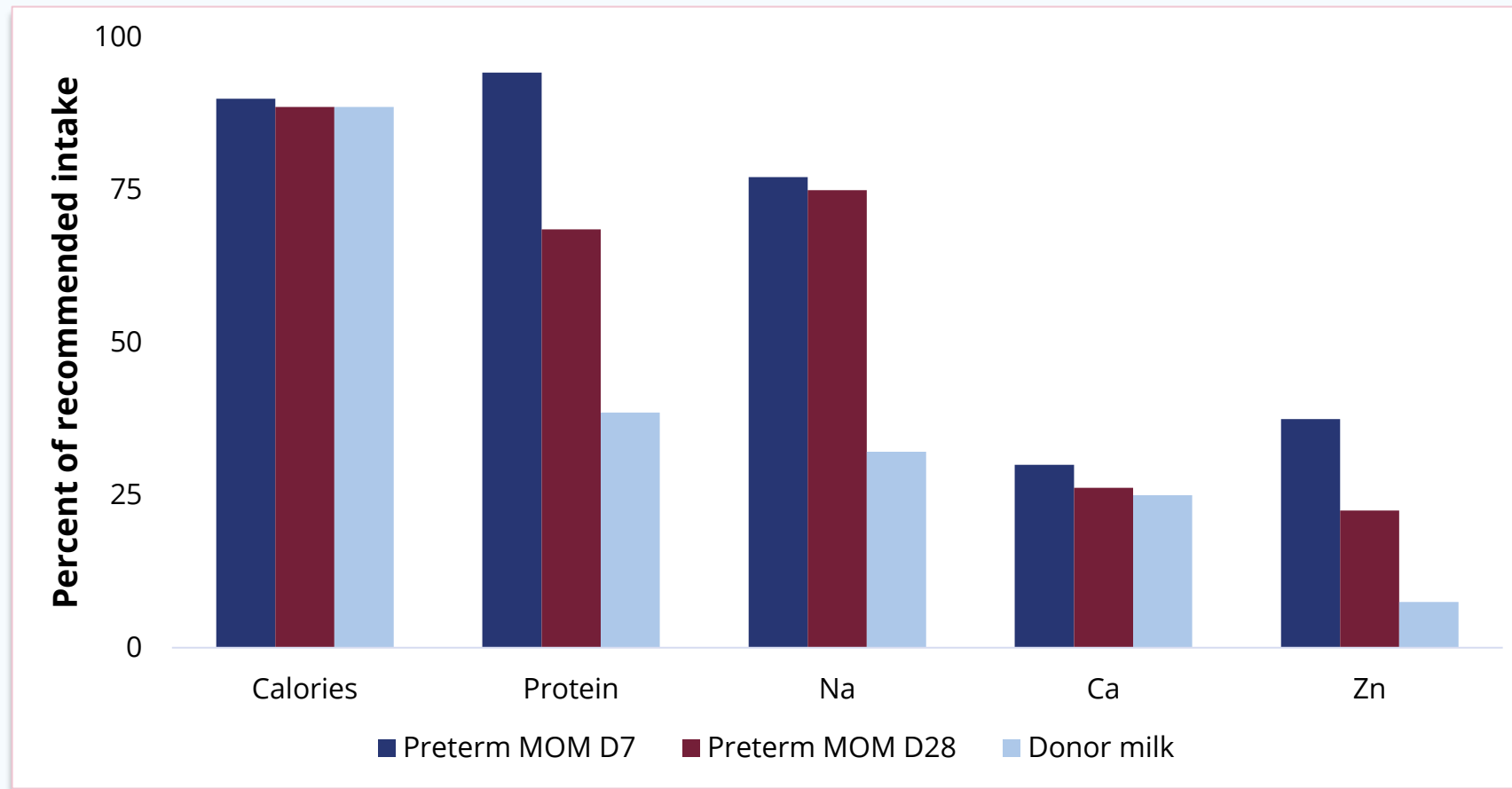
Adjustable vs Targeted Fortification [1]



Note: In 2023, ESPGHAN updated the recommended intake range for protein to 3.5–4.0 g/kg/d [2]



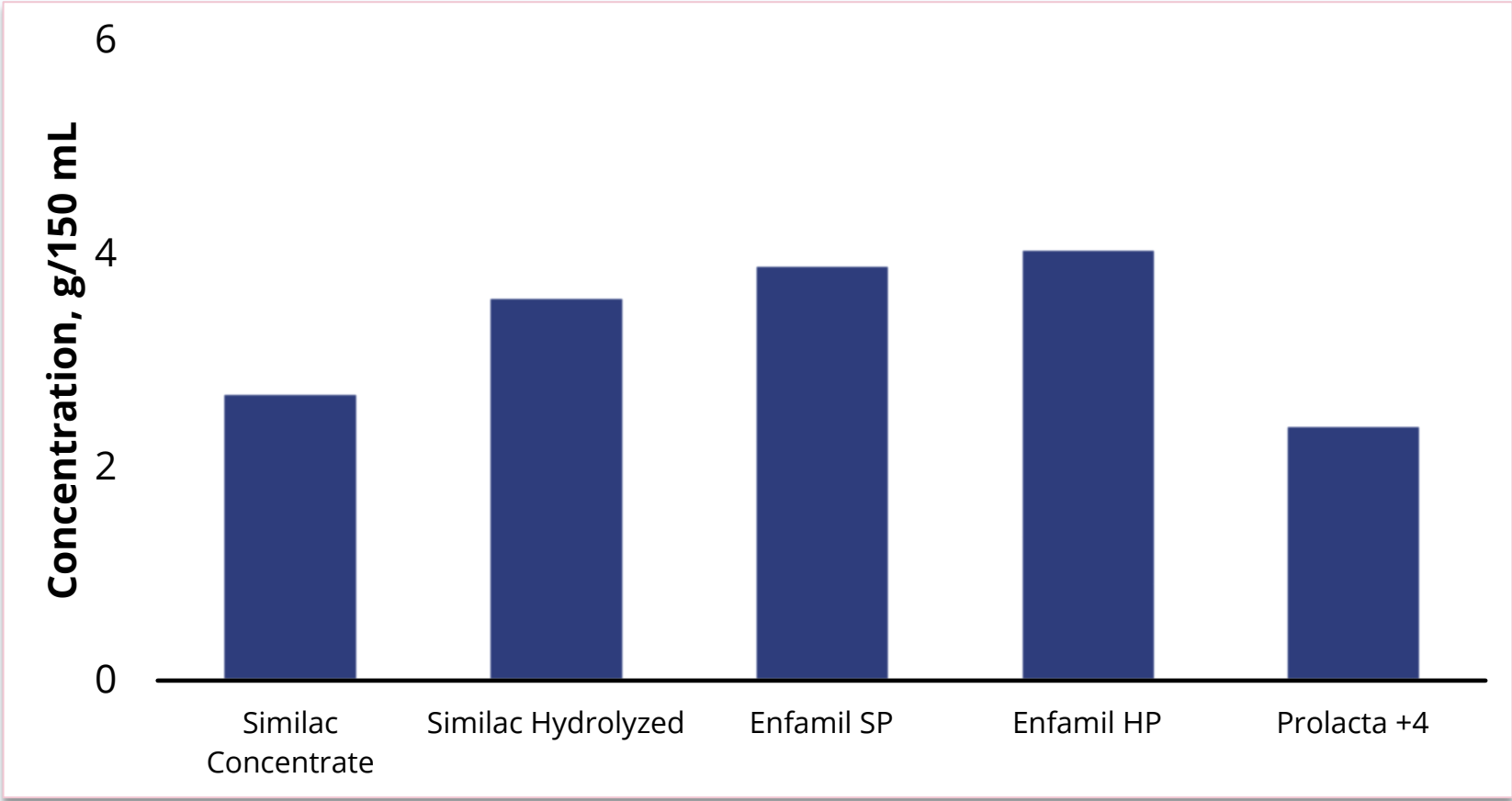
Reaching for the Goal



Lowest measured value to reach lowest recommended intake at 150 mL/kg/day



Protein in Fortified Donor Human Milk [a]

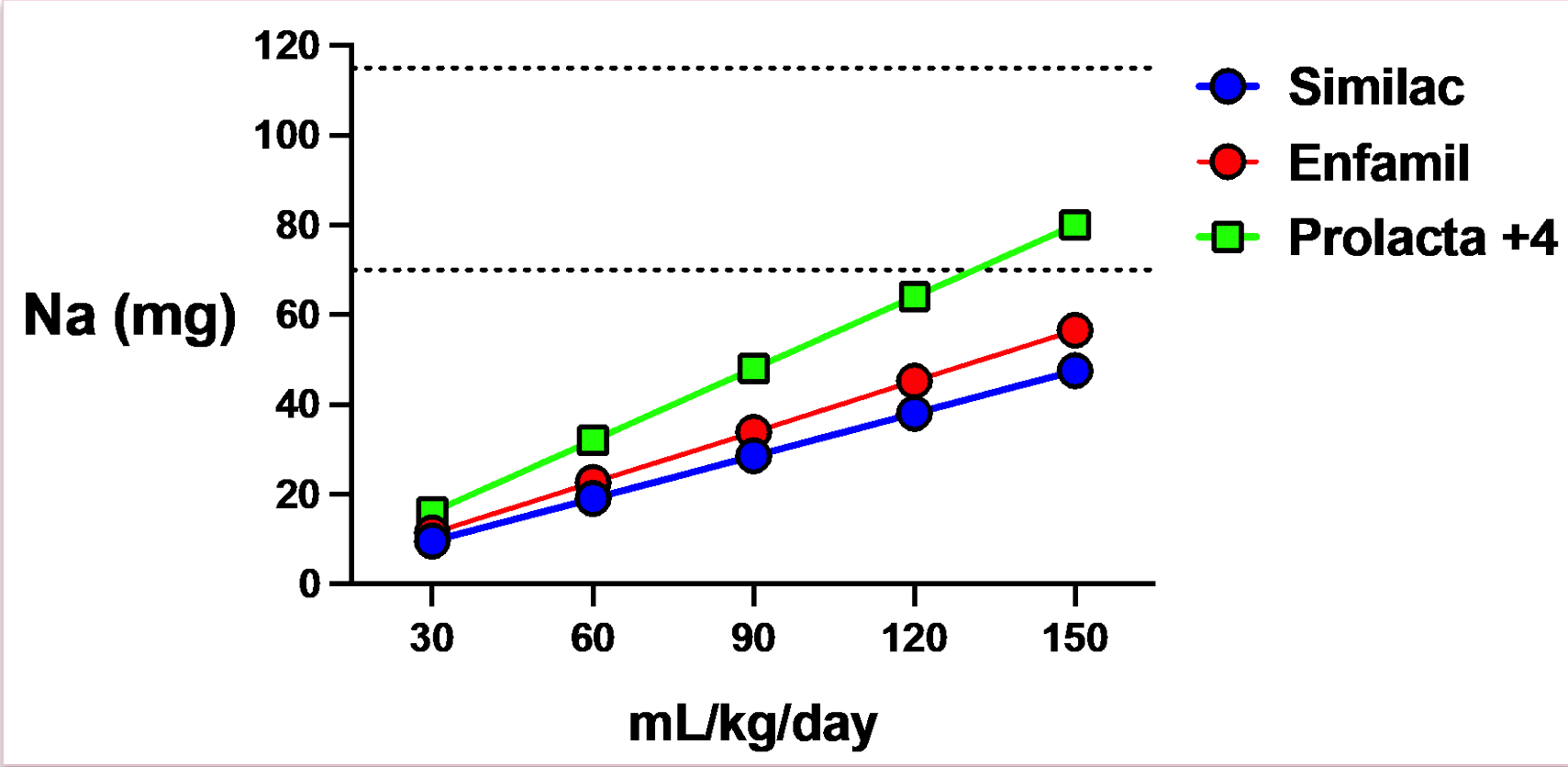


a. 24 kcal/oz

[1]. Maly J et al. *Arch Dis Child Fetal Neonatal Ed.* 2019;104(1):F50-F56. [2]. Gates A et al. *Nutr Clin Pract.* 2021;36(6):1163-1172. [3]. Gates A et al. *Am J Clin Nutr.* 2021;114(5):1719-1728.



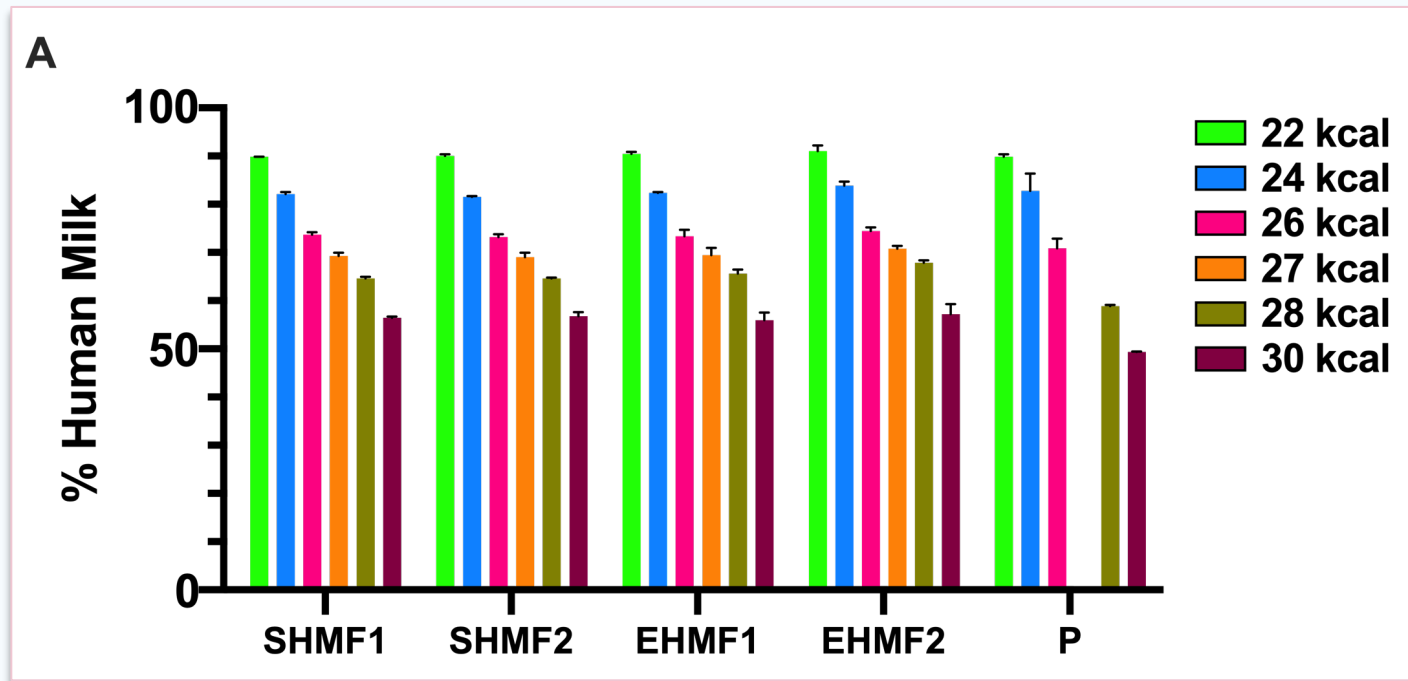
Sodium in Fortified Donor Human Milk [a]



a. 24 kcal/oz



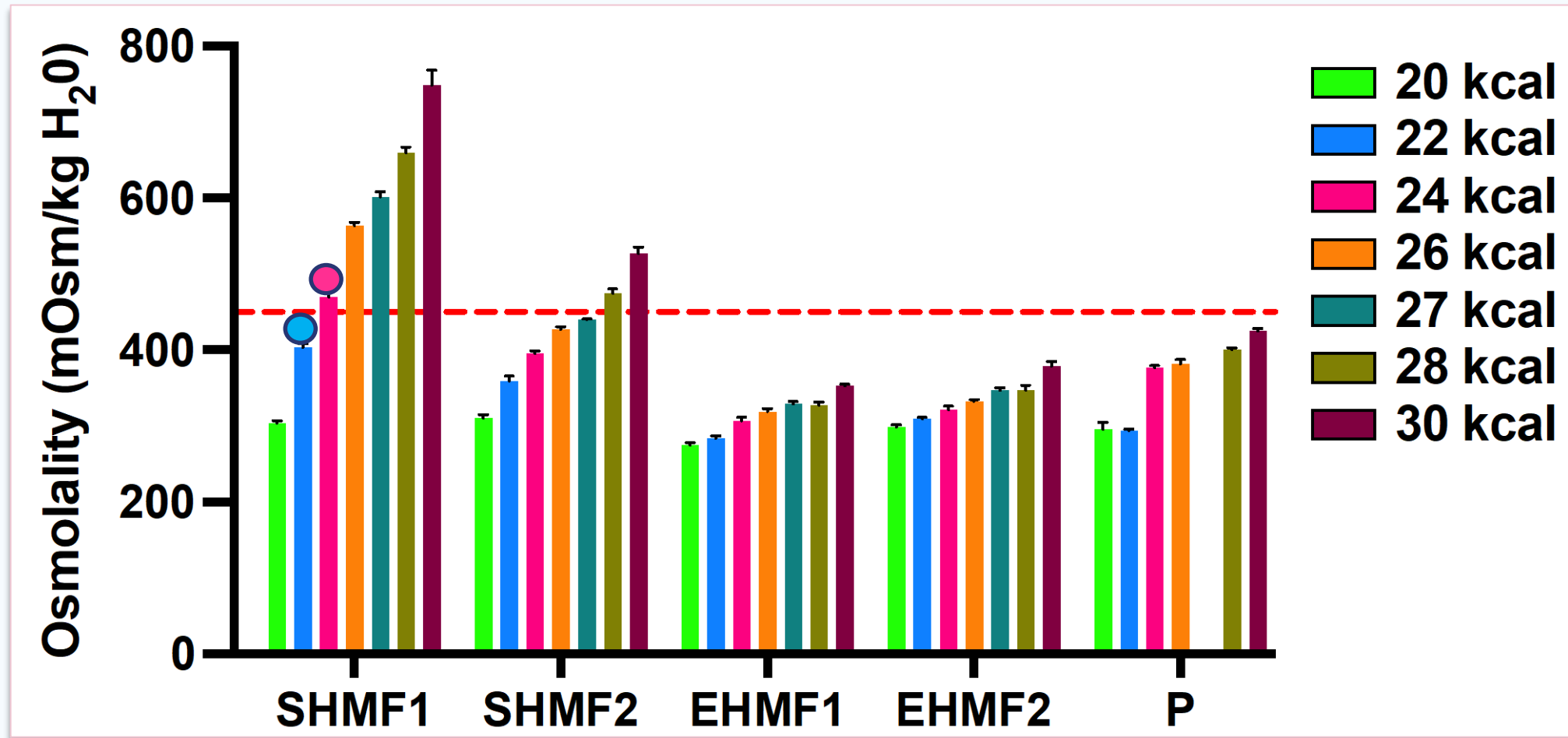
Other Considerations: Displacement



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; EHM3, Enfamil® Human Milk Fortifier Powder, P, Prolact CR; Prolact +4, +6, +8, +10 H²MF.



Other Considerations: Osmolality



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; EHM3, Enfamil® Human Milk Fortifier Powder, P, Prolact CR; Prolact +4, +6, +8, +10 H²MF.



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) provides more even distribution of nutrients**



Key Takeaways: Optimizing Human milk

Preterm mother's
own milk



Donor
human milk

- **Donor human milk is...**
 - Pooled and pasteurized
 - Variable in composition
 - Inadequate in protein, sodium, and zinc
- **Fortification considerations:^[a]**
 - Consider displacement if mother's own milk is primary
 - Osmolality may contribute to feeding intolerance (?)
 - High protein for 24 kcal/oz
 - Standard protein for early milk and if >24 kcal/oz
 - Powder formula meets caloric needs, but not calcium, sodium, protein, or zinc

a. For day 28 mother's own milk.

