Importance of Early Nutrition

The neonatal period represents a time in which the brain is especially vulnerable to nutritional deficits, therefore, attention to detail of nutritional management is critical particularly for the VLBW infant (<1500 grams) who has missed the last trimester of pregnancy. When an infant is born before term gestation, the rich supply of nutrients that has supported the growth and development of the fetus is interrupted abruptly. With the birth of the VLBW premature infant, we aim to keep the interruption as short as feasible by initiating parenteral nutrition (PN) quickly. As PN is providing nutrients to maintain an anabolic state, trophic feeds are begun enterally to foster the immature gastrointestinal (GI) tract. Mom's milk is preferred during this time of development for its tropic and anti-infectious effects on the GI tract. As the GI tract matures, enteral nutrition advances and parenteral nutrition can be discontinued. Before discontinuing PN, this transition period requires close attention to all nutrients.

Use of Protein in Nutritional Strategies for Very-Low-Birth-Weight (VLBW) Infants to Promote Adequate Growth

David H. Adamkin, MD
Professor of Pediatrics, University of Louisville; Associate Director of the Neonatal Fellowship Program and Director of Neonatal Nutrition Research.

Dr. Adamkin is an experienced researcher in the area of Neonatal Nutrition. He is a Neonatologist with over 100 articles published, 40 book chapters, 5 books and 20 webinars dealing with methods and strategies to nourish premature infants. He is a pioneer in the area of human milk analysis. He served a six-year appointment to the Committee on Fetus and Newborn for the American Academy of Pediatrics. In 2009, he received a Honoris Causa Doctorus from Poznan University of Medical Sciences in Poland. He has received awards in education and service from the University of Louisville, the Kentucky Perinatal Association, the Southern Society for Pediatric Research and Kosair Charities. Most recently, he has received the Avroy Fanaroff Neonatal Educator Award for 2018 and the Southern Society Pediatric Research Educator Award in February 2019. Dr. Adamkin is the Rounsavall Endowed Professor in Neonatal Medicine.

Objectives

To obtain 1.0 CPEU and CE credit, please read this article and follow the links to answer the knowledge check questions in their entirety.

After reading this article, the learner will be able to:
1. Describe protein requirements for very-low-birth-weight (VLBW) infants.
2. Discuss the use of human milk in the VLBW infant.
3. Review human milk fortification and strategies to enable adequate growth in the VLBW infant.

Considerable evidence suggests that early nutritional and growth deficits in the first 1000 days have long-lasting consequences on, neurodevelopmental outcomes.
Human Milk Feeding for VLBW Infants: Composition and Protection

As fetal body weight advances, protein requirements increase proportionally to meet the nutritional needs of preterm infants, especially protein and minerals. This may be associated with postnatal growth failure which is a surrogate for inadequate nutrition and the potential for increased risk of neurodevelopmental impairment. The conundrum is we want the short- and long-term benefits of feeding human milk to the VLBW infant but not the risk of postnatal growth failure. Therefore, the conundrum of preventing NEC in the short term but risking poor growth at the same time.

The major limitation to the provision of human milk is the inadequate supply for the premature or hospitalized infant. When mother’s milk is unavailable, despite significant lactation support, pasteurized donor milk can be used, and that recommendation started the growing use of donor milk in the neonatal intensive care unit (NICU). The CDC estimates 65% of preterm infants are fed donor human milk during their hospital stay.1

Protein and Energy Requirements

Human milk alone is insufficient to meet the nutritional needs of preterm infants, especially protein and minerals. This may be associated with postnatal growth failure which is a surrogate for inadequate nutrition and the potential for increased risk of neurodevelopmental impairment. The conundrum is we want the short- and long-term benefits of feeding human milk to the VLBW infant but not the risk of postnatal growth failure. Therefore, the conundrum of preventing NEC in the short term but risking poor growth at the same time.

Human Milk

Human milk, beyond the initial trophic feeds, either from mother’s own milk or from pasteurized donor human milk, are a priority for all preterm infants, especially VLBW infants. The American Academy of Pediatrics (AAP) recommendation on breastfeeding management of preterm babies in 2012 included the numerous potent benefits of human milk, as such that all preterm infants should receive human milk, and that mother’s own milk, fresh or frozen, should be the primary diet and requires a multi-nutrient fortification to meet the nutritional demands. The figure above displays unique composition of human milk and protection afforded by these factors in human milk. Research conducted by the National Institute of Child Health Neonatal Network was analyzed in a secondary study by Meinzen-Derr et al. and suggested a dose-related association of mother’s own human milk feeding with a reduction in necrotizing enterocolitis (NEC) or death in VLBW infants.

The following guidance shows a range of protein and energy for VLBW infants through 1800 g. It applies to stable growing infants. These apply to stable growing preterm infants through 1800 g. It shows these relationships. The figure “Impact of Protein Energy Ratio (PE ratio) on Body Composition” shows these relationships. The clinician must target both adequate energy to get the full benefit of the protein that you’re providing as well as adequate total protein per body weight. Refer to the table above for current enteral nutrient requirements of VLBW infants. These apply to stable growing preterm infants through 1800 g. It shows a range of protein and energy for these preterm infants. For optimal growth, premature infants need fortification of human milk to meet their increased nutrient needs. The following guidance is a stepwise approach for the clinician to consider.

Practice Pearls

PE ratio and total protein positively correlates with lean body mass. Protein also correlates with weight gain, as does energy. Energy correlates with fat mass gain. PE ratio negatively correlates with fat mass gain. So, to increase lean body mass accretion and limit fat mass deposition, an increase in PE ratio is mandatory. Our newer preterm formulas and new human milk fortifiers have increased the protein levels which will impact the proportionality of growth by enhancing the PE ratio.

Enteral Nutrient Requirements for Fully Enteraly Fed Preterm VLBW Infants (<1500 g)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid</td>
<td>40-140 mL/kg</td>
<td>35-60 mL/kg</td>
</tr>
<tr>
<td>Energy</td>
<td>110-130 kcal/kg</td>
<td>110-135 kcal/kg</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>11.6-13.2 g/kg</td>
<td>11.6-13.2 g/kg</td>
</tr>
<tr>
<td>Protein</td>
<td>3.5-4.5 g/kg</td>
<td>3.5-4.5 (1-1.8 g/kg)</td>
</tr>
<tr>
<td>Fat</td>
<td>4.8-6.6 g/kg</td>
<td>4.8-6.6 g/kg</td>
</tr>
<tr>
<td>DHA</td>
<td>55-60 mg/kg</td>
<td>12-30 mg/kg</td>
</tr>
<tr>
<td>AA</td>
<td>35-45 mg/kg</td>
<td>18-42 mg/kg</td>
</tr>
<tr>
<td>Calcium</td>
<td>120-200 mg/kg</td>
<td>120-140 mg/kg</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>60-140 mg/kg</td>
<td>60-90 mg/kg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>8-15 mg/kg</td>
<td>8-15 mg/kg</td>
</tr>
<tr>
<td>Sodium</td>
<td>3.5-6 mEq/kg</td>
<td>3-5 mEq/kg</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.7-3.4 mEq/kg (78-195 mg/kg)</td>
<td>160-320 mEq/kg (160-320 mg/kg)</td>
</tr>
<tr>
<td>Chloride</td>
<td>3.5-6 mg/kg (105-177 mg/kg)</td>
<td>3-5 mg/kg (105-177 mg/kg)</td>
</tr>
<tr>
<td>Iron</td>
<td>2-3 mg/kg</td>
<td>2-3 mg/kg</td>
</tr>
</tbody>
</table>

Abbreviations: DHA, docosahexaenoic acid; AA, arachidonic acid; VLBW, very low birth weight

Protein and Energy Requirements: Best Estimates by Factorial and Empirical Methods

As fetal body weight advances, protein requirement decreases a bit from 4 g/kg/d to 3.7 g/kg/d. Energy does the opposite. Energy increases as body weight increases: 106 kcal/kg/d, 115 kcal/kg/d, and 123 kcal/kg/d, respectively from 500 g body weight to 2000 g. The protein energy (PE) ratio decreases. Protein (g) in the numerator is decreasing and energy is increasing in the denominator (per 100 calories) so that the protein energy ratio decreases. That’s very important because it affects the proportionality of growth.

Growth

Preterm infants are more vulnerable to calorie and protein deficits, which can disrupt rapid lean body mass accretion, brain growth, and maturation. In this population, malnutrition can occur with nutrient intake deficits of only a few days. In 2018, malnutrition indicators for the preterm infant and neonate population were developed to help define the criteria for malnutrition in this vulnerable population. Assessment of growth should either be based on the Fenton growth charts or the Olsen growth charts for preterm infants. These charts are appropriate for preterm infants with a gestational age of less than or equal to 36/7 days. Achievement or rate of weight gain equivalent to the rate of gain of the fetus at the same postconceptional age is the goal but not easily achieved.

The figure “Impact of Protein Energy Ratio (PE ratio) on Body Composition” shows these relationships. PE ratio and total protein positively correlates with lean body mass. Protein also correlates with weight gain, as does energy. Energy correlates with fat mass gain. PE ratio negatively correlates with fat mass gain. So, to increase lean body mass accretion and limit fat mass deposition, an increase in PE ratio is mandatory. Our newer preterm formulas and new human milk fortifiers have increased the protein levels which will impact the proportionality of growth by enhancing the PE ratio.

Lean Body Mass and Limit Fat Mass Deposition, an Increase in Protein/Energy Ratio is Mandatory

As fetal body weight advances, protein requirement decreases a bit from 4 g/kg/d to 3.7 g/kg/d. Energy does the opposite. Energy increases as body weight increases: 106 kcal/kg/d, 115 kcal/kg/d, and 123 kcal/kg/d, respectively from 500 g body weight to 2000 g.
Guidance for Fortification of Human Milk

Fortification should increase the amount of nutrients for preterm infants to meet requirements at feeding volumes (135-200 mL/kg/day). Nutrient requirements are defined as the intakes that enable the same growth rate as the fetus.¹

Foremilk vs Hindmilk at 46 Days of Life, Former 29 Weeks

Using the Calais, we analyzed 99 discrete preterm samples from 24 women as our first study, and nutrient variability became obvious. The protein was consistent with the assumed value that the industry uses to make a fortifier of 1.6g/dL. However, the ranges for protein were 0.9 g/dL to 2.5 g/dL. The first sample would need extra packets of fortifier, while the second would need no fortification at all. The fat range on a particular sample from a particular woman was 0.9 g/dL versus another sample of 7.43 g/dL. That means the first sample would have an energy of 11 calories per ounce; the second sample 32 kcal/oz. We quickly learned that the nutrient variability was very significant from mother to mother and sample to sample and would make fortification quite challenging.

The next example is of foremilk vs hindmilk. This was a mother getting ready to take her baby home at 46 days of life, a former 29-weeker, and she came in with two milk samples. One looked very rich and white like a shake, and the other was very watery, and we asked her what was and, she said one was the beginning of her day and the other was the later expression, or hindmilk. So, after we analyzed the samples, the results showed the foremilk versus hindmilk had the same protein content. However, look at the difference in fat; an eightfold difference in the same expression as referenced below. How does that difference affect the energy? Eleven kcal/oz in the foremilk, 32 kcal/oz in the hindmilk. Therefore, we would promote hindmilk fortification which has been shown to improve growth.²

Next Step: Multi-Nutrient Human Milk Fortification

It is very important to have human milk strategies for fortification to benefit these very-low-birth-weight babies. Evidence for preterm infant supplementation with protein and minerals, particularly calcium and phosphorus, came from clinical observations and dietary trials as long as the 1940-1960s. These trials in preterm infants showed us that human milk required additional nutrients to produce appropriate weight, length, and bone growth. Initially, casein-dominant protein fortification quite challenging. As our knowledge of the variability of human milk has expanded, there have been many advancements in liquid human milk fortifiers over the past three decades and now many different methods of fortification exist. There are some nutrient differences among the fortifiers available as well as sources of protein to consider. The majority of human milk fortifiers have bovine (cow) milk as their base, with one fortifier with donor human milk as

Human Milk Protein Requirements to Provide Nutritional Needs of Preterm Infants

<table>
<thead>
<tr>
<th>Protein (g/dL)</th>
<th>Energy (kcal/oz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>12 - 263</td>
</tr>
<tr>
<td>10.5-12</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>120 - 200</td>
</tr>
<tr>
<td>6.2, 10.1</td>
<td></td>
</tr>
<tr>
<td>20.1 ± 4.1</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Lactose (g/dL)</td>
<td>10.8 – 13.5</td>
</tr>
<tr>
<td>8.0 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>6.1 – 8.32</td>
<td></td>
</tr>
<tr>
<td>290 - 320</td>
<td></td>
</tr>
<tr>
<td>9.8</td>
<td></td>
</tr>
</tbody>
</table>

Nutrient per 100 kcal

- Protein g: 3.2-6.1
- Carbohydrate g: 15.4-18.5
- Fat g: 6.6-10.0
- DHA, mg: 50 - 80
- ARA, mg: 35 - 45
- Calcium (mg): 120 - 200
- Phosphorus (mg): 60 - 120
- Vitamin D, IU: 100 - 300
- Iron, mg: 2 - 3

- Osmolality, mOsm/kg: 290 - 330

- Recommended intake 11-45 g/kg

- Human Milk Protein and Fortification

- Base and Variability in Human Milk

- First Step: Understand the Base and Variability in Human Milk

- The provision of fortified human milk to the preterm infant comes with the challenge of meeting estimated requirements in the face of nutrient variability. Milk composition varies with the volume of milk expressed, the type of milk, whether it’s foremilk or hindmilk, and the stage of lactation. For example, there are two- to threefold differences in protein, fat and energy, regardless of the state of lactation. The lipid content in human milk is the most variable macronutrient, with high variability within and between mothers, and is the component most affected by routine handling, processing, and feeding of human milk.

- Protein is highest in expressed breast milk produced in the first few weeks by mothers delivering prematurely.

- Human Milk Analysis

- Breast milk analyzers have been available for research use in the US for several years, and we have had experience with the Calais Milk Analyzer (Metron Instruments, Inc, Saloon, OH) device. There are now devices approved for clinical application.

- Using the Calais, we analyzed 99 discrete preterm samples from 24 women as our first study, and nutrient variability became obvious. The protein was consistent with the assumed value that the industry uses to make a fortifier of 1.6g/dL. However, the ranges for protein were 0.9 g/dL to 2.5 g/dL. The first sample would need extra packets of fortifier, while the second would need no fortification at all. The fat range on a particular sample from a particular woman was 0.9 g/dL versus another sample of 7.43 g/dL. That means the first sample would have an energy of 11 calories per ounce; the second sample 32 kcal/oz. We quickly learned that the nutrient variability was very significant from mother to mother and sample to sample and would make fortification quite challenging.

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- Next Step: Multi-Nutrient Human Milk Fortification

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the base. Within the bovine fortifiers, the protein source is different, providing whey or casein options and varying hydrolyzation of protein sources with some on the market today; however the benefits of a hydrolyzed bovine fortifier for NEC and/or allergy reduction when mixed with human milk has not been studied in good randomized controlled trials (RCT). A study by O’Connor et al. was a prospective RCT that compared bovine- vs human-based human milk fortifiers in infants <1250g, and the researchers concluded there was no statistical difference in the mortality and morbidity index between the two or a difference in feeding tolerance. Clinicians need to be knowledgeable of the complete nutrient profile of the fortification used in a study evaluation as well as the outcomes measured to choose the best for their VLBW infant growth goals.

The graph on the previous page illustrates the range of protein in the baseline milk falls throughout gestational age. It is important to know what proportion of diet is being consumed from the mother’s own milk and donor milk respectively to ensure adequate protein. Recommended intakes of 3.5-4.5 g/kg/day of protein should be the goal. Commercial products are available to safely add to human milk to achieve these intakes. Each product, however, is different, and the clinical team should evaluate the nutrients provided against the current recommendations.

### Clinical Watch-Out

The transition from total parenteral nutrition to enteral feedings of fortified human milk can create large gaps in nutrients, resulting in growth failure. From a recent examination of the limitations during the transition time, it was apparent protein was the key contributor in failure to thrive. So how can we prevent this fall in protein? To aid in discussions, we created a “How to Transition” chart for our NICU which lists all of the different milk (mom’s own milk at 1.4 g/dL, standardized DHM at 1.1 g/dL, or term HM at 0.9 g/dL).

We can use this chart to determine our protein by the base human milk profile provided at different volumes: 100 mL/kg, 120 mL/kg, up to 160 mL/kg and match with the fortification we are transitioning from TPN to human milk feedings as a goal in your unit.

### Summary

In conclusion, protein requirements are dynamic and decrease with advancing gestational age and weight. Protein energy ratio is important to determine proportionality of growth. VLBW infants benefit from human milk feeding but require a sterile, liquid, higher protein-containing fortifier and minimal dilution of human milk. For infants where there is no human milk available, higher protein containing preterm formulas should be used. The most reasonable approach to growth is to target intrauterine goals for obtaining the best developmental trajectory.

### References


### Additional Growth References


### Evaluation and Critical Thinking Tool Questions

Completing ALL fields for ALL questions is required. No credit will be awarded if incomplete.

1. The following statement about fetal growth macronutrient requirements are true except which one?
   - **A.** Protein requirement decreases as fetal growth and gestational age advance.
   - **B.** The P:E ratio, grams of protein per 100 kcal of energy, decreases as fetal growth and gestational age advance in utero.
   - **C.** Energy requirement decreases as fetal growth and gestational age advance.

2. Did you or will you change your practice(s) based on what you learned in the program?
   - **Yes**
   - **No**

3. What barriers or limitations do you anticipate when trying to implement this new information into your practice?

4a. What are the strengths and limitations of the information presented?
4b. What are the identified gaps in the information provided? (Ex. outcomes that apply to a specific patient/client population; limited data in gender, age, other races, etc.)

______________________________________
______________________________________
______________________________________

5. Human milk protein is lower in donor milk from women donating their milk to a milk bank over the first months of lactation vs. a VLBW (<1500g BW) infant mother’s milk the first weeks of lactation?

☐ True  ☐ False

For Commission on Dietetic Registration (CDR) credentialed practitioners to receive a certification of completion, you must complete the next four additional evaluation questions.

6. Which of the following statements about protein, energy and fat in the VLBW infant is NOT true?

☐ A. Dietary protein increases lean body mass.

☐ B. Fortification of human milk increases amounts of nutrients provided to the VLBW infant.

☐ C. Higher protein-containing preterm formulas vs. a standard preterm formula increases nitrogen absorption and nitrogen retention.

☐ D. Dietary protein that meets estimated requirement for VLBW infants will promote lean body mass while decreasing velocity of weight gain.

7. The following statements about human milk and human milk fortification are true except which one?

☐ A. Fat is the most variable macro-nutrient in human milk.

☐ B. Protein increases in the milk from women providing preterm milk for their VLBW infant as lactation proceeds over the first weeks of life.

☐ C. Calcium is deficient in human milk provided both in donor and mother’s own milk for the VLBW infant.

☐ D. Protein does not meet the requirement for VLBW infants in either their own mother’s milk or from donor milk.

8. Which one of the following statements is not true?

☐ A. If human milk is unavailable for a VLBW infant (own mother’s milk or donor milk), a higher protein-containing preterm formula should be used.

☐ B. Fortification of human milk increases amounts of nutrients provided to the VLBW infant.

☐ C. Higher protein-containing preterm formulas vs. a standard preterm formula increases nitrogen absorption and nitrogen retention.

9. Did you find the education valuable?

☐ Yes  ☐ No

If yes what aspects of the education was valuable?

______________________________________
______________________________________
______________________________________

If no, why not?

______________________________________
______________________________________
______________________________________

This self-study activity has been approved for one contact hour by Kendra Schreiner, 18160 Cottonwood Rd., PMB 352, Sunriver OR, an independent provider approved by the California Board of Registered Nursing, Provider #15828. Application to the CDR has been made for 1.0 CPEU credit for Registered Dietitians.

To receive credit and a certificate, go to: https://www.surveymonkey.com/r/QN7TPXQ to complete the post-test and evaluation.

Allow 30 days for your certificate. Maintain a copy for your records.