Bridging the Protein Gap: Navigating Variable Milk Composition and Delivery in High-Risk Neonates and Infants

Saturday, April 25, 2026
6:00–8:00 AM

Presented by

Sarah Fleet, MD, PNS
Ting Ting Fu, MD, MS

Omni Boston Hotel at the Seaport
Contemporary (Level 3)
450 Summer Street
Boston, MA

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Symposium Overview

A data-driven discussion about:

- The biological variability of protein in human milk
- Gaps between protein targets and actual delivery in critical care
- Strategies to provide adequate protein to high-risk neonates and infants
- Balancing higher protein targets with safety

Presenters

Sarah Fleet, MD, PNS
Program Director, Advanced Nutrition Training Program
Pediatric Gastroenterology, Hepatology & Nutrition
Boston Children's Hospital
Assistant Professor of Pediatrics
Harvard Medical School
Boston, MA

Ting Ting Fu, MD, MS
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Bridging the Protein Gap: Navigating Variable Milk Composition and Delivery in High-Risk Neonates and Infants

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Assistant Professor of Pediatrics
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Dr. Sarah Fleet is a Pediatric Gastroenterologist and Physician Nutrition Specialist, specializing in pediatric feeding disorders and inpatient nutrition support at Boston Children's Hospital. Dr. Fleet obtained her MD at the University of Connecticut, and completed her residency and fellowship at Columbia University Medical Center in New York. She then pursued her board certification from the National Board of Physician Nutrition Specialists. She is the Program Director for the Advanced Nutrition Training Program at Boston Children's Hospital, and Division Director of Medical Student Education. Dr. Fleet is also an Assistant Professor of Pediatrics at Harvard Medical School where she teaches in all phases of the curriculum and holds several leadership roles including pediatrics clerkship core faculty, course co-director for Integrated Human Pathophysiology 1, the required GI physiology course for first year students, and course co-director for several advanced nutrition courses for 3rd and 4th year students. She currently serves as the Past President of the International Association of Pediatric Feeding and Swallowing and is working towards her Masters of Medical Science in Medical Education at Harvard Medical School. With her collaborators, she recently developed and launched an online simulator for pediatric parenteral nutrition. Her current research centers around improving pre-clerkship education in medical school through both faculty development efforts and curriculum design.

Ting Ting Fu, MD
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Ting Ting Fu is an Associate Professor of Pediatrics at Cincinnati Children's and University of Cincinnati. She studied biology at MIT and obtained her medical degree from the University of Kentucky. She completed her pediatric residency at Maine Medical Center and neonatal-perinatal medicine fellowship at Cincinnati Children's. Currently she is Co-Director of the Infant Nutrition Research & Clinical Hub. She oversees nutrition management and interventions across the region's six Level III/IV NICUs and leads the CCHMC Human Milk Research Biorepository. As an academic neonatologist, she is dedicated to improving our understanding of the nutritional needs and growth of preterm infants. Her current research efforts focus on human milk composition and strategies to optimize human milk feedings to modulate growth and improve the utilization of donor milk in the preterm population.

Bridging the Protein Gap: Navigating Variable Milk Composition and Delivery in High-Risk Neonates and Infants

Target Audience

This activity is developed to support pediatricians, pediatric sub-specialists, pediatric nurses, dietitians, neonatologists, NICU RNs and other healthcare providers who treat infants and children.

Learning Objectives

By participating in this education, participants will better:

- Analyze the latest clinical guidelines for fortifying human milk to meet the heightened metabolic demands of the medically complex neonatal and pediatric populations.
- Identify the impact of cumulative protein deficits on clinical and growth outcomes in both preterm infants and term infants with medical complexity.
- Describe the differences in nutrient composition and bioactive components in Mother's Own Mik vs. Donor Human Milk.

Faculty

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Commission on Dietetic Registration
the credentialing agency for the Academy of Nutrition and Dietetics

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Faculty
Ting Ting Fu, MD
Speakers Bureau: Medela

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Sarah Fleet, MD

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Jessica Martin, PhD (Medical Writer)

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Faculty Presenters

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Sarah Fleet, MD, PNS

No relationships to disclose.

Ting Ting, Fu, MD, MS

Speakers Bureau	Medela

Faculty have documented that this presentation will involve discussion of unapproved or off-label, experimental, or investigational use. For complete disclosure information, please see our course syllabus.

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Learning Objectives

By participating in this education, you will better:

- Describe the differences in nutrient composition and bioactive components in mother's own milk vs donor human milk
- Identify the impact of cumulative protein deficits on clinical and growth outcomes in both preterm infants and term infants with medical complexity
- Analyze the latest clinical guidelines for fortifying human milk to meet the heightened metabolic demands of the medically complex neonatal and pediatric populations

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

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Introduction: Why the Emphasis on Protein?

Ting Ting Fu, MD, MS

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Amino Acids and Protein During Fetal Development

Amino acids serve critical functions during fetal development.

- Energy
- Growth and organ development
- Cell structure and maturation
- Cellular remodeling
- Immune system development

Manta-Vogli PD et al. *J Matern Fetal Neonatal Med*. 2020;33(2):334-340.

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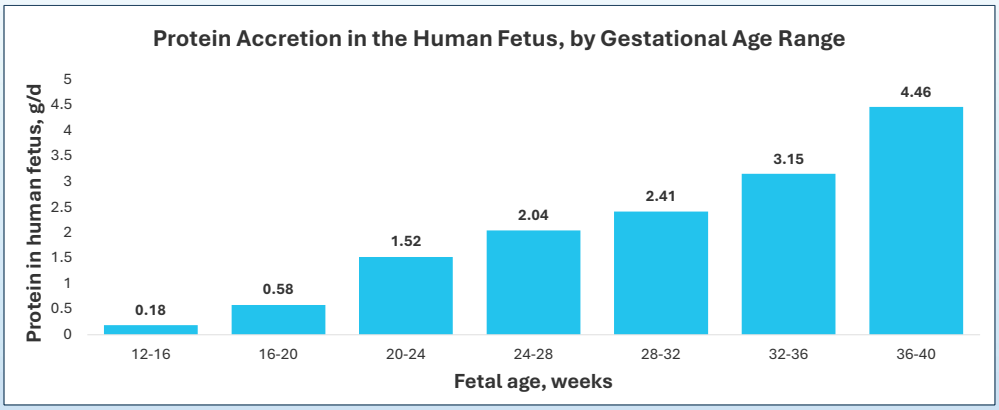
Protein Accretion and Body Composition by Gestational Age in the Human Fetus

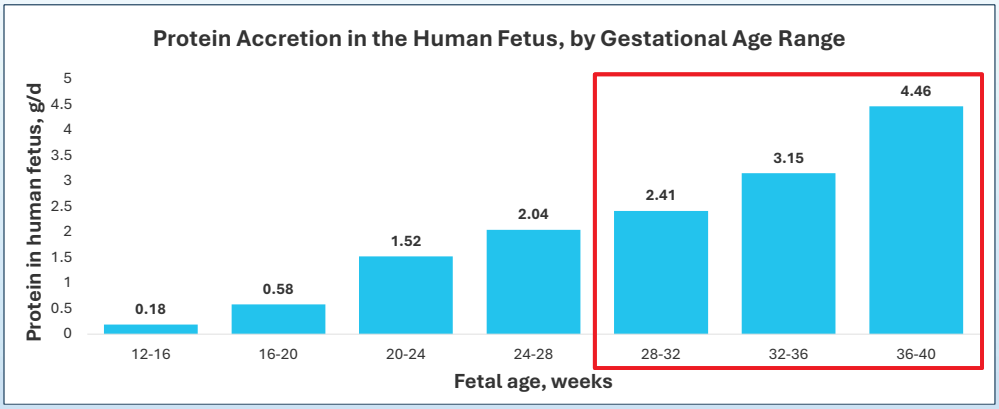


The placenta supplies high levels of amino acids to the fetus to meet the energy and nutritional requirements for rapid fetal growth, with most protein deposition occurring in the third trimester.

Davidson Brown L et al. In: Polin RA et al (eds). *Fetal and Neonatal Physiology, fifth edition*. 2017; Elsevier.

7

Protein Accretion and Body Composition by Gestational Age in the Human Fetus



Preterm birth abruptly interrupts critical periods of in utero protein delivery.

Davidson Brown L et al. In: Polin RA et al (eds). *Fetal and Neonatal Physiology, fifth edition*. 2017; Elsevier.

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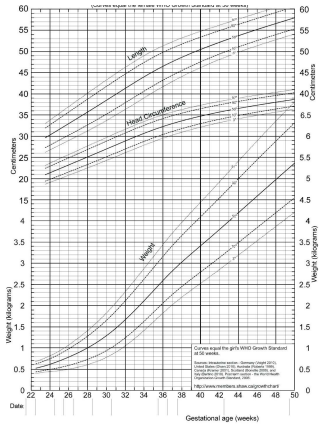
Goals for Preterm Infant Growth

2022 ESPGHAN Growth Targets for Preterm Infants[1]:

- Regain birth weight by days 7 to 10 after initial loss of up to 10% at days 3 to 4
- After days 7 to 10, achieve **growth along a target fetal growth percentile**, with gradual transition to corresponding percentile on postnatal growth references
- Promote catch-up growth in infants with growth faltering while avoiding very rapid catch-up growth

Adequate protein intake is key for meeting growth targets.[1]

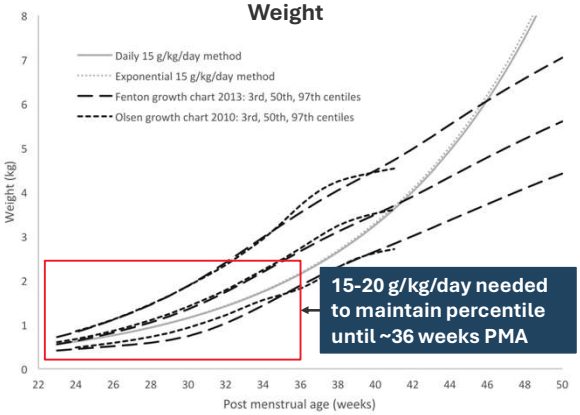
Fenton Fetal-Infant Growth Chart for Preterm Girls[2]



1. Embleton ND et al. *J Pediatr Gastroenterol Nutr*. 2023;76(2):248-268. **2.** Fenton TR, Kim JH. *BMC Pediatr*. 2013;13:59.

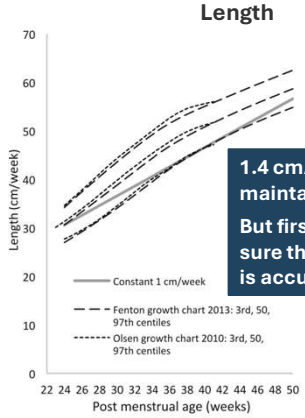
Actual Target Velocities for Preterm Infants

Weight



15-20 g/kg/day needed to maintain percentile until ~36 weeks PMA

Length



1.4 cm/week needed to maintain velocity

But first need to make sure the measurement is accurate!

Fenton TR et al. *J Pediatr*. 2018;196:77-83.

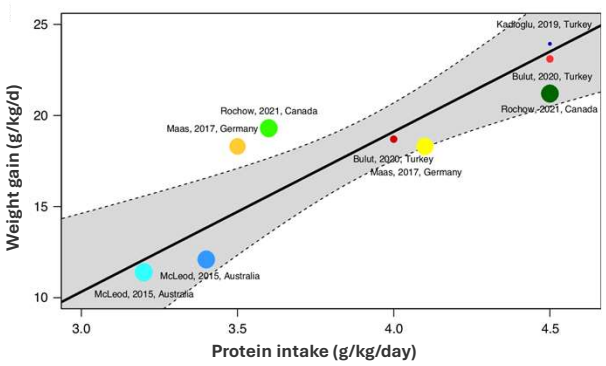
Enteral Protein Intake and Growth in Preterm Infants

Systematic Review and Meta-Analysis

- 10 RCTs comparing higher vs lower enteral protein intake
- Included 646 preterm infants born at <32 weeks GA
- Analyses adjusted for concurrent energy intake

↑8.8 g/kg/day change in weight gain for each g/kg/day increase in protein intake (*P*≤.001)

Association Between Protein Intake and Weight Gain



Sanchez-Holgado M et al. *Pediatr Res*. 2025;98(5):1696-1710.

Protein Requirements in Infancy and Childhood

Protein requirements are highest for VLBW and preterm infants and decline with older age.[1]

Recommendations for Protein Intake[1-3]

VLBW/Preterm Infant	Term Infant	Older Infant	Toddler	Adolescent
3.5-4.0 g/kg/day*	**2.0-2.5 g/kg/day**	**1.5-2.0 g/kg/day**	**1.0-1.5 g/kg/day**	**0.8-1.5 g/kg/day**

*Up to 4.5 g/kg/day in infants not meeting growth targets

Note: During periods of critical illness and catch-up growth, protein requirements may be up to 20% to 50% higher.[1]

1. Herrera OR, Helms RA. In: Corkins MR et al (eds). *ASPEN Pediatric Nutrition Support Core Curriculum, 3rd Edition.* American Society for Parenteral Nutrition (ASPEN); 2025. **2.** Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed.* Karger; 2021. **3.** Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.

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*Up to 4.5 g/kg/day in infants not meeting growth targets

Recommendations for Critically Ill Children

Toddler	Adolescent
2.0-3.0 g/kg/day	**1.5-2.0** g/kg/day

1. Herrera OR, Helms RA. In: Corkins MR et al (eds). *ASPEN Pediatric Nutrition Support Core Curriculum, 3rd Edition.* American Society for Parenteral Nutrition (ASPEN);2025. **2.** Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed.* Karger; 2021. **3.** Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.

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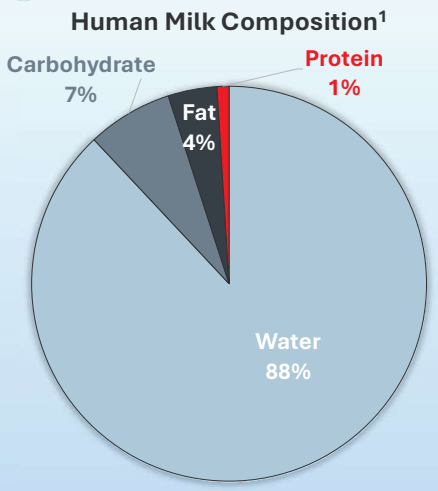
Human Milk Composition and the Neonatal Protein Gap



Think of "g/dL" as %

Milk source	Protein concentration	Protein intake at recommended preterm feeding volumes	
		140 mL/kg/day[4]	200 mL/kg/day[4]
Preterm milk (MOM)	1.6-2.2 g/dL[2]	~2.3 g/kg/day	~3.2 g/kg/day
Term milk (DHM)	0.9-1.2 g/dL[3]	~1.3 g/kg/day	~1.8 g/kg/day

Unfortified human milk is associated with a **protein gap of 0.3-3.3 g/kg/day** when using the recommended protein intake of **3.5-4.5 g/kg/day**.

1. Perrin MT et al. *Adv Nutr*. 2020;11(4):960-970. **2.** Gates A et al. *Am J Clin Nutr*. 2021;114(5):1719-1728. **3.** Kim SY, Yi DY. *Clin Exp Pediatr*. 2020;63(8):301-309. **4.** Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed*. Karger; 2021.

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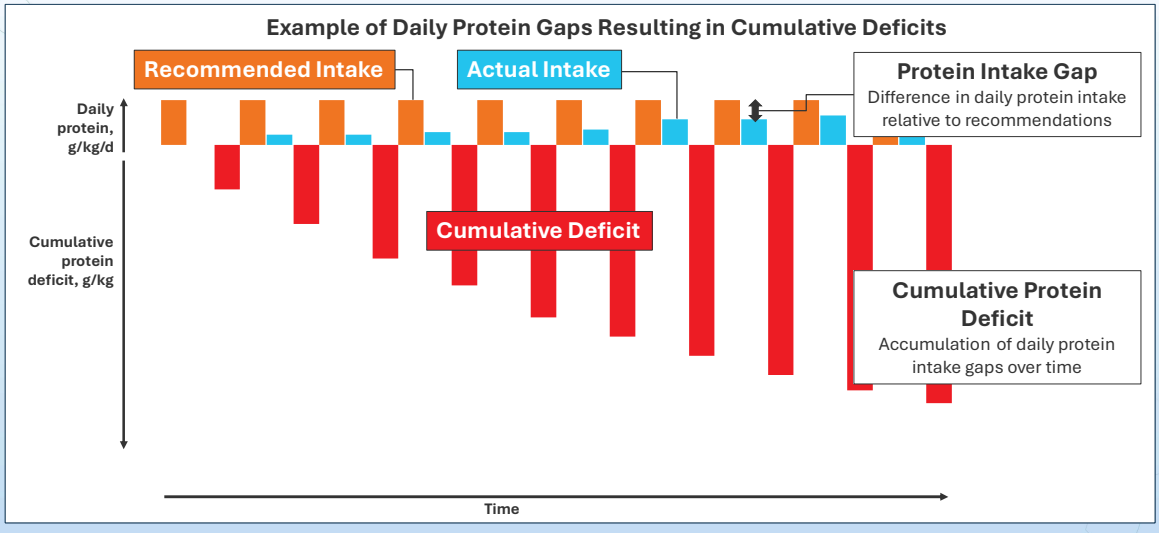
Daily Gaps in Protein Intake Can Yield Cumulative Deficits Over Time



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NICU: Human Milk Composition and the Protein Gap

Ting Ting Fu, MD, MS

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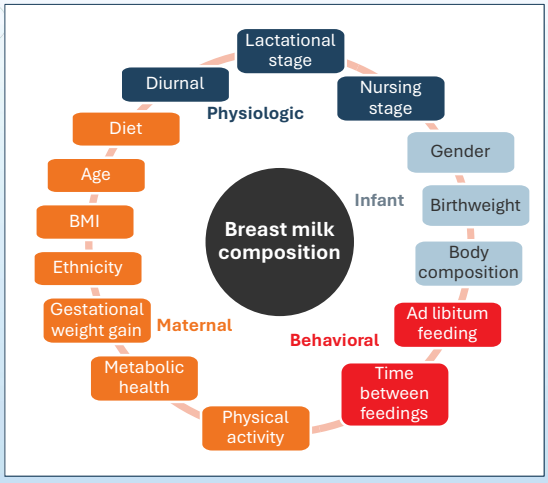
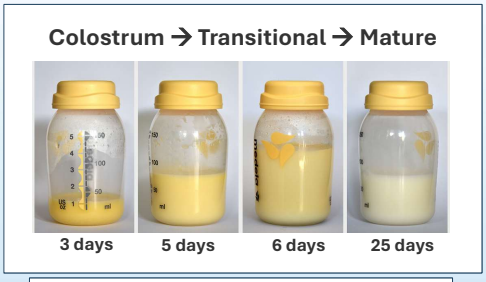
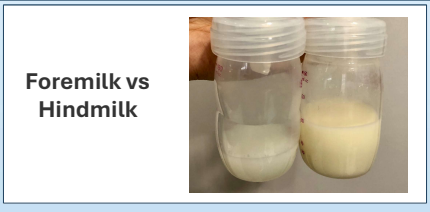
Not All Human Milk Is Equal (or 20 kcal/oz)







Fields DA et al. *Obesity*. 2016;24(6):1213-1221.

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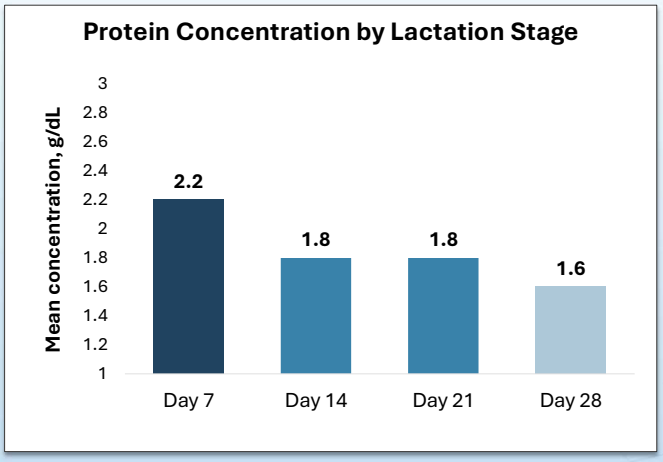
Preterm Human Milk Composition: Declining Protein Concentration Later in Lactation

Prospective, Longitudinal Cohort Study

- Women who delivered ≤33 weeks' gestation (N = 38)
  - Average GA of 28.2 weeks, with 42% delivering <28 weeks
- Pooled 24-hour milk samples
- Assessed macro- and micronutrient composition



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

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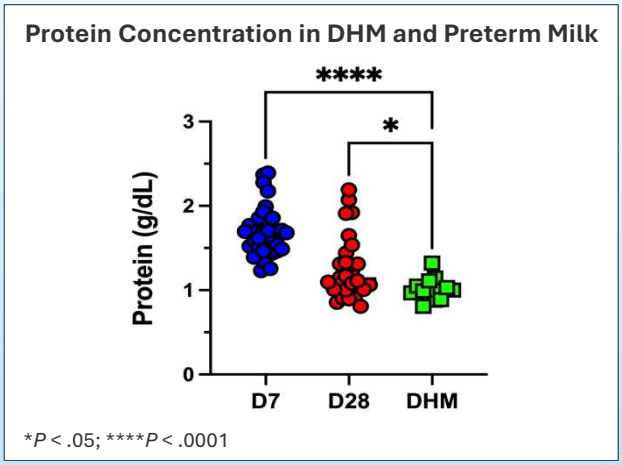
Consistently Lower Protein Levels in DHM

Observational Study

- Analyzed DHM samples (n = 15) from 7 sources
- Compared nutrient profiles of DHM to those of:
  - Early preterm human milk (day 7; n = 36)
  - Mature preterm human milk (day 28; n = 28)



Gates A et al. *J Nutr.* 2023;153(9):2622-2630.

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Nutrient Variability in DHM: Potential Sources

In a systematic review and meta-analysis, the macronutrient composition of DHM varied by ≥2-fold

Potential Sources of DHM Variability

Donors

- Gestation stage (term vs preterm)
- Lactation stage
- Maternal diet
- Collection method
- Collection time

Milk Banks

- Pasteurization processes
- Use of pre-pooling analysis
- Mixing practices

Note: Pooling DHM can reduce variability and is an important consideration for milk banks.

Perrin MT et al. *Adv Nutr.* 2020;11(4):960-970.

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Key Characteristics of DHM Impacting Composition

Heat-pasteurized to destroy microbes, which can also reduce activity and levels of bioactive components

Primarily expressed by healthy mothers of term infants at later lactation stages

Pooled from multiple mothers to reduce donor-to-donor and lot-to-lot variability

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.

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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 micronutrient composition [1]

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

⚠ **Human Milk Banking Association of North America (HMBANA) uses Holder pasteurization (62.5 °C for 30 minutes), but other sources may use different pasteurization methods.[4]**

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.** HMBANA. Standards for Donor Human Milk Banking. January 2024. https://www.hmbana.org/file_download/inline/78058d21-b0c4-48e7-93ca-6f64445a91f7

Measuring Protein Levels in Human Milk

Gross protein is the total nitrogen content and includes[1,2]:

- **True protein** (nitrogen in amino acids), the metabolizable content providing necessary nutrients for growth and maintenance
- **Non-protein nitrogen (NPN)** (nitrogen in compounds such as urea and ammonia)

Total Protein = True Protein + NPN

(NPN estimated to be ~20-30% of N in human milk)[2]

1. Fenton TR, McLeod G. In: *Human Milk*. Elsevier; 2021:175-190. **2.** Stansfield BK et al. *Nutr Clin Pract.* 2025;40(1):217-226.

Measuring Protein Levels in Human Milk

Total Protein
(total nitrogen content)

=

True Protein
- Nitrogen from amino acids
- Provides nutrients for growth and maintenance

+

Non-Protein Nitrogen (NPN)
- Non-nutritional nitrogen compounds (eg, urea, ammonia)
- Estimated to be ~20%-30% of nitrogen in human milk)[2]

1. Fenton TR, McLeod G. In: *Human Milk*. Elsevier; 2021:175-190. **2.** Stansfield BK et al. *Nutr Clin Pract.* 2025;40(1):217-226.

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DHM Labels: What's On Them & What's Not?

PASTEURIZED HUMAN MILK
Local Milk Bank, Inc.
Batch: 012345-01
Milk type: Term
Exp: JAN 01, 2027
Volume: 100 mL
Cal/oz: 20 Prot: 1.0 g/dL

May indicate milk type (eg, term, preterm, targeted)

Doesn't distinguish total vs true protein

Nutritional information dependent on milk bank having a human milk analyzer (HMA)

Not included on labels:
- Information on carbohydrate or fat levels (in most cases, may be included on the packing sheet)
- Micronutrients
- Bioactive components
- Pooling method or number of donors pooled

ICCBBA. Labeling of human milk banking products. November 2025. Accessed April 8, 2026. https://iccbba.org/wp-content/uploads/2025/08/83d6e1_5b26ceac0f2242ae9de14197499aee62.pdf.

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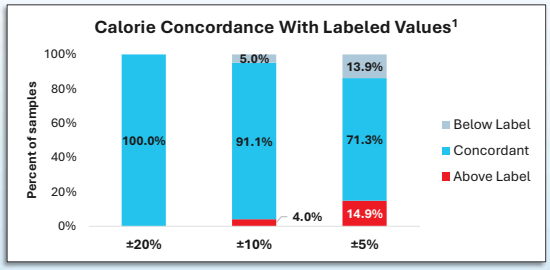
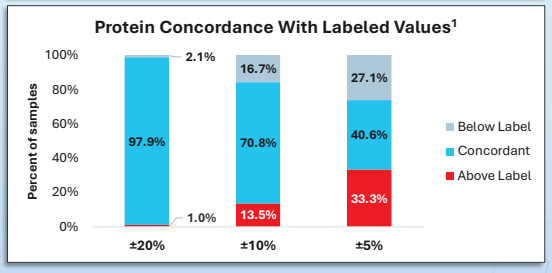
Accuracy of Donor Milk Labels[1-3]

- Secondary analysis of **101 donor milk samples** from an ongoing prospective cohort study[3]
  - Rigorous sample collection with mid-infrared HMA analysis in triplicate
- Calorie and protein levels **not** statistically different from labeled values
- Intra-batch variability (within the same pool) can occur due to mixing and bottling practices if not using automated processes





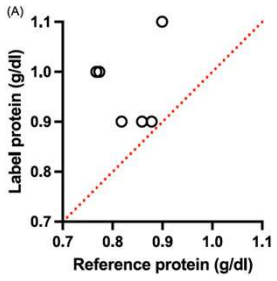
1. Fu TT, Schroder PE, Poindexter BB. *Nutrients*. 2019;11(8):1884. **2.** Jo DB et al. *J Perinatol*. 2020;40(4):666-671. **3.** King C, Fu TT. Poster presented at: International Donor Milk Conference; April 2024; Austin, TX

Overestimation of Protein in DHM

Observational Study

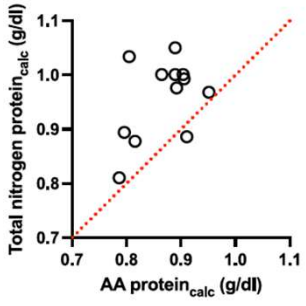
- Triplicate measures of total nitrogen, NPN, and amino acid profiles from DHM samples
- Values compared against labeled and calculated protein content (using assumption of 20% NPN)

Overestimation of Reported Protein Content on DHM Labels (n = 6)



0.15 g/dL median overreporting of protein content on DHM labels

Overestimation of Calculated Total Nitrogen in DHM (n = 15)



33% mean NPN content in DHM

Stansfield BK et al. *Nutr Clin Pract*. 2025;40(1):217-226.

Key Takeaways: the Protein Gap

- Human milk alone does **not** meet recommended protein targets for preterm infants
- Human milk composition is variable, with differences in protein levels by preterm vs DHM and other factors
- Nutritional **interventions are needed to meet protein requirements** to optimize growth and development in preterm infants

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NICU: Bridging the Gap With Fortification

Ting Ting Fu, MD, MS

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Methods of Human Milk Fortification

Standard most common & easiest	Adjustable more cost efficient & less labor intensive than targeted	Targeted most accurate & most costly
• Fixed amount of fortifier added to fixed milk volume • Based on manufacturer's instructions (typically assumes starting protein and energy content of 1.5 g/dL and 20 kcal/oz, respectively)	• Protein concentration adjusted based on serial blood urea nitrogen (BUN) measurements • Additional protein supplementation added if level is <10 mg/dL	• Macronutrient concentrations in human milk analyzed with an HMA • Fortification procedures based on analysis

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

31

Standard Fortification Using Traditional Assumptions May Not Be Sufficient

Standard[1]
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

- Traditional assumptions regarding human milk composition have recently been challenged[1,2]
- Only 11% of human milk samples fortified using standard methods reached 4 g/kg/day protein[2]
  - **No** samples reached 4.5 g/kg/day protein with standard fortification

1. Bergner EM et al. *Clin Perinatol.* 2022;49(2):447-460. **2.** Fu TT et al. *Pediatr Res.* Published online ahead of print January 15, 2026. doi:10.1038/s41390-025-04754-y

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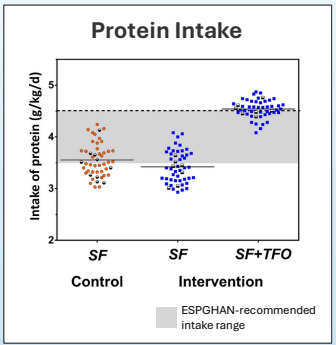
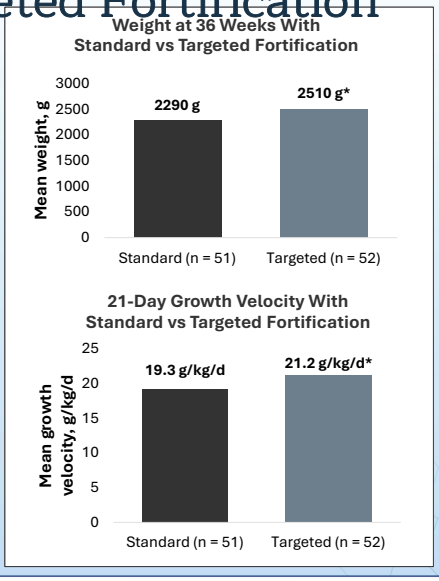
Comparison of Standard and Targeted Fortification

Double-Blind Randomized Controlled Trial

- Enrolled infants <30 weeks GA
- Compared standard fortification (n = 51) with standard fortification plus targeted fortification using modular protein, lipids, and carbohydrates (n = 52)
- Analyzed milk samples (n = 2810) and infant body composition





*P < .001

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

33

Baseline Protein Enrichment of DHM

- Initial **prospective cohort study** of 69 VLBW infants who received **target-pooled donor milk** (20 kcal/oz)[1]
  - Protein content was still 0.9 g/dL
  - Change in *z* scores from birth to 36 weeks PMA:
    - » Weight *z* score decreased by 0.5
    - » Length *z* score decreased by 1.0
- A **protein-enriched donor milk (DBM+) for clinical use** was developed by adding a liquid protein product[2]
  - 6 mL liquid protein per 90 mL DHM
  - Fed as early as initiation of enteral feeding

Comparison of Protein Levels With DHM and DBM+

	Protein (g/dL) (baseline)	Protein (g/dL) (fortified to 24 kcal/oz)
DHM (20 kcal/oz)	0.9	2.4
DBM+	1.9	3.2

PMA, postmenstrual age

1. Fu TT et al. *Nutrients*. 2019;11(8):1884. **2.** Fu TT et al. *Nutrients*. 2021;13(8):2869.

34

Baseline Protein Enrichment: Growth With MOM, DHM, or DBM+

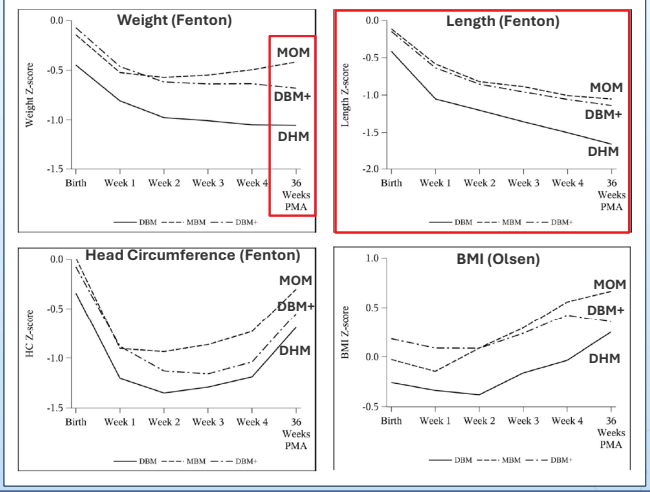
Prospective Cohort Study

- Compared VLBW infants receiving DHM, DBM+, or MOM as primary feeds
- Evaluated safety and growth
- Limited by lack of randomization, exclusion of certain infants by clinical team due to size or illness, and inadequately powered to detect differences in length trajectory

Conclusions

- Appears to be safe in stable VLBW infants
- No difference in incidences of NEC or feeding intolerance
- Weight gain greatest with MOM
- Linear growth with DBM+ comparable to MOM

Comparison of Growth by Primary Feed Type



Fu TT et al. *Nutrients*. 2021;13(8):2869.

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Enhanced Fortification: MAGIC Study

⚠ Not exclusive to DHM feedings

Ongoing Prospective Cohort Study

- VLBW infants <33 weeks GA from 2 level III NICUs
- Fortified to 26 kcal/oz for **all** VLBW infants after reaching full enteral feeds (day ~12-14)
  - 15 mL bovine milk–based fortifier with extensively hydrolyzed protein per 50 mL human milk[a]
- Representative samples of human milk fed to infants collected and analyzed
  - MOM: 24-hour pools sampled up to 3 times per week, depending on supply (n = 198)
  - DHM: 1 bottle from each lot sampled (n = 168)

Enrollment Criteria

Inclusion	Exclusion
• Birth weight <1500 grams • GA at birth <33 completed weeks • Parental clinical consent to the provision of DHM • Attainment of full enteral feeding volume with fortification to 26 kcal/oz within the first 30 days of life, per clinical team	• Significant chromosomal/genetic abnormalities impacting growth potential

a. Off-label recipe not studied by the manufacturer, but this recipe has been utilized by our NICU since 2016 and is used across Greater Cincinnati NICUs.

Fu TT et al. *Pediatr Res*. Published online ahead of print January 15, 2026. doi:10.1038/s41390-025-04754-y

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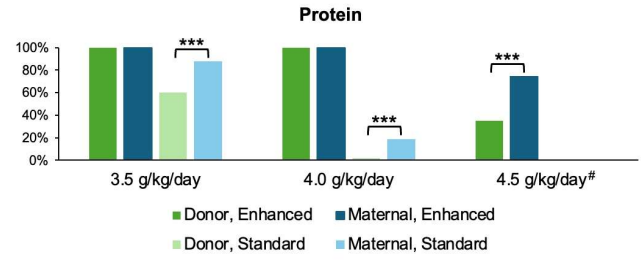
Enhanced Fortification: MAGIC Study

Not exclusive to DHM feedings

Frequency at Which Enhanced Fortification Meets Recommended Protein Targets, Assuming Intake of 150 mL/kg/day



- Lowest targets consistently met with fortification
- Standard fortification did not adequately meet protein targets with DHM
- **Limitations:** results may differ by fluid intake or fortifier; reflects pooling practices from our regional milk bank; infant outcomes pending

a. Off-label recipe not studied by the manufacturer, but this recipe has been utilized by our NICU since 2016 and is used across Greater Cincinnati NICUs.

Fu TT et al. *Pediatr Res.* Published online ahead of print January 15, 2026. doi:10.1038/s41390-025-04754-y

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Fortification Timing: Beginning Fortification at Onset of Feeding

Not exclusive to DHM feedings

Retrospective Study[1]

- Infants <31 weeks GA (n = 95)
- Compared early fortification at time of first feed vs delayed fortification at 50-100 mL/kg/day using bovine milk-based powdered fortifier

Conclusions

- No difference in weight gain
- No difference in incidence of NEC

Randomized Controlled Trial[2]

- Infants <29 weeks GA (n = 150)
- Randomized to receive human milk–based fortifier at onset of feeding or a standard unfortified diet prior to usual bovine milk–based fortifier at 14 days

Conclusions

- Improved length and head circumference with early fortification
- No difference in fat-free mass accretion
- No difference in incidence of NEC or spontaneous intestinal perforation

1. Tillman S et al. *J Perinatol.* 2012;32(7):525-531. **2.** Salas AA et al. *Pediatrics.* 2023;152(3):e2023061603.

38

Increased Volumes of Human Milk or Formula May Increase Growth

Not exclusive to DHM feedings

Randomized Clinical Trial

- Enrolled infants born at <32 weeks' gestation weighing 1001-2500 g
- After reaching full enteral feeds, randomized infants to receive:
  - Higher-volume feeds (180-200 mL/kg/d)
  - Usual-volume feeds (140-160 mL/kg/d)
- Included infants fed fortified human milk and preterm formula

	Higher volume (n = 104)	Usual volume (n = 113)	*P* value
Mean growth velocity, g/kg/day *Primary end point*	**20.5**	**17.9**	**<.001**
Mean weight, g	2365	2200	<.001
Head circumference, cm	31.9	31.4	.01
Length, cm	44.9	44.4	.04
Mean (range) days on respiratory support	6 (0–85)	6 (0–85)	0.81
NEC stage ≥2, n (%)	0 (0%)	0 (0%)	1.00
Feeding intolerance, n (%)	2 (2)	3 (3)	1.00

Travers CP et al. *J Pediatr*. 2020;224:66-71.e1.

39

Safety Considerations With High-Protein Fortification

Systematic Review and Meta-Analysis

- Data from 44 randomized and quasi-randomized clinical trials
- Included trials providing protein (both **parenteral** and **enteral**) to preterm infants <37 weeks GA (n = 5338)
- Evaluated long-term effects in children

RISK RATIO 0.95 (95% CI, 0.90-1.01)

Slightly **decreased** chance of **neurodisability-free survival** at age ≥12 months (*P* = .13; low-certainty evidence)

RISK RATIO 1.36 (95% CI, 0.89-2.09)

Slightly **increased** chance of **cognitive impairment** at toddler age (*P* = .16; low-certainty evidence)

ADDITIONAL FINDINGS

- **Increased weight** and **head circumference** *z* scores at discharge
- **No significant differences** in NEC, late-onset sepsis, or other neonatal morbidity markers

Das S et al. *Pediatr Res*. 2025;97(1):67-80.

40

Safety Considerations With High-Protein Fortification: Important Study Limitations

Limitations identified in commentaries on the meta-analysis by Das et al:

- Low level of certainty for most findings
- Included studies evaluating parenteral amino acids and enteral protein, which are not comparable interventions
  - Lower protein requirements with parenteral nutrition (PN) vs enteral nutrition
  - Amino acids in parenteral nutrition not well studied
- Lack of adequately powered studies of nutrition intake in preterm infants
- Need for a more holistic approach focused on all macronutrients

Embleton ND et al. *Pediatr Res.* 2025;97(1):8-10.

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Safety of Protein Fortification

- Routine fortification to **protein levels of 3.5-4.0 g/kg/day** is safe and beneficial for growth
- Consider increasing fortification **up to 4.5 g/kg/day** on an individualized basis, including:
  - For infants not meeting growth targets
  - Extremely preterm or VLBW infants
  - Infants on exclusive DHM diets, where standard assumptions may magnify the protein gap
  - Surgical neonates (eg, post-NEC, gastroschisis)

1. Embleton ND et al. *Pediatr Res.* 2025;97(1):8-10. **2.** Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.

42

Clinical Integration & Key Takeaways

In concert with individualized nutrition and growth goals, with monitoring

- **Be knowledgeable** about the donor milk product you are selecting and purchasing
  - Understand the processing methods and the limitations
- Although **labels aren't perfect**, if available, they may still be useful to identify a pool to meet the needs of an infant with growth faltering
  - Look for pools with higher protein or energy
- **Prioritize MOM** when possible, and **tailor fortification** strategies for DHM
  - Targeted fortification: ideal, but may not always be practical
  - Universal approach: acknowledge the macronutrient content is low (especially protein) and give more

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Protein Metabolism and Requirements in Critically Ill Infants and Children

Sarah Fleet, MD, PNS

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Protein Requirements in Infancy and Childhood

Protein requirements are highest for VLBW and preterm infants and decline with older age.[1]

Recommendations for Protein Intake[1-3]

VLBW/Preterm Infant	Term Infant	Older Infant	Toddler	Adolescent
3.5-4.0 g/kg/day*	**2.0-2.5** g/kg/day	**1.5-2.0** g/kg/day	**1.0-1.5** g/kg/day	**0.8-1.5** g/kg/day

*Up to 4.5 g/kg/day in infants not meeting growth targets

Note: During periods of critical illness and catch-up growth, protein requirements may be up to 20% to 50% higher.[1]

1. Herrera OR, Helms RA. In: Corkins MR et al (eds). *ASPEN Pediatric Nutrition Support Core Curriculum, 3rd Edition.* American Society for Parenteral Nutrition (ASPEN);2025. **2.** Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed.* Karger; 2021. **3.** Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.

45

Protein Requirements in Infancy and Childhood

Protein requirements are highest for VLBW and preterm infants and decline with older age.[1]

Recommendations for Protein Intake[1-3]

Infant	Toddler	Adolescent
1.5-2.0 g/kg/day	**1.0-1.5** g/kg/day	**0.8-1.5** g/kg/day

Recommendations for Critically Ill Children

2.0-3.0 g/kg/day	**1.5-2.0** g/kg/day

1. Herrera OR, Helms RA. In: Corkins MR et al (eds). *ASPEN Pediatric Nutrition Support Core Curriculum, 3rd Edition.* American Society for Parenteral Nutrition (ASPEN);2025. **2.** Koletzko B et al, eds. *Nutritional Care of Preterm Infants. Scientific Basis and Practical Guidelines, 2nd ed.* Karger; 2021. **3.** Embleton ND et al. *J Pediatr Gastroenterol Nutr.* 2023;76(2):248-268.

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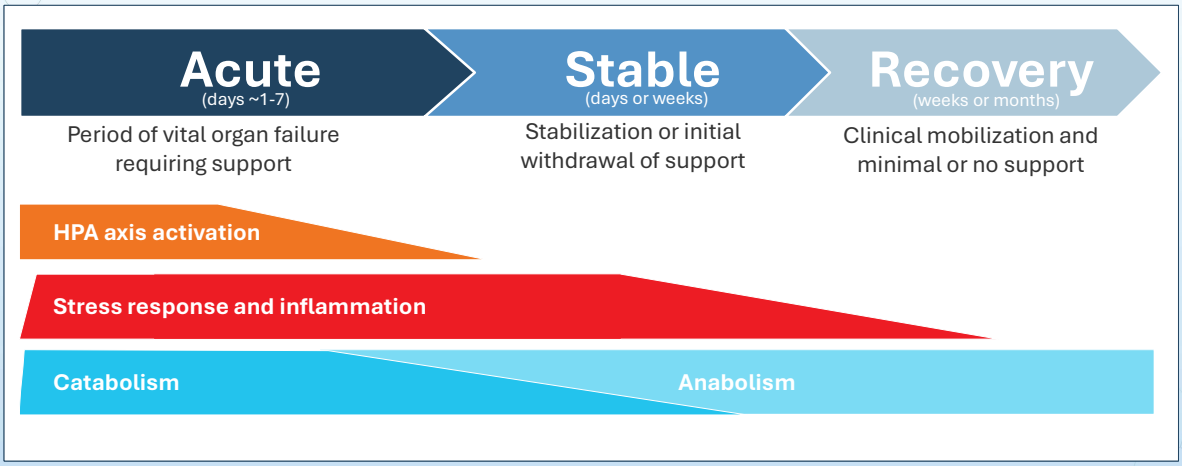
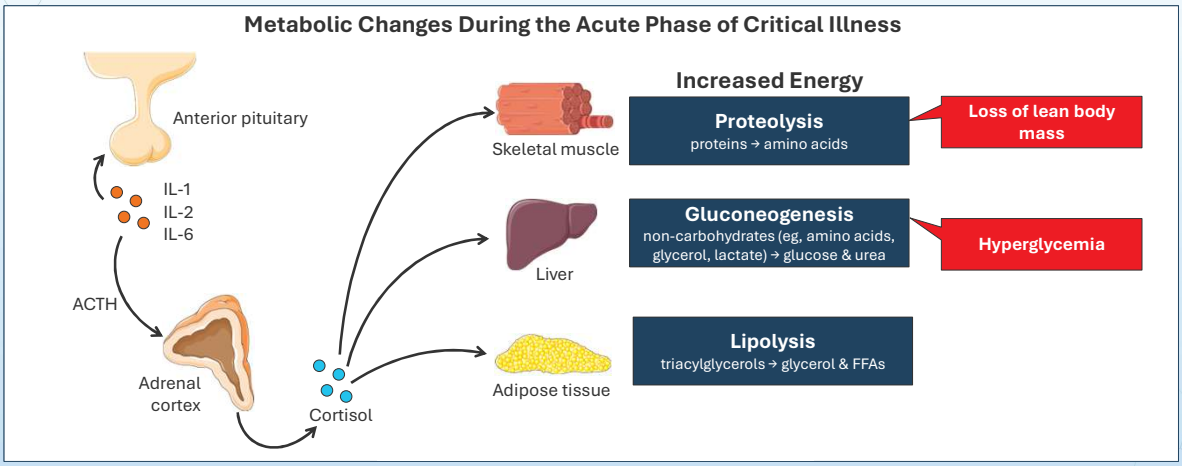
Metabolism During the Phases of Critical Illness[1,2]



1. Briassoulis G et al. *Nutrients*. 2024;16(20):3523. **2.** Moltu SJ et al. *J Pediatr Gastroenterol Nutr*. 2021;73(2):274-289.

47

Catabolism Replaces Energy Loss But Can Have Adverse Outcomes in Children



1. Briassoulis G et al. *Nutrients*. 2024;16(20):3523. **2.** Mehta NM. Accessed March 27, 2026. https://aneskey.com/nutrient-metabolism-and-nutrition-therapy-during-critical-illness/.

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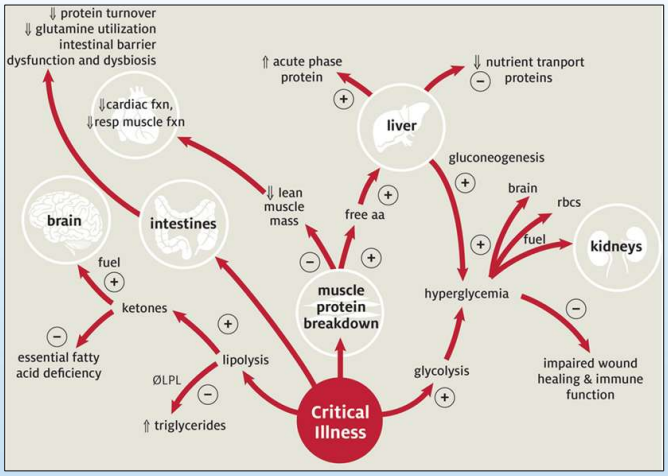
Protein Catabolism in Critical Illness

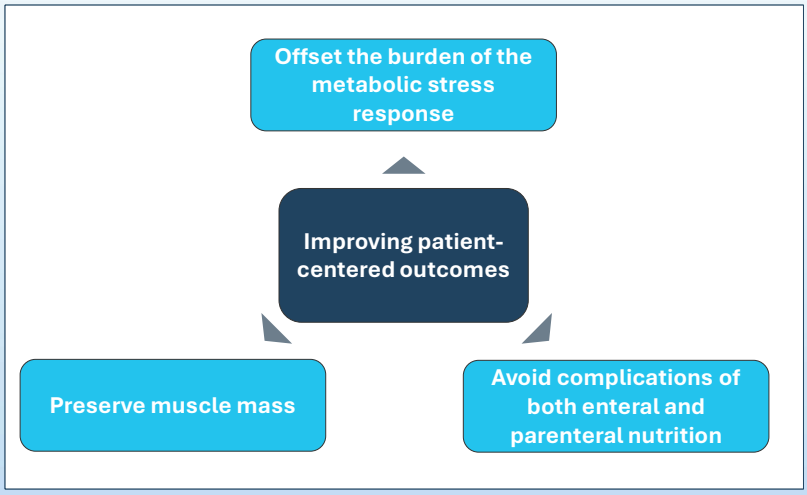


Muscle loss increases the risk of life-threatening complications:

- Difficulty weaning from ventilation
- Swallowing difficulty

Briassoulis G et al. *Nutrients*. 2024;16(20):3523.

Goals of Nutritional Support in the PICU



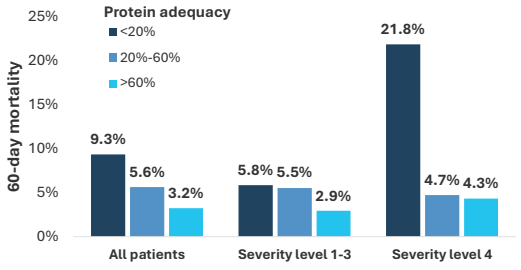
Irving SY et al. *Pediatr Med.* 2022;5:9.

Landmark Study: Adequate Protein Intake Decreases Mortality in the PICU

Prospective Cohort Study

- Included 1245 children from 59 multinational PICUs
- Enrolled children aged 1 month to 18 years who were mechanically ventilated for at least 2 days
- Evaluated mortality based on the percentage of the prescribed daily goal of energy and protein delivered

Mortality by Protein Adequacy and Severity of Illness at Admission



↓86% **decreased odds of 60-day mortality among patients receiving ≥60% prescribed protein vs those receiving <20% of prescribed protein**

Mehta NM et al. *Am J Clin Nutr.* 2015;102(1):199-206.

51

Calculating Protein Delivery Targets in the PICU

Do **not** use RDA values

Use **indirect calorimetry** to estimate needs

Minimum protein intake of 1.5 g/kg/day to achieve positive nitrogen balance and avoid cumulative deficits

- Intake of **2.5-3 g/kg/day recommended** for infants and young children on mechanical ventilation

In infants, consider implications of **human milk–based diets** and **potential protein gaps**

Mehta NM et al. *JPEN J Parenter Enteral Nutr.* 2017;41(5):706-742.

52

PICU Enteral Feeding Considerations: Formula

- Carefully **evaluate infant** and **pediatric formulas** for protein adequacy
  - ~1.4 g/dL protein in most formulas and will **not** meet protein goals for PICU patients[1,2]
- **To meet protein goals in the PICU, consider[2,3]:**
  - Adding modular protein supplementation to standard formulas
  - Using high-protein formulas (if tolerated)
- For patients with fluid restrictions or malnutrition, consider **energy- and nutrient-dense formula** feeding, with potential protein supplementation as-needed[2,3]

1. Abrams SA et al. *Adv Nutr.* 2015;6(2):178-188. **2.** Mehta NM et al. *JPEN J Parenter Enteral Nutr.* 2017;41(5):706-742. **3.** Klepper CM et al. *Nutr Clin Pract.* 2023;38(2):302-317.

Considerations for High-Risk Populations

Sarah Fleet, MD, PNS

Congenital Heart Disease (CHD): High Burden of Malnutrition

- Prevalence of malnutrition ranges from **15%** to **64%**
- Attributed to:
  - Increased cardiac metabolic demands
  - Volume and/or pressure overload
  - Chronic hypoxemia
- **Risk factors for malnutrition:** low birth weight, preterm birth, pulmonary hypertension, pneumonia, congestive heart failure, and age <1 year

Adverse Outcomes of Malnutrition in CHD

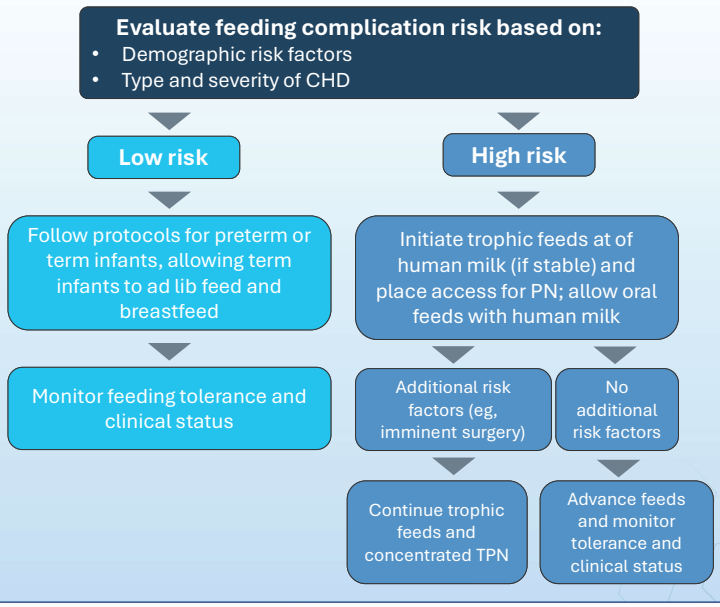
- Longer hospitalization
- Greater infection risk
- Higher mortality risk
- Higher risk of adverse neurodevelopmental outcomes
- Worse quality of life

Vazzana GF et al. *Nutrients*. 2025;17(24):3936.

55

Proposed Feeding Strategies for Infants With CHD

General approach of maximizing nutrition while preventing NEC and fluid overload by using a risk-stratified approach that focuses on protein-dense trophic feeds



Chan B et al. *J Cardiovasc Dev Dis*. 2025;12(2):38.

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Benefits of Pre- and Perioperative Human Milk Feeds in CHD

Registry-Based Study[1]

- Included infants with single ventricle CHD (n = 2491)
- Evaluated human milk–fed infants during the first 2 surgical stages based on feed exposures

Conclusions: Benefits of Human Milk Feeds

- Before stage 1 surgery, decreased risk of preoperative NEC and length of stay
- During stage 1 hospitalization, decreased risk of postoperative NEC, risk of sepsis, and length of stay
- During stage 2 surgery, decreased length of stay

Retrospective Study[2]

- Included infants with CHD and isolated cardiac lesion at high risk for NEC from single site (n = 546)
- Evaluated preoperative human milk feeding and effects on NEC

Conclusions: Benefits of Human Milk Feeds

- Reduced risk of preoperative NEC after controlling for cardiac lesion, race, feeding volume, birth weight, and preterm birth

1. Elgersma KM et al. *J Am Heart Assoc.* 2023;12(17):e030756. **2.** Cognata A et al. *J Pediatr.* 2019;215:11-16.e2.

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Other Complex PICU Populations: Acute Kidney Injury (AKI)

- AKI is a commonly cited reason for inadequate protein intake
- Nitrogen loss from continuous renal replacement therapy (CRRT) is approximately **20% of intake**
- No evidence that higher protein intake in children with AKI is associated with delayed kidney recovery

Nutritional Considerations

- Account for CRRT nitrogen losses when prescribing protein
- Prioritize EN feeding

Coss-Bu JA et al. *Nutr Clin Pract.* 2017;32(1_suppl):128S-141S.

58

Other Complex PICU Populations: Postoperative Care

- Nutritional support begins **prior to surgery**:
  - Identify and address malnutrition preoperatively, when possible
  - Avoid prolonged fasting prior to surgery
- After surgery, nutrition support is intended to **restore normal GI function** to allow for nutrient intake and absorption:
  - Sufficient protein intake is required to reduce the impact of catabolism and promote wound healing
  - Early enteral nutrition (within 24 hours) can decrease the risk of nutritional deterioration following surgery

Irving SY et al. *Pediatr Med.* 2022;5:9.

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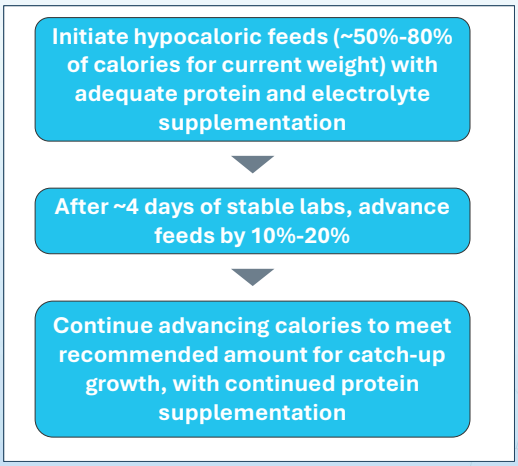
Other Complex PICU Populations: Severe Malnutrition at Risk for Refeeding Syndrome

- Often defined as **weight-for-age or BMI-for-age *z* score of -3 or less**
  - **Other at-risk patients:** weight loss ≥15% in last 3-6 months, little or no nutritional intake for ≥5 days, or baseline electrolyte depletion
- Initial hypocaloric feeds should **include adequate protein** (up to goal range)



Children's Hospital Colorado. Clinical Pathway. Accessed April 8, 2026. https://www.childrenscolorado.org/globalassets/healthcare-professionals/clinical-pathways/protein-energy-malnutrition.pdf?v=48cfd0

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Clinical Integration & Key Takeaways

- **Define** and **individualize protein targets** in the PICU
- **Incorporate nutritionists** into PICU rounds to support optimal nutrition
- **Aggressively target protein goals** using PN and/or trophic feeds, as needed
- When possible, **assess adequacy** of protein delivery and proactively adjust when indicated
- For infants, **identify milk sources** (DHM vs MOM) and utilize updated reference values when estimating protein content