Nutritional Support in Respiratory Failure

57

David H. Adamkin

I. Introduction

Respiratory distress remains a leading cause of neonatal morbidity despite new strategies with both invasive and non-invasive mechanical ventilation. The relationship between early nutrition and its impact on severity of illness in extremely low-birthweight (ELBW) infants (birthweight <1000 g), recently studied, indicates why nutrition is so important in infants with respiratory distress syndrome (RDS).

A. Infants were divided into more critically ill (BW 734 g, mean 41 days on assisted ventilation) versus less ill (BW 842 g, mean 13 days on assisted ventilation). Using mediation framework statistical analyses data from 1366 ELBW neonates answered three questions

1. Is critical illness in the first weeks of life associated with later growth and other outcomes? Those babies defined as more ill experienced:
   a. An increase in late onset sepsis
   b. An increased risk of bronchopulmonary dysplasia (BPD)
   c. An increase in neurodevelopmental impairment
   d. Decreased growth velocity of 2 g/kg/day for weight
   e. Increased mortality
2. Is critical illness in the first weeks of life associated with early nutritional support?
   a. Those babies in the more critically ill group received less total nutritional support during the first 3 weeks of life.
   b. Over the first week of life, the less ill had total energy intake of 52.0 cal/kg/day versus the more ill babies at 42.7 cal/kg/day for the week.
   c. However, fluid intake was greater in the more ill babies versus the less ill (130 ml/kg/day compared to 123 ml/kg/day, respectively).
3. Most importantly: Is early nutritional support associated with later growth and other outcomes after controlling for critical illness in the first 3 weeks of life?
   a. It showed that nutrition could mitigate severity of illness. If the more critically ill babies received the same nutrition as the less critically ill, then for each increase of

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1 cal/kg/day in the first week of life, the following morbidities and risk of death decreased by 2 %:
(a) Necrotizing enterocolitis (NEC)
(b) Late onset sepsis
(c) BPD
(d) Death

B. The following lessons are learned from this study
1. Early nutritional decisions on ELBW are influenced by clinician perceptions of severity of illness.
2. Early Total Parenteral Nutrition (TPN) and enteral support are associated with lower rates of death, short-term morbidities, improved growth, and neurodevelopmental outcomes.
3. Early initiation of enteral nutrition was well-tolerated and associated with an earlier achievement of full enteral feeding and no increase in NEC.
4. Daily energy intake during the first 7 days of life mediates the influence of critical illness on the risk of adverse outcomes.
5. Management decisions made in the first days of life may have long-lasting effects.

C. Conclusions that can be made to optimize nutritional support for these infants
1. The first week of life is critical to promote growth.
2. Postnatal weight loss and postnatal growth failure may be limited to the first days of life in most of these infants, which emphasizes the importance of early initiation of amino acids.
3. Subsequent growth may also be optimized and catch-up growth is supported with higher protein containing human milk fortifiers, preterm formulas, and caloric-dense strategies for volume-restricted infants.

D. Nutritional strategies for these VLBW infants with respiratory distress begin within the first hours of life with stock solutions of parenteral amino acids that afford a number of benefits:
1. Limiting catabolism by achieving early positive nitrogen balance
2. Promoting growth of lean body mass
3. Reducing postnatal weight loss
4. Earlier return to birthweight
5. Preventing the co-morbidities of hyperglycemia and non-oliguric hyperkalemia
6. Synergy with early enteral feedings to maintain growth
7. Enhancing neurodevelopmental outcome

E. The guiding principle for all nutritional strategies is that undernutrition is, by definition, non-physiologic and undesirable. Any measure that diminishes undernutrition is inherently good provided that safety is not compromised.
1. Considerable evidence suggests that early growth deficits have long-lasting consequences, including short stature and poor neurodevelopmental outcomes.
2. Data linking neurodevelopmental consequences with inadequate early nutrition come from studies in preterm infants fed a preterm formula containing higher protein and energy over the first postnatal month. They had higher neurodevelopmental indices at both 18 months and 7–8 years of age compared to preterm infants fed term formula.
3. Another study demonstrated improved neurodevelopmental and growth outcomes at 18–22 months of age for ELBW infants who had higher growth velocities for weight and head circumference during their NICU hospitalization.

II. Nutritional Management

Nutritional management of these infants may be divided into three phases: exclusive TPN, transition from TPN to enteral nutrition, and finally exclusive enteral nutrition. The goal is to maintain nutrition at requirement levels during all three phases. Requirements for protein and energy are reviewed first.

Table 57.1 Enteral protein and energy requirements of preterm infants[a]

Body weight, g	Protein, g/kg/day	Energy, kcal/kg/day	P/E, g/100 kcal
500–700	4.0	105	3.8
700–900	4.0	108	3.7
900–1200	4.0	119	3.4
1200–1500	3.9	127	3.1
1500–1800	3.6	128	2.8
1800–2200	3.4	131	2.6

P/E = Ratio of protein to energy, expressed as grams of protein per 100 kcal
[a]Adapted from Ziegler, J Ped Gastro/Nutr 2007

A. Requirements for protein and energy
   1. The two methods for estimating protein intake necessary to maintain approximate in utero growth of a fetus of the same gestational age
      a. Factorial method, which includes an estimate of the amount of protein deposited in utero corrected for efficiency of absorption and deposition as well as an estimate of the inevitable urinary nitrogen losses. The main advantage of the factorial method is that it provides estimates of energy requirements, which may be applied to ELBW infants where there are no empirical estimates available.
      b. Empirical method, which determines the actual intakes that support intrauterine rates of growth and nitrogen accretion. Only the empirical method provides estimates for catch-up growth. The empirical method does not estimate energy requirements.
   2. Table 57.1 shows enteral protein and energy requirements determined by the factorial approach. Protein requirements decrease with increasing body size as does the protein to energy ratio.

B. Energy requirements are lower during parenteral nutrition compared to enteral nutrition because energy is neither utilized for thermic effect of feeding nor malabsorbed in stools.

C. Energy expenditure measurements in critically ill very low birthweight infants (VLBW, <1500 g BW) receiving assisted ventilation are extremely difficult to perform using existing measurement techniques. Collectively, studies suggest a mean energy expenditure of approximately 54 kcal/kg.
   1. Technical limitations hampered these investigations, including the minimal inspired oxygen level at which the patients could be studied.
   2. Smaller infants had lower energy intakes but lower energy expenditure of the same magnitude.
   3. Critically ill ELBW infants have limited energy stores; it is important to provide adequate energy sources early, which should also include early intravenous amino acids.
   4. In general, a total energy intake varying from 90 to 100 kcal/kg/day is sufficient for most neonates receiving mechanical ventilation as long as they are normothermic and receiving parenteral nutrition. Additional intakes ranging from 10 to 20 kcal/kg/day (120 kcal/kg/day) are indicated for infants who are premature, physically active, and receiving full enteral feedings.
   5. Intravenous carbohydrates should supply 50 % of total calories in TPN. Glucose infusion rate (GIR) will depend on the volume of fluid provided and the percent dextrose chosen. As the amount of fluid is changed, the amount of glucose infused will change. Table 57.2 provides an easy guide to determine GIR.
      a. A steady infusion of 6–8 mg/kg/min of glucose should be provided parenterally.

Table 57.2 Quick calculation rate glucose infusion rate (GIR)
Chowning R, Adamkin DH. J Perinatol. 2015;35:463

Dextrose %	5	6	7	7.5	8	9	10	11	12	13	14	15	20
mL/kg/day													
20	0.7	0.8	1.0	1.0	1.1	1.3	1.4	1.5	1.7	1.8	1.9	2.1	2.8
40	1.4	1.7	1.9	2.1	2.2	2.5	2.8	3.1	3.3	3.6	3.9	4.2	5.6
60	2.1	2.5	2.9	3.1	3.3	3.8	4.2	4.6	5.0	5.4	5.8	6.3	8.3
70	2.4	2.9	3.4	3.6	3.9	4.4	4.9	5.3	5.8	6.3	6.8	7.3	9.7
80	2.8	3.3	3.9	4.2	4.4	5.0	5.6	6.1	6.7	7.2	7.8	8.3	11.1
90	3.1	3.8	4.4	4.7	5.0	5.6	6.3	6.9	7.5	8.1	8.8	9.4	12.5
100	3.5	4.2	4.9	5.2	5.6	6.3	6.9	7.6	8.3	9.0	9.7	10.4	13.9
110	3.8	4.6	5.3	5.7	6.1	6.9	7.6	8.4	9.2	9.9	10.7	11.5	15.3
120	4.2	5.0	5.8	6.3	6.7	7.5	8.3	9.2	10.0	10.8	11.7	12.5	16.7
130	4.5	5.4	6.3	6.8	7.2	8.1	9.0	9.9	10.8	11.7	12.6	13.5	18.1
140	4.9	5.8	6.8	7.3	7.8	8.8	9.7	10.7	11.7	12.6	13.6	14.6	19.4
150	5.2	6.3	7.3	7.8	8.3	9.4	10.4	11.5	12.5	13.5	14.6	15.6	20.8
160	5.6	6.7	7.8	8.3	8.9	10.0	11.1	12.2	13.3	14.4	15.6	16.7	22.2

b. GIR (mg/kg/min) = % glucose × total mL × 100 mg ÷ 1440 (minutes/day) ÷ wt (kg) (Table 57.2).
c. Glucose intake >18 g/kg/day or >13 mg/kg/min, 60 kcal/kg/day increases CO_2 production which affects respiratory gas exchange. Excessive glucose energy induces lipogenesis, which is an inefficient process and increases energy expenditure and CO_2 production.
d. Glucose intakes at or below energy expenditure have no effect on respiratory gas exchange (CO_2 production).

D. Glucose intolerance can limit delivery of energy to the infant to a fraction of the resting energy expenditure, resulting in negative energy balance.
1. Administration of early intravenous amino acids after birth helps prevent hyperglycemia in the majority of ELBW infants. Stimulation of endogenous insulin secretion and increased insulin activity with specific parenteral amino acids explains how early amino acids prevent hyperglycemia.
2. Regular insulin may be necessary for hyperglycemia (serum glucose >180–220 mg/dL) at a GIR <4 mg/kg/min.
3. Prophylactic infusion of insulin to increase glucose utilization and energy intake in the euglycemic infant does not increase protein balance. It decreases both proteolysis and protein synthesis by approximately 20 %. It is also associated with metabolic acidosis and increases the risk of hypoglycemia.
4. Table 57.3 is a guide for using TPN.

E. Early intravenous amino acid infusion allows the transition from fetal to extrauterine life to occur with as minimal an interruption of growth and development as possible.
1. The administration of amino acids should begin within the first hours of life to avoid early malnutrition. This nutritional strategy initiates efforts at preventing growth failure in ventilated ELBW infants and neurodevelopmental outcome is enhanced.
2. A moderate increase in blood urea nitrogen (BUN) after the start of TPN is usually not adverse or a sign of toxicity; rather, it is related to metabolism of the amino acids.
3. The early administration of amino acids simulates the nutrition of the early fetus, as 50 % of amino acids provided to the fetus are used for energy. These amino acids are oxidized

Table 57.3 Parenteral nutrition guide

Nutrient	Standard	Advance by	Acceptable labs	Notes
Fluid	DOL 1–3: 80–100 mL/kg DOL 4: 100–120 mL/kg DOL 5: 130–150 mL/kg	Increase by 10–20 mL/kg/day	Na 130–145 mEq/L K 3.5–5.5 mEq/L	Adjust fluid based on I and O's and electrolytes and weight
Dextrose	Peripheral: D10–12.5 % Central: D10–15 %	Adjust to keep glucose delivery at 6–8 mg/kg/min	Glucose 45–130 mg/dL	Dextrose calories not to exceed 50 % of total calories
Lipids	3 g/kg/day	Begin with 1–2 g/kg/day and increase by 1 g/kg/day until goal is met	Triglyceride ≤200 mg/dL	Calories from fat not to exceed 40 % of total calories
Protein	3 g/kg/day	Begin with 2.0–3 g/kg and increase by 1 g/kg/day until goal is met	BUN[a] 6–40 mg/dL Creatinine 0.8–1.2 mg/dL	Calories from protein not to exceed 12 % of total calories
Cysteine	40 mg/g of amino acids			Not to exceed 100 mg/kg/day
Carnitine	8 mg/kg ≤1250 g begin on DOL 14 ≥1250 g begin on DOL 30			Carnitine is a cofactor required for the oxidation of fatty acids
Sodium	3 mEq/kg	Adjusts per labs and fluid status	Na 130–145 mg/dL	No sodium until Na level is ≤130 mg/dL
Magnesium	0.25 mEq/dL	Adjust per labs	Mg 1.7–2.1 mg/dL	Watch for increased levels in the first few days of life
Potassium	2 mEq/kg	Adjust per labs and fluid status	K 3.5–5.5 mEq/L	
Calcium	1–3 mEq/kg	Adjust per solubility and labs	Ca 7.6–10.4 mg/dL ionized Ca	Maintain a 2:1 ratio with PO_4
Phosphorus	0.5–1.5 mEq/kg	Adjust per solubility and labs	PO_4 5–7 mg/dL	Maintain a 2:1 Ca to PO_4 ratio
Chloride	1–2 mEq/kg	Adjust per labs	Cl 95–110 mEq/L	Chloride can be used to adjust acetate
Acetate	1 mEq/kg	Adjust per labs	CO_2 18–24 mEq/L	Acetate can only be manipulated by decreasing/increasing chloride
Pediatric MVI	1 mL/kg/day			Given to all infants when TPN begins
Iron	200 μg/kg			Begin if EPOGEN used or prolonged TPN (>3 weeks)
Zinc	200 μg/kg			Added to infants weighing <3 kg
Iodine				Only given to infants receiving TPN for >4 weeks (1 mcg/kg/day)
Copper[b]	30 μg/kg			Added to infants weighing ≤3 kg

(continued)

Table 57.3 (continued)

Nutrient	Standard	Advance by	Acceptable labs	Notes
Manganese[b]	6 μg/kg			Added to all TPN
Chromium	0.2 μg/kg			Added to all TPN
Selenium	2 μg/kg			Added to all TPN
Trace Pack	0.2 mL/kg			Added to all TPN
Heparin	0.5–0.7 units/mL			Maximum 1 unit/mL (100 units/kg)
Osmolarity				Not to exceed 1200 mOsm/L in a peripheral line. Adjust protein or sodium if osmolarity is too high

Adamkin, Nutritional Strategies VLBW. Cambridge Press 2009

[a]BUN: An elevated BUN may represent appropriate amino acid delivery, utilization, and subsequent oxidation, or it may represent amino acid intolerance. Modification of amino acid intake should not be based on BUN concentrations alone. A continually rising Bun value may indicate a mismatch between production and excretion

[b]Remove if evidence of TPN-associated cholestasis, D Bili. 2.2 mg/dL. Add back weekly if on long-term exclusive TPN

and generate carbon dioxide and ammonia. The ammonia is converted to urea and elevates the BUN. Therefore, with early amino acid administration, there is a rise in BUN.

4. Several controlled studies have demonstrated the efficacy and safety of amino acids initiated within the first 24 h after birth. No recognized metabolic derangements, including hyperammonemia, metabolic acidosis, or abnormal aminograms, have been observed.
5. In our experience, a minority of patients, especially those <25 weeks' gestation, may develop hyperazotemia with BUN values exceeding 50 mg/dL and occasionally the parenteral amino acid content will need to be decreased. The majority of the time the elevated BUN resolves in short order without any adjustment in dose of amino acids.
6. Amino acid dose does not directly correlate with the BUN value. An elevation in BUN is also related to acuity of illness, state of hydration, and renal function.
7. Glucose tolerance improves in infants receiving early amino acids because they stimulate insulin secretion. If TPN with amino acids is not provided soon after delivery, insulin activity falls because of an insufficiency of specific amino acids. The provision of early amino acids prevents hyperglycemia and allows the provision of more energy with less fluid because of this relationship with insulin secretion.
8. Similarly, non-oliguric hyperkalemia may be prevented. Early amino acids stimulate insulin activity and prevent intracellular energy failure. Without sufficient insulin, glucose delivery to the cell is impaired and intracellular energy failure occurs. As glucose transport is reduced at the cellular membrane level, there is a resultant decrease in Na+, K+ ATPase activity, and leakage of intracellular potassium. Therefore, non-oliguric hyperkalemia is avoided with early amino acid therapy.
9. Early TPN amino acids may be initiated with a stock solution of 4% to easily provide 2.4–3.0 g/kg/day of amino acids in the first hours of life. The dose of amino acids delivered to the infant is dependent upon the volume per kg of the 4% solution. The stock solution usually has a glucose concentration of 10%.
10. Parenteral amino acid intakes of up to 4.0 g/kg/day for ELBW infants may be used when enteral feedings are delayed or withheld for prolonged periods.
11. Intake of amino acids should not exceed 12% of total calories.

F. Intravenous lipids serve as a source of linoleic acid to prevent or treat essential fatty acid deficiency (EFAD). Larger quantities serve as a partial replacement for glucose as a major source of calories (balanced TPN).
   1. Use 20% lipid emulsion to decrease risk of hypertriglyceridemia, hypercholesterolemia, and hyperphospholipidemia.
   2. Premature infants can clear 0.15–0.2 g/kg/h. Lipid infusion hourly rate correlates best with plasma lipid concentrations. Hourly infusion should not exceed 0.15–0.20 g/kg/h. However, SGA infants and infants with sepsis may not be able to clear standard doses of intravenous lipids and will demonstrate hypertriglyceridemia.

G. Total Parenteral Nutrition
   1. TPN is the main mode of alimentation for critically ill neonates receiving mechanical ventilation, especially during the immediate neonatal period when they cannot be fed enterally.
   2. TPN is usually continued until enteral feedings are providing sufficient volume to replace TPN. The transition from TPN to enteral is critical in preventing postnatal growth failure and will be discussed below.
   3. Parenteral nutrition solutions should supply all necessary nutrients at maintenance rates, including electrolytes and minerals, to correct the common biochemical abnormalities that occur during the neonatal period (Table 57.3).
      a. Premature infants receiving parenteral nutrition are at risk of developing vitamin A deficiency because of their low hepatic stores and low serum-binding protein levels at birth.
      b. There are also significant losses of vitamin A into the delivery system used for parenteral nutrition.
         (1) In 2005, the largest randomized, controlled trial was performed in 807 premature infants with a birthweight of <1 kg who received 5000 IU of vitamin A IM three times per week for the first month of life.
         (2) The results showed a modest but beneficial effect of vitamin A supplementation in reducing the incidence of BPD.
         (3) It has become increasingly difficult to find supplies of parenteral vitamin A and its use has declined.

H. The "routine" use of intravenous lipid emulsions has not been universally accepted in critically ill ventilated ELBW infants because of potential pulmonary complications.
   1. No differences in gas exchange were found in infants randomly assigned to various lipid doses (including controls without lipids) when using lower rates and longer infusion times of intravenous lipids (<0.2 g/kg/h).
   2. For the late preterm infant with increased pulmonary vascular resistance (PVR) or any preterm infant with respiratory failure, it appears a more prudent approach with intravenous lipids should be taken.
   3. Figure 57.1 shows that the high polyunsaturated fatty acid content of lipid emulsions as linoleic acid may lead to pathways resulting in vasoactive prostaglandins, leukotrienes, and thromboxanes through their conversion from arachidonic acid. This may exacerbate pulmonary hypertension.
   4. The oxidation of fat produces less CO_2 for the same amount of oxygen consumed. This reduction in CO_2 production and its elimination may be beneficial for patients with compromised lung function. Therefore, lipids partially replace glucose as a source of energy (balanced TPN).
   5. Initiate lipids the day following birth after starting the amino acid stock solution at a dose 0.5 or 1.0 g/kg/day for ELBWs with respiratory disease.

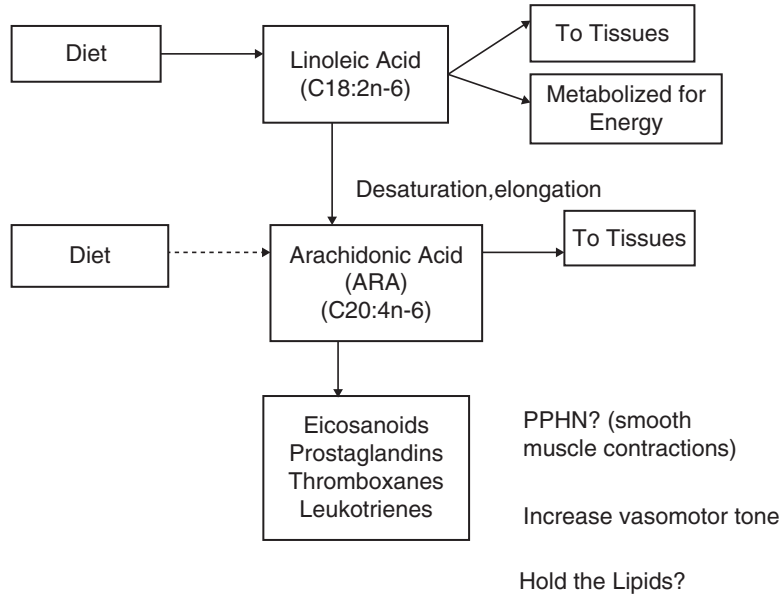

Fig. 57.1 Metabolic derivatives of linoleic acid and ARA (arachidonic acid). *Reference*: Adamkin DH. Clin Perinatol. 2006

6. Plasma triglycerides are monitored after each increase in dose, and levels are maintained <200 mg/dL.
7. Maximum lipid administration is usually 3 g/kg/day over 24 h of infusion to not exceed 0.2 g/kg/h.
8. See Table 57.3.

I. Transitioning from TPN to Enteral and the Prevention of Postnatal Growth Failure.
1. A recent study showed a high rate of postnatal growth failure among VLBW infants. The study divided nutritional management into three phases: TPN, transition, and exclusive full enteral nutrition.
2. Almost 50 % of the infants experienced growth failure and it was linked to inadequate nutrition during the transition phase from TPN to enteral nutrition.
3. The infants did not receive adequate protein during the transition from TPN to enteral nutrition. A number of suggestions can be made to avoid this period of inadequate protein and they involve both TPN amino acids and enteral feedings:
   a. Continue approximately 0.7–1.2 g/kg/day of TPN amino acids when total enteral feeds are 100–120 mL/kg/day.
   b. Fortify human milk at 40 mL/kg/day when using the human concentrated fortifier prepared from donor milk or fortifiers at 80 mL/kg/day when using the concentrated bovine fortifiers. This will increase the enteral protein during transition when the highest volumes of enteral nutrition are being fed.
   c. Determine the enteral protein that is being provided from the human milk or formula and subtract it from 4.0 g/kg/day of protein (the amount of protein that is necessary for transition with TPN at 100–120 mL/kg/day of enteral) (Table 57.4).

J. Enteral Nutrition

Enteral protein feeding requirements have been re-evaluated and emphasize the concept of protein/energy ratio and lean body mass gain. The relationships among protein and energy to promote lean body mass and limit fat accretion are shown in Fig. 57.2.

1. Additional protein is also necessary for catch-up growth. The first weeks of life are associated with an accumulated protein and energy deficit. The protein deficit is most important

Table 57.4 Protein content

Human milk and formula feeds	@ 100 mL/kg		@ 110 mL/kg		@ 120 mL/kg		@ 130 mL/kg		@ 140 mL/kg		@ 150 mL/kg		@ 160 mL/kg		@ 170 mL/kg		@ 180 mL/kg	
Breast milk																		
Breast milk (plain) (BM)	0.9	1.4	1.0	1.5	1.1	1.7	1.2	1.8	1.3	2.0	1.4	2.1	1.4	2.2	1.5	2.4 1.6	2.5	
Breast milk w/Prolacta (human) (PL)																		
BM24/ PL (80 % BM + 20 % PL + 4)	1.9	2.3	2.1	2.6	2.3	2.8	2.5	3.0	2.7	3.3	2.9	3.5	3.1	3.7	3.3	4.0	3.5	4.2
BM26/ PL (70 % BM + 30 % PL + 6)	2.4	2.8	2.7	3.1	2.9	3.3	3.2	3.6	3.4	3.9	3.6	4.2	3.9	4.5	4.1	4.7	4.4	5.0
BM28/ PL (60 % BM + 40 % PL + 8)	2.9	3.2	3.2	3.6	3.5	3.9	3.8	4.2	4.1	4.5	4.4	4.9	4.7	5.2	5.0	5.5	5.3	5.8
BM30/ PL (50 % BM + 50 % PL + 10)	3.5	3.7	3.8	4.1	4.1	4.4	4.5	4.8	4.8	5.2	5.2	5.6	5.5	5.9	5.9	6.3	6.2	6.7
Breast milk w/Enfamil HMF-AL (bovine)																		
BM22/ EHMF (50 MBM + 1 pack HMF)	1.9	2.4	2.1	2.6	2.3	2.8	2.5	3.1	2.7	3.3	2.9	3.5	3.1	3.8	3.2	4.0	3.4	4.2
BM24/ EHMF (25 MBM + 1 pack HMF)	2.6	3.0	2.8	3.3	3.1	3.6	3.4	3.9	3.6	4.2	3.9	4.5	4.1	4.8	4.4	5.1	4.6	5.4
Breast milk w/Similac HMF-HPCL (bovine)																		
BM22/ SHMF (50 MBM + 1 pack HMF)	1.8	2.3	2.0	2.5	2.2	2.7	2.4	2.9	2.5	3.2	2.7	3.4	2.9	3.6	3.1	3.8	3.3	4.1

(continued)

Table 57.4 (continued)

Human milk and formula feeds	@ 100 mL/kg		@ 110 mL/kg		@ 120 mL/kg		@ 130 mL/kg		@ 140 mL/kg		@ 150 mL/kg		@ 160 mL/kg		@ 170 mL/kg		@ 180 mL/kg	
BM24/ SHMF (25 MBM + 1 pack HMF)	2.4	2.8	2.7	3.1	2.9	3.4	3.1	3.7	3.4	4.0	3.6	4.2	3.9	4.5	4.1	4.8	4.4	5.1
Breast milk w/30 kcal/oz formula (bovine)																		
BM22 (80 % BM + 20 % SSC30)	1.3	1.7	1.5	1.9	1.6	2.1	1.7	2.2	1.8	2.4	2.0	2.6	2.1	2.8	2.2	2.9	2.4	3.1
BM24 (60 % BM + 40 % SSC30)	1.7	2.0	1.9	2.2	2.1	2.4	2.3	2.7	2.4	2.9	2.6	3.1	2.8	3.3	3.0	3.5	3.1	3.7
BM27 (30 % BM + 70 % SSC30)	2.4	2.5	2.6	2.8	2.8	3.0	3.1	3.3	3.3	3.5	3.6	3.8	3.8	4.0	4.0	4.3	4.3	4.5
Premature formula (regular or high protein)																		
24 cal	2.4	2.8	2.6	3.0	2.9	3.3	3.1	3.6	3.4	3.9	3.6	4.1	3.8	4.4	4.1	4.7	4.3	5.0
27 cal (50 % 24 cal + 50 % 30 cal)	2.7	2.9	3.0	3.2	3.2	3.5	3.5	3.7	3.8	4.0	4.1	4.3	4.3	4.6	4.6	4.9	4.9	5.2
30 cal	3.0		3.3		3.6		3.9		4.2		4.5		4.8		5.1		5.4	
Hypoallergenic formulas																		
Extensively hydrolyzed 24 cal	2.2		2.5		2.7		2.9		3.1		3.4		3.6		3.8		4.0	
Elemental 24 cal (all brands)	2.2	2.5	2.4	2.7	2.7	3.0	2.9	3.2	3.1	3.5	3.3	3.7	3.6	4.0	3.8	4.2	4.0	4.5

Abbott Nutritional Products
Mean Johnson Nutritionals
Adapted from American Academy of Pediatric Nutrition Handbook, 6th Edition
Prolacta Biosciences California

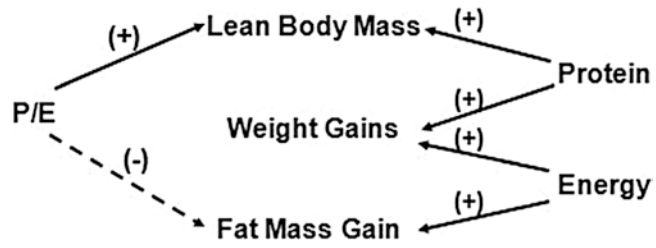

Fig. 57.2 Impact of protein/energy ratio (P/E) on body composition

Table 57.5 Revised recommended protein intake and protein–energy ratio for premature infants according to postconceptional age and the need for catch-up

	Without need of catch-up growth	With need of catch-up growth
26–30 weeks PCA: 16–18 g/kg/day LBM 14 % protein retention	3.8–4.2 g/kg/day PER: ±3.0	4.4 g/kg/day PER: ± 3.3
30–36 weeks PCA: 14–15 g/kg/day LBM 15 % protein retention	3.4–3.6 g/kg/day PER: ±2.8	3.6–4.0 g/kg/day PER: ± 3.0
36–40 weeks PCA: 13 g/kg/day LBM 17 % protein retention	2.8–3.2 g/kg/day PER: 2.4–2.6	3.0–3.4 g/kg/day PER: 2.6–2.8

PCA postconceptual age, *LBM* lean body mass, *PER* protein/energy ratio
PER = gram of protein/100 cal
Based on Rigo, in Tsang, J Peds, Nov 2006;149:S80–88

and must be addressed to allow catch-up growth to occur and improve both growth and neurodevelopmental outcome.

2. An increase in the protein/energy ratio of feeding is mandatory to improve the lean body mass accretion and to limit fat mass deposition.
3. Human milk plays a significant role in promoting lean body mass and avoidance of maldistribution of adipose tissue.
4. Table 57.5 shows recommendations for protein intake and protein/energy ratio for preterm infants according to postmenstrual age and need for catch-up. Table 57.1 presents requirements based on the reference fetus. These may be taken together to address both growth and the need for catch-up growth.
5. Preterm formulas and supplemented human milk provide protein intakes of 3.6–4.8 g/kg/day at an energy intake of 120 kcal/kg/day. The "higher" protein preterm formulas with P/E ratio of 3.3–3.6 instead of the 3.0 in standard preterm formula will promote more lean body mass accretion when meeting a protein requirement of 4.0 g/kg/day than will the standard preterm formulas which must be fed at higher volumes and excessive energy to achieve 4.0 g/kg/day.
6. The higher protein levels found in the concentrated liquid bovine fortifiers and the high-protein preterm formulas allow higher protein to meet catch-up growth requirements with less energy.

K. Enteral feeding guideline practicum.

1. Begin minimal enteral/trophic (<25 mL/kg/day) feedings by the second day of life in ELBW infants after they are physiologically stable, unless contraindications exist.
2. Human milk is the definitive preference for feeds. This includes the use of donor human milk.
3. Advancing feeds in a safe standardized fashion is helpful.
   a. Each institution should have guidelines for initiation of feedings, advancement of feedings, and for stopping feeding if intolerance is identified.

b. Any situation associated with gut hypoxia or decreased intestinal blood flow may contraindicate initiation of enteral feeding until the situation resolves.
c. Nutrition advances of ≤20 mL/kg/day do not increase the incidence of NEC.
d. Dilute formulas and dilute human milk fail to provide sufficient energy intake and fail to stimulate motor activity of the GI tract and should not be used.
e. Slow bolus feeds ("compressed"), those lasting at least 30 min up to an hour or two, may be used, particularly in infants with feeding intolerance and gastroesophageal reflux.
f. Gastric residuals do not indicate NEC, or impending NEC; other signs of NEC are much more important. Clinical exam and thorough evaluation of the infant are critical when feeding intolerance is diagnosed.
g. In fact, gastric residuals may have a protective function, serving as markers of gut maturation, and help the clinician advance feeding volumes based on the volume of the residuals.

4. Human milk provides substantial benefits for the preterm infant and is the feeding of choice and may include the use of donor human milk.
   a. It should be encouraged unless contraindications exist.
   b. The substantial benefits of human milk for the preterm infant and the importance of a mother's contribution should be emphasized.
   c. Breast pumping and manual expression should be initiated within the first 6 postpartum hours.
   d. The value of colostrum should be emphasized. Fresh colostrum should be collected and used in first feeds.
   e. Lactation consultations should occur, ideally, prenatally, or on DOL 1, or when mother is available (e.g., in cases where baby has been transferred from another hospital).
5. Human milk fortification is necessary in ELBW infants and most VLBW infants to provide optimal nutrient intake.
   a. Since the composition of mother's milk varies greatly from one mother to another, and the concentration of nutrients in preterm milk changes over time, it is difficult to determine the actual intake of nutrients, particularly protein, that the VLBW infant is receiving.
   b. To confer the potential non-nutritional advantages and provide optimal nutrient intake, human milk should be supplemented or fortified, with protein, calcium, phosphorus, vitamin D, and sodium.
   c. Human milk alone does not meet the nutritional needs of VLBW infants. Assuming a protein requirement for these infants of between 4.0 and 4.3 g/kg/day, a premature infant, taking his or her own mother's milk at full volume, would receive approximately 2.5 g/kg/day. If receiving donor human milk, which has a lower protein than mother's own milk, an infant would receive only approximately 1.5 g/kg/day. It is critical in managing human milk fortification to meet the protein requirement.
   d. Regardless of donor or mother's own milk, the calcium and phosphorous provided by human milk does not come close to meeting the required calcium and phosphorous for growth and bone mineralization.
   e. The protein level assumed to present in milk from a mother delivering a preterm infant is 1.5 g/dL. However, as lactation progresses and in the same window that a fortifier is being provided, the protein level is falling. Donor human milk provides 0.8–1.0 g/dL.
   f. The high variability in nutrient content in human milk makes meeting nutrient requirements inherently imprecise.

g. Milk composition varies with volume of milk expressed, the type of milk obtained (foremilk or hindmilk), and the stage of lactation.
h. Sterile bovine concentrated liquid fortifiers which may be added to human milk have been developed providing more protein than the non-sterile powdered bovine fortifiers. The Centers for Disease Control and Prevention no longer recommend powdered formulas and fortifiers for preterm infants because of the risk of bacterial contamination and subsequent bacteremia. There is also a human milk fortifier prepared from concentrated donor human milk and provides additional protein, energy, calcium, and phosphorous. It provides an exclusive human milk diet.
i. Earlier fortification (40 mL/kg/day for human concentrate and 80 mL/kg/day for bovine concentrated liquid) is important to prevent protein deprivation during transition from TPN to enteral feedings.
j. Table 57.4 shows the protein intake of various preterm formulas and human milk fortifiers. The primary goal with human milk fortification is to support postnatal growth rates above the intrauterine growth rate of 15 g/kg/day to prevent malnutrition and allow catch-up growth.
k. To achieve this goal of growth, there must be an adequate balance between protein and energy.

L. Additional studies: Human milk versus formula feedings and BPD
1. In this study, we looked at the influence human milk vs. formula intake had on growth and outcomes in VLBW infants receiving predominantly human milk or more than 50 % of their diet the first year of life vs those predominantly formula fed.
a. Infants who received predominantly formula were larger by all anthropometrics at 6 months of life.
b. However, duration of human milk feeding correlated with significantly improved mental developmental index scores at 12 months of age after controlling for home environment and maternal intelligence.
c. Those receiving more human milk had improved visual acuity despite the fact that the formula was supplemented with DHA.
d. Those predominantly human milk-fed also had less post-discharge morbidity, including readmission to the hospital.
e. For those infants predominantly fed human milk, who also had BPD, there was a significant advantage in mental developmental scores (11 points) vs. those receiving predominantly formula.
2. Another study that looked at donor human milk versus mother's own milk or preterm formula for growth and outcomes made an observation that was surprising.
a. Those infants who received human milk had a significant reduction in the occurrence of BPD.
b. Many infants, because of poor growth on donor human milk, crossed back over to the preterm formula group.
c. These two studies demonstrate how important human milk fortification is to achieve immunologic benefits associated with human milk and also achieve catch-up growth.

III. Nutritional Management of BPD

Nutritional management of infants with BPD plays a role in prevention, amelioration, and recovery for these patients. There are no specific evidence-based guidelines for the nutritional management of infants with BPD. The best nutritional practices for any VLBW infant apply to these infants, but there are specific strategies to consider for those with a high likelihood of developing BPD or those with established BPD.

Table 57.6 Nutrient comparisons per 100 kcal formula

Nutrient	PTF 24	PTF 24 high protein	PTF 27 (PTF 24HP + PTF 30)	PTF 30	30 kcal (PTF 24 + Polycose® + MCT)
Protein (g)	3.0	3.3	3.15	3.0	2.2
Fat (g)	5.43	5.43	6.09	6.61	5.53
CHO (g)	10.3	10.0	8.9	7.73	10.73
Ca (mg)	180	180	180	180	133
P (mg)	100	100	100	100	74
Vitamin D (IU)	150	150	150	150	122
OSMOL	280	280	305	325	N/A
Volume (mL)	124	124	111	99	100

Abbott Nutritional Products
Mean Johnson Nutritionals
Adapted from American Academy of Pediatric Nutrition Handbook, 6th Edition

A. Caloric-dense enteral feedings (>24 kcal/oz) are intended for use in critically ill VLBW infants unable to tolerate sufficient feeding volumes (volume restricted) to meet their needs for growth using standard premature formulas or standard fortified breast milk. The feedings should promote proportional growth, which is more important than absolute weight gain.
   1. Over half of the infants with BPD in the NICHD growth observation study grew in the lowest quartile at 12 g/kg/day from return to birthweight to discharge and had the worst growth and developmental outcomes at 18–22 months.
   2. Table 57.6 shows the nutrient comparisons among preterm formulas, and caloric-dense formulas.
   3. Before the advent of ready-to-feed 27 and 30 cal per ounce formulas, many clinicians would devise their own "recipes" to make a 30 cal milk by adding glucose polymers and MCT oil to a base 24 cal preterm formula. The resultant P/E ratio of this was 2.2 g protein/100 cal of energy. This will only promote the growth of fat and not lean mass but was the only way to make caloric-dense recipes until the new formulas and human milk fortifiers became available.
   4. Using the ready-to-feed 30 cal per ounce milk, a protein of 3.0 g/kg/day can be reached even at 100 mL/kg/day. At 130 mL/kg/day, the protein is 3.9 g/kg/day. Using the 27 cal/oz formula at 130 mL/kg/day one can provide 3.5 g/kg/day of protein with appropriate energy.
   5. There is also a caloric-dense strategy for the infant with BPD on exclusive human milk with the human milk fortifier. Using the 28 or 30 cal per ounce human donor concentrated product, a volume of 120 mL/kg/day will provide approximately 4.0 g/kg/day.
   6. In a study more than 10 years ago including 200 ELBW infants, we diagnosed BPD in 45 % of them with gestational age of 25 weeks and BW 739 g using the oxygen requirement and X-ray findings at 36 weeks' PMA to make the diagnosis.
   7. Their nutritional data included the receipt of less protein and energy over the first 14 weeks of life with more TPN than those ELBW infants who did not develop BPD.
   8. Their growth rate was slower than those who did not develop BPD and they were more likely to develop postnatal growth failure.
   9. Ten years later we examined another cohort of ELBW infants who developed BPD and discovered significant differences in growth and nutritional management had taken place for these infants over 10 years.
   10. The latest cohort from 2012 showed that two thirds of ELBW infants with BPD were growing at or above the fetal weight gain rate of 15 g/kg/day. These infants were approximately 800 g BW and 26 weeks' gestation. In fact, 40 % grew at 18 g/kg/day which matches

the goal for catch-up growth and improved neurodevelopmental outcome according to the NICHD growth observation study.

11. Those managed 10 years before had a mean postnatal weight loss of 18.5 % vs 10 % in the later group. The comparison of time to return to birthweight decreased from 20 days to 10 days, respectively.
12. There was initiation of amino acids at 3 h in the most recent cohort of ELBW with BPD vs 2 days of life for those 10 years before. Protein intake and growth velocity were greater for the later cohort.
13. The major difference in nutrition responsible for these differences over the 10 years included early initiation of amino acids, earlier initiation of enteral feedings with advancing to full feeds sooner, expanded use of human milk, using higher protein preterm formulas, and the liberal use of caloric-dense feedings for babies who were volume restricted on diuretics as part of their management for their BPD.

B. Post-discharge nutrition is another strategy with nutrient-enriched formulas and multi-nutrient fortifiers for human milk to promote catch-up growth in ELBW infants with BPD.
   1. The first postnatal year provides an important opportunity for human somatic and brain growth to compensate for earlier deprivation.
   2. Available data suggest that many smaller/sicker preterm infants are in a state of suboptimal nutrition at the time of discharge and are frequently below the tenth percentile on the growth curve (postnatal growth failure).
   3. These infants have also accumulated significant nutrient deficits for protein, energy, calcium, and phosphorus by the time of discharge.
   4. Nutrient-enriched formula for preterm infants after hospital discharge (post-discharge formula [PDF]) is generally intermediate in composition between preterm and term formulas.
   5. Compared to term formula (TF), PTF contains an increased amount of protein with sufficient additional energy (22 cal/oz) to permit utilization.
   6. PDF contains extra calcium, phosphorous, and zinc, which are necessary to promote linear growth.
   7. Studies demonstrated that the use of either PTF or PDF after discharge in preterm infants results in improved growth, with differences in weight and length persisting beyond the period of intervention.
   8. Such findings suggest that nutrition during the post-discharge period may have longer-term effects on growth trajectory.
   9. Several non-randomized controlled trials have shown that breast-fed infants do not grow as well as their formula-fed counterparts after discharge.
   10. Options include replacing some breast feeds with nutrient-enriched formula feeds or fortifying expressed breast milk.
   11. In a post-discharge feeding study in preterm infants receiving at least 80 % of their daily feedings as human milk, half of the feedings were supplemented with four packets of a powdered multi-nutrient human milk fortifier for 12 weeks. Infants demonstrated improved growth at 1 year. Also noted was the fact that for the smaller babies in the study, head circumference growth was positively affected.
   12. An important study looked at growth and body composition in preterm infants discharged on a nutrient-enriched formula or standard term formula and the infants were fed these two different diets through 6 months' corrected age.
   13. Results included the observations that all of the AGA infants demonstrated catch-up growth on the higher protein discharge formula.

14. The most important advantages for the preterm infant fed nutrient-enriched formula were the combination of increased fat-free mass at 6 months of age and a larger head circumference. Those infants <34 weeks or <1800 g at birth should be discharged on a PDF to gain these advantages for the formula-fed infant.
15. Follow anthropometrics carefully post-discharge and maintain the PDF strategy for 9–12 months' corrected age, especially for VLBW infants who were the most ill and those that developed BPD.
16. VLBW infants discharged on human milk require an individualized approach based on anthropometrics and whether or not there is evidence of osteopenia of prematurity as they approach discharge.
17. Human milk-fed babies with growth failure or evidence of osteopenia at discharge may receive fortification by alternating breast feedings with the PDF or other fortification strategies reviewed in the human milk and caloric-dense sections.
18. Growth post-discharge should be monitored with the CDC, NCHS Growth Curves, and not the IHDP Curve.

IV. Feeding Disorders
   A. Feeding disorders may develop in infants treated with mechanical ventilation, impairing long-term growth, nutritional status, and developmental outcome.
   B. In general, feeding disorders are first recognized after the patient is extubated and then fails multiple attempts to be orally fed.
   C. Oropharyngeal hypersensitivity, defined as a pathologic aversion to oral stimulation, is evidenced by an avoidance behavior to the introduction of any type of oral feeding.
      1. This disorder results from prolonged endotracheal intubation, frequent oral and nasal pharyngeal suctioning, prolonged use of nasal and oral gastric feeding tubes, and the use of nasal cannula oxygen at high flow rates.
      2. Delays in the critical time to learn how to feed may result in the loss of rooting and sucking reflexes and contribute to the feeding problem.
      3. The treatment of oropharyngeal hypersensitivity includes a program of desensitization of the infant's oral pharynx with positive stimulation and attempts to minimize negative stimuli. The latter implies replacement of nasogastric and orogastric feeding tubes with gastrostomy tubes and the use of tracheostomy instead of continuing endotracheal intubation if mechanical ventilation needs to be continued.
   D. Swallowing disorders may also be observed after prolonged courses of mechanical ventilation.
      1. These disorders may affect the three phases of swallowing: oral, pharyngeal, and esophageal.
      2. Swallowing disorders can be seen in association with congenital anomalies, such as micrognathia, choanal atresia, cleft lip and palate, tracheoesophageal fistulas, and laryngeal clefts. They can also be acquired and are seen in infants with severe laryngotracheomalacia, BPD, and neurologic insults that result in cerebral palsy.
      3. Assessment of swallow dysfunction includes a comprehensive history, physical examination, and evaluation of neurologic, pulmonary, and gastrointestinal status. Videofluoroscopy is the radiologic evaluation of choice to detect abnormalities in the different phases of swallowing and the risk of aspiration.
      4. Treatment depends on the signs, etiology, and feeding history and usually requires special therapy in five categories: positioning, oral sensory normalization, modification of food consistency, adaptation of feeding devices, and oral feeding exercises.

E. Pathologic gastro-esophageal reflux (GER) may be seen in infants who received mechanical ventilation, especially in those who develop BPD, neurologic insults resulting in cerebral palsy, and tracheomalacia or subglottic stenosis from prolonged endotracheal intubation.
   1. The clinical presentation of pathologic GER includes the presence of frequent gastric residuals, episodes of vomiting, failure to thrive, and aspiration pneumonia.
   2. Medical management has included antacids, H_2 receptor antagonists, and proton pump inhibitors. These, however, have been linked to the development of NEC. They are not used in the NICU during the first weeks or months of intensive care.
   3. In severe cases of GER that are refractory to medical management, Nissen fundoplication may be indicated.

Suggested Reading

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