Got Milk? Optimizing Nutrition of Human Milk for Premature Infants

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I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

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Objectives

- Review the nutritional goals for premature infants.
- List the macronutrient requirements for premature infants.
- Describe the unique nutritional challenges of premature infants.
- Describe the need for fortification of human milk to meet the nutritional goals of premature infants.
- Identify key differences between human milk fortifiers.

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Human Milk is Preferred Feeding for All Infants

- American Academy of Pediatrics support feeding of human milk for all infants, term and preterm
- And….
- Human milk is nutritionally insufficient to fully support the growth needs of very low birth weight and extremely low birth weight infants

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Human Milk and Prematurity

Benefits of HM in Premature Infants
Preterm Infant Nutrition and Growth Goals

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Human Milk and Prematurity

- Over 63,000 very preterm (<32 weeks) infants born in US
- At risk for undernutrition during long NICU stay
- Critical time for organ development
- Short- and long- term benefits of HM for preterm infants
- Addition of fortifiers to HM is standard practice
- Fortifiers designed to meet recommended nutrient goals when added to milk with average nutrient values at typical volumes
- Several products and strategies are available to fortify HM

Belfort, M. Macronutrient Intake from Human Milk, Infant Growth, and Body Composition at Term Equivalent Age: A Longitudinal Study of Hospitalized Very Preterm Infants. *Nutrients* 2020.

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Human Milk and Prematurity

- NICU growth outcomes have improved in recent years
- Fortified HM-fed infants have shown slower weight gain and head growth compared to preterm formula-fed infants
- Current fortification strategies may not meet nutritional requirements for all infants
- Increase in use of maternal and donor human milk
- Macronutrient content of HM highly variable

Belfort, M. Macronutrient Intake from Human Milk, Infant Growth, and Body Composition at Term Equivalent Age: A Longitudinal Study of Hospitalized Very Preterm Infants. *Nutrients* 2020.

Human Milk Benefits for Preterm

- Protection against Necrotizing Enterocolitis
- Protection against Late Onset Sepsis
- Priming of the immature gut
- ?Protection against Severe Retinopathy of Prematurity
- ?Protection against Bronchopulmonary Dysplasia
- ?Improvement of long-term Neurocognitive Development
- ?Improvement of Cardiovascular Health

JPGN Human Milk in Feeding Premature Infants Consensus Statement September 2015

Preterm Nutrition and Growth Goals

- Meet goals of *in utero* growth of normal fetus of same post-conceptional age
  - Body weight and length
  - Body composition
  - Organ development and maturity
- Catch up growth for deficiencies

AAP Committee on Nutrition (2019). Pediatric Nutrition, 8th Ed

Preterm Nutrition and Growth Goals

- Achieving adequate/optimal growth in preterm infants
- Extremely relevant for long-term neurodevelopment
- Reducing extrauterine growth restriction (EUGR)
- Goal not to lose more than 1 standard deviation in weight and HC from birth to discharge
- Growth ≠ only weight gain, don't forget length and HC

JPGN Human Milk in Feeding Premature Infants Consensus Statement September 2015

Preterm Nutritional Requirements

- Energy
- Protein
- Fat
- Carbohydrates
- Oligosaccharides
- Sodium, Potassium, Chloride
- Calcium, Phosphorus, Magnesium
- Iron
- Zinc, Copper, Iodine, other trace elements

AAP Committee on Nutrition (2019). Pediatric Nutrition, 8th Ed

Preterm Nutritional Requirements

Table 1

Requirements for protein and energy; best estimates by factorial and empirical methods (44).

Body weight, g	500–1,000	1,001–1,500	1,501–2,000
Weight gain of fetus, g/kg/d	19.0	17.4	16.4
Protein, g/kg/d	4.0	3.9	3.7
Energy, Kcal/kg/d	106	115	123
Protein/energy, g/100 kcal	3.8	3.4	3.0

Arslanoglu S et al. Fortification of HM for Preterm Infants: Update and Recommendations of EMBA Working Group. *Front Pediatr.* 2019

Preterm Nutritional Requirements

Table 2

Requirements for major minerals and electrolytes determined by factorial method, listed by body weight (51).

	500–1,000 g		1,001–1,500 g		1,501–2,000 g	
	Accretion	Requirem.	Accretion	Requirem.	Accretion	Requirem.
Ca (mg)	102	184	99	178	96	173
P (mg)	66	126	65	124	63	120
Mg (mg)	2.8	6.9	2.7	6.7	2.5	6.4
Na (meq)	1.54	3.3	1.37	3.0	1.06	2.6
K (meq)	0.78	2.4	0.72	2.3	0.63	2.2
Cl (meq)	1.26	2.8	0.99	2.7	0.74	2.5

Arslanoglu S et al. Fortification of HM for Preterm Infants: Update and Recommendations of EMBA Working Group. *Front Pediatr.* 2019

Preterm Nutritional Requirements

Table 3

Recommended enteral protein and energy intakes for clinically stable very low birthweight infants (50, 52, 53).

	Munich consensus 2014	ESPGHAN 2010	Ziegler et al.
Energy (kcal/kg/d)	110–130	110–135	105-127
Protein (g/kg/d)	3.5–4.5	4.0–4.5 (<1 kg) 3.5–4.0 (1–1.8 kg)	3.9-4.0
Protein/Energy (g/100 kcal)	3.2–4.1	3.2–4.1	3.1–3.8
Lipids (g/kg/d)	4.8–6.6	4.8–6.6	–
Carbohydrates (g/kg/d)	11.6–13.2	11.6–13.2	–

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Human Milk: Known vs Unknown

Table 1 The knowns and unknowns about human milk and its use in preterm infants

	Knowns	Unknowns
Human milk	▸ More rapid achievement of full feeds ▸ ↓NEC ▸ ↓Sepsis ▸ Improved brain development and neurodevelopmental outcome ▸ ↓Hospital admission up to 30 months ▸ Possibly ↓ROP ▸ ↓Cost of care ▸ Many effects dose-related ▸ Nutrient provision improved with HMF	▸ Uncertainty of size of effect on morbidities in context of modern neonatal care ▸ What is/are the critical period(s) of exposure ▸ Variability in composition ▸ Effect on nutrient composition of standing, refrigeration and freeze-thawing ▸ Possibility of sensitisation to foreign protein with HMF ▸ Optimal approach to risk of transmission of viruses and bacteria
DEBM	Probable ▸ Improved feed tolerance ▸ ↓NEC ▸ Improved cardiovascular health ▸ Improved cognition ▸ Better bone mineral content Definite ▸ Less nutrient rich than preterm MEBM ▸ Bacteria and blood borne viruses inactivated by pasteurisation ▸ Pasteurisation reduces concentration of immune factors	▸ Uncertain size of effect on preterm morbidities of DEBM versus MEBM ▸ Possible techniques to inactivate viruses with less destruction of nutrients ▸ Variability in composition ▸ Uncertainties about effect of maternal nutrient and toxin intake ▸ Small concern about emerging pathogens

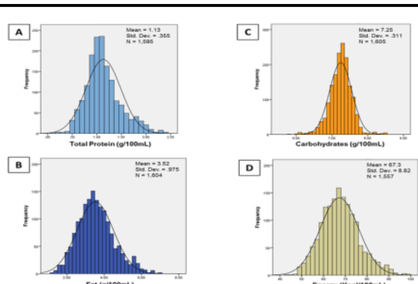
DEBM, donor breast milk; HMF, human milk fortifier; MEBM, mother's expressed breast milk; NEC, necrotising enterocolitis.

Menon G, et al. *Arch Dis Child Fetal Neonatal Ed* 2013;98:F559-F562.

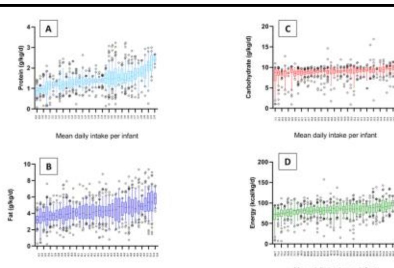
Macronutrient Intake from HM Varies

- Longitudinal study
- 37 infants <32 weeks gestation
- Analyzed 1626 HM samples
- Study aims:
  - Determine between-infant variation in macronutrient intake from HM
  - Examine associations of macronutrient intake with growth outcomes

Belfort, M. Macronutrient Intake from Human Milk, Infant Growth, and Body Composition at Term Equivalent Age: A Longitudinal Study of Hospitalized Very Preterm Infants. *Nutrients* 2020.



Belfort, M. Macronutrient Intake from Human Milk, Infant Growth, and Body Composition at Term Equivalent Age: A Longitudinal Study of Hospitalized Very Preterm Infants. *Nutrients* 2020.



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Macronutrient Intake from HM Varies

- Greater intakes of fat and energy associated with higher weight
- Greater protein intake associated with greater body length
- Higher fat intake associated with higher fat mass and fat-free mass
- Macronutrient intakes from HM highly variable and associated with growth outcomes despite routine fortification

Belfort, M. Macronutrient Intake from Human Milk, Infant Growth, and Body Composition at Term Equivalent Age: A Longitudinal Study of Hospitalized Very Preterm Infants. *Nutrients* 2020.

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Sources of Human Milk

Mother's Milk
Donor Milk

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Sources of Human Milk

- Mother's milk
- Donor milk
- **NOT** the internet

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Cow's Milk Contamination of Human Milk Purchased via the Internet
Sarah A. Keim, Manjusha M. Kulkarni, Kelly McNamara, Sheela R. Geraghty, Rachael M. Billock, Rachel Ronau, Joseph S. Hogan and Jesse J. Kwiek
Pediatrics 2015;135;e1157
DOI: 10.1542/peds.2014-3554 originally published online April 6, 2015;

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Breastmilk Black Market

- Discourage families from direct HM sharing/purchasing online
- Increased risks of bacterial or viral contamination
- Exposure to medications, drugs, other substances
- No guarantee it was stored properly
- Cow's milk Contamination

Keim, Sarah et al. *Pediatrics* 2015;135;31157.

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Donor Human Milk

- Prioritization for preterm infants <1500 g
- Ideally a temporary bridge to obtaining mother's milk
- Does not compete with mother's own milk
- Growth outcomes:
  - Lower protein content
  - Lower energy content
  - Loss of bile salt-dependent lipase activity
- Pasteurization:
  - Loss of nutrients
  - Anti-inflammatory factors
  - Can eliminate bacterial strains with probiotic properties
  - Bioactive components substantially decreased
  - Much less effect on macro- and micro- nutrients

AAP Committee on Nutrition, AAP Section on Breastfeeding, AAP Committee on Fetus and Newborn 2017

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Donor Human Milk

- Donor HM should be obtained from a well-established milk bank
- HMB must follow specific safety guidelines
- Collection, treatment, distribution of DHM processes
- Need universal quality principles for all HMB
- DHM currently requires pasteurization, freezing, thawing
- Currently recommend Holder pasteurization for DHM
- New methods of DHM treatment are under investigation

JPGN Human Milk in Feeding Premature Infants
Consensus Statement September 2015

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Promotion of Breast Feeding in the NICU

- Begin milk expression as soon after delivery as possible
- Use colostrum for oral cares
- Encourage kangaroo care
- Strategies to promote and support breast-feeding for preterm infants in every maternity or children's hospital
- Hospital-based lactation programs
- Fresh mother's own milk is first choice
- Ensure processes in place for safe centralized handling of HM

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Fortification of Human Milk

Multi-nutrient Fortifiers
Single-nutrient Supplements
Fortification Strategies

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Multi-Nutrient Fortifiers

- Most multi-nutrient fortifiers contain bovine milk protein
- Donkey milk recently proposed as composition similar to HM
- HM based fortifier

Arslanoglu S et al. Fortification of HM for Preterm Infants: Update and Recommendations of EMBA Working Group. *Front Pediatr.* 2019

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Human Milk Fortifiers

- Formula
- Human Milk Fortifier
  - Powder vs Liquid
  - Sterilization: heat vs acidification
  - Human vs Bovine vs Donkey?
- Supplements
  - Protein
  - Lipids
  - Carbohydrates

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Table 4

Nutrient composition of selected fortifiers and supplements.

	Bovine-based products (per gram of powder)										Human milk-based fortifier (per volume)			
	Multicomponent fortifiers					Protein supplements								
Fortifier	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Volume (ml)	/	/	/	/	/	/	/	/	/	/	20	30	40	50
Energy (kcal)	4.4 (L)	3.5	3.6	4.9 (L)	3.9 (L)	3.4	3.6	3.6	4	3.7	28	42	56	71
Protein (g)	0.36[PH]	0,25[EH]	0.2[EH]	0.4	0.3	0.82[EH]	0.72[EH]	0.86[W]	0.8[W]	0.9[W]	1.2	1.8	2.4	3
Na (mg)	9.2	8,0	5.4	5.6	4.2	7.8	8.2	2.1	2	0	20	40	42	45
Ca (mg)	18.9	14.9	10	32	33	5.2	12.8	0	4	0	103	106	108	111
P (mg)	11	8.7	7	18	19	5.2	0.73	0	3	0	53.8	54.9	56	57.5
Iron (mg)	0.5	0	0	0.5	0.1	0	0.007	0	0	0	0.1	0.15	0.2	0.25

L, lipids; PH, partially hydrolyzed; EH, extensively hydrolyzed; W, whole protein; HMBF, human milk-based fortifier. A-Fortipre®, Nestle; B-Fortema®, Danone; C-FM85®, Nestle; D-Enfamil®, Mead Johnson; E-Similac®, Ross; F-Aptamil PS®, Danone; G-Preemie®, Nestle; H-Beneprotein®, Nestle; I-Pro-Mix®, Corpak; J-Protein instant®, Resource; K- HMBF+4®, Prolacta; L- HMBF+6®, Prolacta; M- HMBF+8®, Prolacta; N- HMBF+10®, Prolacta.

Arslanoglu S et al. Fortification of HM for Preterm Infants: Update and Recommendations of EMBA Working Group. *Front Pediatr.* 2019

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Single-Nutrient Supplements

- Protein
  - Many protein supplements not specifically designed for neonates
  - +/- Partially or extensively hydrolyzed protein
  - New products designed for preterm infants
  - No consensus on how to use these products
- Lipids
  - Medium chain triglycerides
  - HM derived cream supplement
- Carbohydrates
  - Dextrin maltose

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Fortification Strategies

- Standard Fortification
- Individualized Fortification
  - Adjustable Fortification
  - Targeted Fortification

Table 5

Current human milk fortification methods (43, 74, 76–79).

Fortification method	Principle	Advantages disadvantages
1. Standard (STD) Fortification	Fortification method currently in use in most of the neonatal units. A fixed amount of fortifier is added to a fixed volume of HM according to the manufacturers' instructions.	Practical. But has not solved the problem of protein undernutrition for VLBW infants. Despite STD fortification many VLBW infants continue to have suboptimal growth.
2. Individualized HM Fortification Methods a. Adjustable (ADJ) Fortification b. Targeted Fortification	Protein adequacy is monitored by BUN twice weekly, cut-off levels of BUN are 10–16 mg/dl[a]. If the level is <10 mg/dl extra protein is added to the STD fortification. Macronutrient concentrations in HM are analyzed and based on the results milk is supplemented with extra protein and/or fat.	Practical, not labor intensive. Doesn't need expensive devices. Monitors protein intake of each infant. Safeguards also against excessive protein intake. Proven to be effective in optimizing growth and protein intake with a RCT. A real individualization method taking into consideration each infant's protein requirement. All macronutrients can be supplemented. Bedside HM analyzers are required. May be labor intensive. Supplementation is done according to the population recommendations, does not take into consideration that each individual infant's requirement may be different.

HM, human milk; VLBW, very low birth weight; BUN, blood urea nitrogen; RCT, randomized controlled trial.

[a]BUN levels of 10–16 mg/dl correspond to blood urea concentrations of 21.49–34.24 mg/dl (3.57–5.71 mmol/l).

Table 6

The products required and the threshold values of the metabolic marker used for the Adjustable (ADJ) fortification method (77).

Fortifier/supplement required	
1. A multi-nutrient fortifier	
2. A protein supplement	
Metabolic marker and threshold values used to adjust protein supply	
Blood urea nitrogen (BUN)	<10 mg/dl–increase the fortification to the next level 10–16 mg/dl–no change
	>16 mg/dl–decrease the fortification by one level

Table 7

The scheme for adjustable fortification (updated in 2012) (77).

Fortifier/supplement	Fortification levels and the amount of fortifier/supplement to be added (g per 100 ml HM)					
	−2	−1	0 Standard (STD)	+1	+2	+3
Multi-nutrient HM fortifier	1/4 strength	Half strength	Full strength	Full strength	Full strength	Full strength
Protein supplement	–	–	–	0.4	0.8	1.2

Conclusions

Conclusions/Comments EMBA

- HM is first choice in preterm feeding
- Unfortified HM insufficient amount of nutrients when fed at usual feeding volumes
- To prevent EUGR, poor neurocognitive outcome and specific nutrient deficiencies, need fortification of HM
- Despite standard fortification, many VLBW infants continue to have suboptimal growth
- Targeted fortification needs to be improved
- HM-based fortification seems promising, still concerns on efficacy, safety, ethical issues
- No strong evidence to support use of hydrolyzed protein source

Recommendations EMBA

- HM feeding is basic right for preterm infants
- Mother's own milk is first choice in preterm infant feeding
- When mother's milk unavailable, donor HM is best alternative
- HM fortification recommended for preterm with BW <1800g
- HM fortification can be started when feeds 50-80 ml/kg/day
- Optimization of HM fortification is required

Conclusions/Comments JPGN

- All preterm infants <1800 grams should be fed fortified HM
- HM should be fortified with protein, vitamins and minerals
- Quantity of HM fortification should optimize growth in NICU stay
- HM fortification should start with standard fortification
- If infants do not grow appropriately, advise individualized fortification
  - Targeted fortification (based on milk analysis)
  - Adjustable fortification (based on BUN measurements)
  - Both advisable depending on the NICU experience and facilities

JPGN Human Milk in Feeding Premature Infants Consensus Statement September 2015

Future Research

- Address nutritional management in specific preterm groups
- Randomized controlled trials assessing efficacy/safety of HM fortification
  - After discharge
  - Adjusted vs targeted
- Defining reasonable and replicable study endpoints in large cohorts
  - Neurocognitive outcomes
  - Body composition
- Optimization of quality of fortifiers

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Nutrition at Discharge

- No consensus about post discharge nutrition
- Nutritional supplementation for premature infants should be continued for 3-6 months to optimize growth and development
- Studies that evaluated post discharge HM fortification showed no deleterious effect on breastfeeding rates
  - Suggested some advantages

Arslanoglu S et al. Fortification of HM for Preterm Infants: Update and Recommendations of EMBA Working Group. *Front Pediatr.* 2019

Changes You May Wish to Make in Practice

CPQCC Potentially Better Practices

PBP #15: Start Fortification Before Full Feeds are Reached

- Early fortification of HM minimizes nutrition gap
- Best to follow standardized local guidelines
- No clear evidence when it is safe to introduce fortification
- Protocols have increasing used earlier fortification steps without intestinal complications
- Increase in osmolality with addition of fortifiers does not exceed significant levels of risk that were associated with NEC
- Powdered fortifiers no longer recommended in NICU

CPQCC Quality Improvement Toolkit: Nutritional Support of the VLBW Infant. September 2018

PBP #16: Enteral Feeds Should be Advanced and Concentrated Until Providing Adequate Nutrition to Sustain Optimal Growth

- Provide optimal nutrition/growth, replace need for TPN
- Advance volume to deliver more nutrients 150-200 ml/kg/d +/-
- May need fortification beyond 24 kcal/oz
  - Not well evaluated, but common practice
- Proactive rather than reactive approach
- Adjust feedings based on daily weights
- Customized fortification may be required
  - Adjustable approach: growth and BUN <9 mg/dL
  - Targeted approach: technology to measure macronutrients in milk*

CPQCC Quality Improvement Toolkit: Nutritional Support of the VLBW Infant. September 2018

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