NICU Diet, Physical Growth and Nutrient Accretion, and Preterm Infant Brain Development

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Education Gaps

1. The NICU diet comprises many macro- and micronutrients, which are critically important to support early brain development in the preterm infant.
2. Measurement and optimization of linear growth and fat-free mass gains may allow for improvement in both cardiovascular health and neurodevelopment.
3. Non-nutritional factors, such as inflammation, influence nutrient accretion, physical growth, and long-term outcomes.

Abstract

Half of very preterm infants experience neurodevelopmental impairments after NICU discharge. These adverse outcomes result in part from abnormal brain development and injury that occur during the NICU hospitalization. Although many factors influence infant brain development, nutritional determinants are of particular interest because they are highly modifiable within clinical care. Physical growth of preterm infants in the NICU continues to lag behind the reference fetus, suggesting reduced nutrient accretion during a critical period for brain development. Nutrient accretion is driven by intake of specific nutrients such as macro- and micronutrients as well as non-nutritional factors such as systemic inflammation. Most often, anthropometric indicators, such as weight, length, and head circumference, are used as proxies for nutrient accretion. A limitation of weight is that it does not differentiate the healthy growth of specific organs and tissues from excess fat accumulation. Body length provides information about skeletal growth, and linear growth stunting predicts neurodevelopmental impairment. Head circumference is only a crude proxy for brain size. More recently, application of new technologies such as air displacement plethysmography and magnetic resonance imaging has allowed the direct estimation of lean tissue accretion and brain growth in the NICU. These newer techniques can facilitate research to improve our understanding of the links among the NICU diet, inflammation, physical growth, and brain development. These new measures may also be relevant within clinical care

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ABBREVIATIONS

ARA	arachidonic acid
DHA	docosahexaenoic acid
LA	linoleic acid
MRI	magnetic resonance imaging

to identify infants who may benefit from specific interventions to enhance nutrient accretion and brain development.

Objectives After completing this article, readers should be able to:

1. Identify specific components of the NICU diet that are linked to improved neurodevelopmental outcomes.
2. Recognize that routine monitoring of linear growth and body composition may facilitate optimized nutritional care and improve long-term health and developmental outcomes.
3. Specify non-nutritional factors such as inflammation that inhibit nutrient accretion, reduce physical growth, and may contribute to poorer neurodevelopmental outcomes.

BACKGROUND

Despite substantial improvements in survival for very preterm infants in the past 3 decades, these infants remain at heightened risk for impaired neurodevelopment compared with their healthy full-term counterparts. Adverse neurodevelopmental outcomes have many determinants ranging from prematurity-associated brain injury, systemic inflammation and infection, and social factors, but nutritional determinants are of particular interest because they are highly modifiable in the context of clinical care.

A critical window of opportunity for optimizing nutritional care exists during the NICU hospitalization. During this 2- to 4-month period, the brain undergoes extensive structural development including a 3-fold increase in size, formation of all gyri and sulci, the establishment of connections between neurons, and the early stages of myelination. To proceed normally, these developmental processes depend on the availability of macro- and micronutrients. Drawing on animal models of undernutrition in the third trimester and on human interventional and observational studies, we recognize 1) the cause-and-effect link between early-life undernutrition and altered brain development; and 2) that altered brain development resulting from undernutrition during this critical period can have an irreversible effect on functioning. (1)(2)

Despite our understanding of the critical importance of nutrition in the NICU, growth outcomes among preterm infants born in the United States continue to lag behind the reference fetus, (3) suggesting gaps in knowledge and translation. The NICU diet must compensate for nutrient delivery across the placenta, which is prematurely interrupted at the time of birth. Once delivered and absorbed, nutrients accrete into various body compartments including the skeleton, skeletal muscles, organs (including the brain), and adipose tissue. Importantly, nutrient accretion is driven not just by diet but also by non-nutritional factors such as inflammation and physical activity.

The concept of nutrient accretion is helpful in considering approaches to improve nutritional assessment and care in the NICU. To assess the adequacy of nutrient accretion, infant weight at NICU discharge or weight gain from birth to discharge is most commonly used as a proxy. However, weight does not differentiate skeletal, muscle, and organ compartments from adipose tissue, and therefore may be limited in its ability to capture information about "healthy growth" that is most relevant to the developing brain. Gain in body length (linear growth) reflects skeletal growth, and stunting of linear growth during infancy predicts later neurodevelopmental impairment, (4) demonstrating its relevance to neonatal brain development. Direct estimation of body composition (fat mass, fat-free mass) with air displacement plethysmography is now possible for small infants, and emerging research suggests that fat-free mass predicts neonatal brain function better than fat mass. (5) Quantitative magnetic resonance imaging (MRI) can be performed in the NICU to measure the volume of nutrition-sensitive brain regions and provide information about developing microstructure in relation to diet composition. Electroencephalography-based measures, such as visual evoked potentials,

assess nutrient-sensitive cognitive functions as early as a few months after NICU discharge.

In this review, we will summarize existing and emerging literature on the role of the NICU diet in promoting optimal brain development. We will further develop the concept of nutrient accretion in various body compartments and the relevance of this concept to our understanding of how nutrition influences the developing preterm brain. We will share exciting developments in the field of neonatal nutrition and brain development that we hope will spark further research and inform improvements in nutritional assessment and care.

PRETERM INFANT DIET: SOURCES OF VARIATION AND ASSOCIATIONS WITH OUTCOMES

The preterm diet comprises parenteral nutrition solutions and lipid emulsions, infant formula, maternal milk and pasteurized donor human milk, multicomponent and modular human milk fortifiers, and micronutrient supplements. The nutrient composition of infant formula and fortifiers is standardized, whereas maternal and pasteurized donor human milk contain variable amounts of nutrients. (6) An infant's intake of specific nutrients depends not just on the content but also on the volume delivered. Both observational studies and randomized trials inform our understanding of how the NICU diet influences short-term brain development and later functional outcomes (Table).

Macronutrients

Macronutrient fortification is a cornerstone of nutritional support for the hospitalized preterm infant. Inspired in part by animal studies that revealed permanent alterations in brain structure and function following pre- and postnatal malnutrition, Lucas and colleagues undertook a series of large, multicenter randomized trials almost 3 decades ago. (7) Those studies established that preterm formula enriched with calories, protein, and other nutrients was superior to standard term formula as well as donor human milk (8) in promoting weight gain, linear growth, and head growth during the NICU hospitalization. Further, among infants fed formula only (no maternal milk), those who had received preterm formula in the NICU had ~1/3 standard deviation higher cognitive scores (not statistically significant) and ~1 standard deviation higher motor scores at 18 months' corrected age compared with infants fed standard term formula. (7)

In a follow-up study, when participants were 15 to 16 years old, those who had received the high nutrient preterm formula had higher verbal IQ scores and larger caudate size on MRI than those who received the standard nutrient (term formula or donor breast milk) diet. (9)(10)(11) Despite the limitations of those studies, such as low cohort retention and post hoc comparisons, the results suggest that nutrient-enriched infant formula provided in the NICU has a lasting impact on brain development. Regarding human milk diets, multicomponent fortification is effective in promoting weight gain, linear growth, and head growth in the NICU

TABLE. **Physical Growth and Nutrient Accretion Measures in the NICU that Predict Later Neurodevelopmental Outcomes**

MEASURE	ADVANTAGES	DISADVANTAGES
Weight gain	Inexpensive Easy Accurate	Does not differentiate lean mass accretion from excess fat deposition Correlates with brain growth but nonspecific
Linear growth	Inexpensive Correlates with skeletal growth, may be better proxy for brain growth than weight gain	Requires special equipment (recumbent length board) and training for accuracy
Head growth	Inexpensive	Requires training for accuracy Crude proxy for brain growth
Fat-free mass	More specific for lean mass accretion than weight gain or linear growth May be better predictor of outcomes	Requires specialized, expensive equipment (air displacement plethysmography)
Brain magnetic resonance imaging	Accurate estimate of overall brain size and size of nutrient-sensitive brain regions Information about brain microstructure	Requires specialized, expensive equipment

but data are lacking regarding long-term benefits to neurodevelopment. (12) With both formula and human milk, it is difficult to discern whether macronutrient fortification alone is responsible for growth benefits, because additional minerals and micronutrients are typically provided as well.

Recent studies have taken advantage of MRI as a window into the impact of macronutrient intake on structural brain development in the NICU. In one such study, serial imaging of 49 infants born at less than 30 weeks' gestation revealed that higher intakes of energy and protein in the first 2 weeks after birth were predictive of greater overall brain growth; enhanced growth of nutrition-sensitive structures, such as the basal ganglia and cerebellum; and greater maturation of early myelinating white matter tracts. (13) Given the timing of the nutritional exposure during just the first 2 postnatal weeks, this study suggests that both parenteral and enteral macronutrient provision are important to support early brain development. Another MRI study of 131 infants born at less than 31 weeks' gestation found that cumulative enteral fat and energy intakes during the first month in the NICU predicted larger cerebellar, basal ganglia, and thalamus volumes at term equivalent age, (14) suggesting enhanced growth of these structures. Higher cumulative energy intake was also associated with a measure of microstructure in an early myelinating white matter tract. Taken together, these neuroimaging studies support the concept that protein and energy intakes in the NICU influence brain development during a critical period.

Long Chain Fatty Acids

During gestation, long chain fatty acids are actively transported across the placenta, supporting high levels of fetal accretion during the third trimester. Arachidonic acid (ARA) and docosahexaenoic acid (DHA) are transferred preferentially compared with linoleic acid (LA) and α-linolenic acid. ARA plays important roles in cell growth and differentiation, both ARA and DHA concentrate in the central nervous system, and DHA is highly concentrated in the retina. Preterm infants rely on exogenous fatty acid provision after the interruption of maternal-fetal transfer at the time of preterm birth. (15) ARA and DHA levels fall rapidly after birth whereas LA levels increase, likely because of a different balance of fatty acids in parenteral nutrition compared with transplacental transfer. (16) A recent MRI study highlights the potential importance of these changing fatty acid levels for brain development; higher red blood cell DHA levels near birth and near term were associated with larger brain tissue volumes at term and these larger brain tissue volumes in turn predicted better cognitive and motor scores at 36 months. (17) In contrast, higher LA levels predicted lower white matter volumes. Somewhat unexpectedly, given the strong biologic rationale, randomized trials of DHA- and ARA-fortified formula have yielded little evidence for benefits to neurodevelopment. (18) Despite this lack of evidence, commercially available preterm formulas in the United States are currently fortified with DHA and ARA.

In human milk, DHA is highly variable and its content depends on maternal diet; therefore, maternal supplementation during lactation is a strategy to increase infant intake. In the DHA for the Improvement of Neurodevelopmental Outcome trial (n=657 infants <33 weeks' gestation), lactating mothers were randomized to DHA supplementation versus placebo groups, which resulted in preterm infants being fed high (1% total fatty acids) or standard (0.3% total fatty acids) maternal milk diets. At 18 months, there was no overall difference in Bayley cognitive scores between high versus standard DHA groups but in a preplanned analysis stratified by sex, scores were ~1/3 standard deviation higher among girls fed the high DHA diet versus standard; there were no differences in scores by diet among boys. (19) Although these findings suggest a benefit of DHA supplementation in the NICU on 18-month neurodevelopmental outcomes (at least among girls), additional follow-up at school age did not reveal any persistent benefits. (20) Addition of long chain fatty acids to human milk fortifier is another strategy to increase infant intake but has not been rigorously tested in clinical trials with respect to neurodevelopmental outcomes.

Zinc

Zinc is an essential micronutrient. (21) In the brain, zinc plays key roles in neuronal proliferation, differentiation, and signaling, (22) and is involved with the processes controlling myelination. (23) Altered zinc balance in the brain contributes to neuronal (24) and oligodendrocyte death, (25) suggesting its relevance to preterm brain injury. Preterm infants are vulnerable to zinc deficiency because of their limited stores at birth and compromised absorption. (26)(27) Zinc content varies 10-fold in human milk (28) and some women have extremely low levels of zinc in their milk because of a genetically determined reduction in zinc transfer by the mammary gland. (29)(30) Other sources of zinc in the preterm diet include parenteral and enteral supplements, preterm formula, and multicomponent human fortifier. Infants with severe zinc deficiency have a typical skin rash, failure to thrive, and irritability, but infants with mild or moderate deficiency may not have any clinical symptoms. (26)

Current dietary guidelines suggest an intake of 1 to 3 mg/kg per day for preterm infants, (31)(32)(33) but these

guidelines are based on limited data. In one randomized trial, more zinc (~10 mg/day) was beneficial for linear growth, (34) and in another study, a similar dose reduced morbidity and mortality. (35) Despite these findings suggesting that higher zinc intake may be beneficial for short-term outcomes, no study of very preterm infants in a high-resource setting has examined zinc in relation to long-term neurodevelopment. Because excess zinc intake may interfere with absorption and function of other micronutrients such as copper, (33) an increase in supplementation should be undertaken cautiously. Overall, despite the biological importance of zinc within the developing brain, many data gaps exist with respect to optimal zinc intake for the preterm infant in the NICU.

Choline

Choline is another essential nutrient that plays important roles in the developing brain. (36) Choline is a precursor of the neurotransmitter acetylcholine and is required for the formation of phosphatidylcholine and sphingomyelin. Choline also influences DNA and histone methylation, which are epigenetic processes that regulate gene expression. Numerous animal studies have demonstrated benefits of choline supplementation during pregnancy on offspring brain development and function, and a few randomized trials of prenatal choline supplementation have demonstrated analogous benefits in humans. (37) In utero, the placenta actively transports choline and thereby provides high amounts of choline to the fetus. In contrast, in human milk, choline is present in variable amounts, and levels are lower in preterm than in full-term milk. (38) Choline is added to preterm infant formula and to some but not all human milk fortifiers. The postnatal fall in plasma choline suggests that the preterm diet does not provide enough choline to match fetal accretion for all infants. (39) However, very little is known about the optimal intake of choline for hospitalized very preterm infants.

Human Milk

Fortified human milk is the recommended diet for virtually all preterm infants. (40) In addition to medical benefits, such as the prevention of necrotizing enterocolitis, a maternal milk diet in the NICU is associated with enhanced brain development, as seen on MRI, and with improved neurodevelopmental outcomes at school age. (41) Possible mechanisms for this beneficial effect include nutrients and non-nutrient bioactive factors that are present in human milk but not formula, as well as differences in parental caregiving. Paradoxically, fortified human milk–fed preterm infants gain less weight and have less head growth than formula-fed infants, suggesting lower nutrient accretion despite routine fortification. (42) Human milk–fed preterm infants also accrete relatively less lean mass by the time of NICU discharge than formula-fed infants. (43) One possible reason for these differences in physical growth is that human milk is highly variable in its nutrient composition and may provide cumulatively less protein and/or energy over time for some infants. Pasteurized donor human milk ("donor milk") is even lower in protein than maternal milk and little is known about its micronutrient content. Current human milk fortification strategies presume typical protein, energy, and other nutrient levels in human milk, and do not explicitly differentiate maternal from donor milk. Further, protein and fat levels are uncorrelated, (44) meaning that some infants may receive a high-energy, low-protein diet that encourages the deposition of excess adiposity, whereas others may receive a high-protein diet that encourages accretion of lean mass. Overall, fortified human milk is the recommended diet in the NICU and appears to confer benefit for neurodevelopmental outcomes. However, current fortification practices may not be adequate to support physical growth for all infants because of the variability of nutrient composition in human milk; the extent to which these differences in macronutrient intake influence the developing brain are unknown. Studies of individualized fortification using point-of-care milk analysis in the NICU may be helpful in clarifying short- and long-term effects on brain development.

ASSESSMENT OF NUTRIENT ACCRETION BY MEASUREMENT OF PHYSICAL GROWTH AND BODY COMPOSITION IN THE NICU

Physical Growth Assessment with Anthropometry

Weight Gain. Current recommendations cite the healthy fetus as the standard to which preterm infant weight gain should be compared (45); however, approximately 50% of very low-birthweight preterm infants are discharged with a weight below the 10th percentile and 30% are discharged with a weight below the 3rd percentile. (3) Because of the ease of accurate measurement, most early literature examining the relationships between physical growth and neurodevelopment focused on weight gain, demonstrating consistently that slower weight gain in infancy is associated with poorer neurodevelopmental outcomes. In one such study of 500 extremely low-birthweight infants born throughout the United States, Ehrenkranz et al found that infants in the top quartile of weight gain (21 g/kg per day) while in the NICU had an 8-fold reduction in cerebral palsy and a 2.5-fold reduction in any neurodevelopmental

impairment at 18 months' corrected age compared with those in the lowest quartile (12 g/kg per day). (46) In another study with 18-month outcomes, in 613 preterm children born before 33 weeks of gestation, faster weight gain before term was associated with higher scores on the Bayley scales (47); weight gain out of proportion to linear growth (increasing body mass index) was also positively associated with neurodevelopment. Regarding adult outcomes in very low birthweight infants in the Helsinki cohort, for each standard deviation faster weight gain before term, performance IQ was higher by 5 points. (48) Associations were also evident between faster weight gain and better executive functioning, visual memory, and verbal flexibility. (48) Overall, these studies demonstrate the importance of weight gain as a growth indicator in the NICU that is relevant for future neurodevelopmental outcomes.

Although the weight gain of the typical fetus is approximately 15 to 18 g/kg per day, this may not be sufficient for preterm infants who need to undergo catch-up growth after an initial period of weight loss or slow gains. Based on the Ehrenkranz et al study, a weight gain velocity of closer to 20 to 30 g/kg per day while in the NICU before reaching term may be necessary to optimize long-term neurodevelopmental outcomes. (46) A limitation of relying on weight gain alone is that it is easily influenced by fluid status, including the significant fluid shifts that preterm infants experience in the first few weeks after birth; often the effect of this early weight loss on the weight gain trajectory is not recovered before hospital discharge. In addition, examining weight gain without considering concurrent linear growth is limited with respect to the balance of excess adiposity gain compared with "healthy" growth of organs and tissues. In conclusion, weight gain is a useful indicator of nutrient accretion in the NICU with direct relevance to neurodevelopmental outcomes, but clinicians should recognize its limitations and consider incorporating other measures to more fully assess the adequacy of nutrient accretion in the NICU.

Length. Linear growth is thought to represent lean body mass and protein accretion and often is an underutilized measurement in clinical practice and research. Linear growth and fat-free mass accretion are more closely associated with organ growth and predict later cognitive outcomes. A challenge is that accurate measurement of infant length requires appropriate equipment (recumbent length board) and 2 trained measurers. (49)

In multiple studies of preterm infants, linear growth stunting has been shown to be more severe and prolonged than diminished growth in weight or head circumference. (47)(50)(51) Specifically, linear growth is most severely depressed at term and 4 months' corrected age for prematurity and remains suppressed to 18 to 24 months' corrected age. (47)(50)(51) When evaluating the relationship between linear growth and later neurodevelopment, Ramel et al found that improved linear growth throughout the first year predicted improved neurodevelopment measured at 24 months using the Bayley Scales of Infant Development among very-low-birthweight preterm infants. (50) Specifically, language scores improved by 8 points for each increase in length *z* score during the hospitalization, and cognitive scores improved by 5 points for increased growth during the first months to year after hospital discharge. These findings persisted after controlling for weight gain and head growth. (50) Similarly, several other studies of preterm infants have shown relationships between improved linear growth in the first months to years of age and improved motor scores on standardized testing, (47) decreased rates of cerebral palsy, (52) and decreased likelihood of IQ less than 85 in adulthood. (51)

Although fetal growth is often used as the goal for optimal preterm infant growth, linear growth is difficult to measure in utero. Fetal crown-heel length is the best surrogate, and varies from 1 cm per week in early and late gestation to as high as 2 cm per week between 20 and 30 weeks' gestation. (53) Therefore, to be most accurate, linear growth should be measured weekly using a length board and 2 measurers with linear growth goals of 1 to 2 cm per week. Because length continues to be an important marker of brain development, it should be followed closely and optimized when possible, especially before age 4 months but potentially up to age 2 years.

Head Circumference. Head circumference is thought to be a marker of brain growth in early infancy and is typically measured weekly in the NICU. Despite relative sparing when compared with weight gain and linear growth, slow head growth has been associated with poorer neurodevelopmental outcomes in multiple studies.

An Austrian study involving more than 250 very preterm infants found positive associations between IQ measured at age 5 years and head circumference measured at multiple follow-up points, including 3, 12, and 24 months, as well as 5 years. (54) The period between discharge and 3 months seemed to be an especially critical time, reiterating the importance of close growth monitoring that continues beyond hospital discharge and is not focused solely on weight gain. Suboptimal head growth, defined as more than 1 standard deviation, but less than 2 standard deviations below the norm was associated with lower IQ as well. (54) In the Helsinki study, similar to weight gain, head circumference gains before term were associated with improved

neurodevelopment, specifically each increase in head circumference *z* score was associated with a 3- to 8-point improvement in IQ. (48) The authors also found associations between faster head growth and verbal flexibility, visual memory, and executive function. (48) Head growth from term to 12 months' corrected age was less consistently associated with improvements in neurocognitive abilities; however, after controlling for neonatal complications and illnesses, faster head growth in the first year after term was associated with improved IQ. (48) Belfort et al also found improved 18-month Bayley scores with faster head growth before term, but no improvement for more rapid growth after term in infants born at less than 33 weeks' gestation. (47) Fetal head circumference gains are approximately 1 cm per week and correlate with brain growth. Microcephaly has been shown to be associated with loss of gray matter. Also, although head circumference appears to be relatively spared when compared with weight and linear growth, (47)(50) up to 30% of preterm infants continue to have suboptimal head growth (55); this suboptimal growth has been associated with poorer neurodevelopment. (54) Head growth up to 5 years, but particularly before term, is critical for optimizing neurodevelopment. For these reasons, head circumference should be measured at least weekly and if restriction occurs early, catch-up growth should be monitored and optimized with goals of at least 1 cm per week.

Assessment of Body Composition

Disproportionate weight gain and linear growth has been recognized for some time, but more recently, the availability of equipment allowing direct estimation of body composition in small preterm infants has facilitated a surge of research on the topic. This literature has revealed that preterm infants have decreased amounts of fat-free mass and increased relative adiposity compared with term infants at term corrected age. (50)(56) In addition, the fat mass in this population has a different distribution from that seen in healthy term infants with increased abdominal adiposity and decreased subcutaneous fat. (57) Some evidence suggests that these early differences in adiposity may resolve in early infancy, (58)(59) but the impact of these short-term changes on long-term growth and metabolic health is still poorly understood.

Fat-free Mass Represents Protein Accretion and Growth of Organs and Tissues. In a series of small studies, it has been shown that gains in fat-free mass throughout infancy and early childhood among preterm infants are associated with improved development, and that gains in fat mass during these same periods do not confer the same benefit. (5)(60)(61)(62) Specifically, faster gains in fat-free mass throughout the NICU stay are associated with higher standardized development scores in motor and cognitive domains measured at 12 months of age by the Bayley Scales of Infant Development (5) and faster speed of processing at 4 years of age (measured via visual evoked potentials). (62) In addition, increased fat-free mass gains before discharge from the NICU and throughout the first 4 months after discharge are associated with 1) faster speed of brain processing in infancy and at preschool age (measured via visual evoked potentials at both time points), and 2) improved working memory at preschool age measured via the Wechsler Preschool and Primary Scales of Intelligence. (60)(61)(62) Finally, increased gains in fat-free mass from infancy to preschool age are associated with faster speed of processing and IQ measured on standardized developmental testing at age 4 years. (61) In each of these studies, no improvement in neurodevelopment was found in relation to fat mass gains.

Given that fat-free mass gains are an important predictor of later neurodevelopment and that early fat mass gains may contribute to later metabolic risk, measurement of infant body composition, coupled with practices that enhance fat-free mass gains, may allow optimization of both long-term neurodevelopment and overall cardiovascular and metabolic health.

NON-NUTRITIONAL INFLUENCES ON PHYSICAL GROWTH AND BODY COMPOSITION

Despite improvements in nutritional care for preterm infants, this high-risk group of children continues to exhibit stunted and disproportionate growth. While this may be secondary to continued inadequate or inappropriately balanced intake, more recently, it was shown that non-nutritional factors may also play a significant role in these altered growth patterns. Growth factors such as insulinlike growth factor 1 act by modulating nutrients into growth and are also important for neuronal growth and differentiation. Without growth factors, cells will not differentiate, even with adequate nutrients. Growth factors are nutritionally regulated and cannot mediate growth without proper nutrient supply, but also have been shown in many pediatric populations to be suppressed by illness and inflammation, likely through increased somatic protein breakdown. Given that premature infants are at risk for both low protein intake and inflammatory states that promote protein breakdown, it is not surprising that they undergo such significant linear growth suppression and decreased fat-free mass accretion.

In part, the role of illness in growth failure is related to restricted nutritional provision to those who are the most critically ill. This can occur for several reasons, including

fear of intolerance leading to a delayed start to enteral feedings and more frequent and prolonged feeding disruptions leading to a longer period to reach full enteral feedings. In addition to delays in enteral feed initiation and advancement, parenteral nutrition is also often limited in the smallest and sickest patients because of intolerance such as hyperglycemia and hypertriglyceridemia. Eherenkranz et al performed a mediation analysis on more than 1,000 preterm infants using days on mechanical ventilation as their marker of critical illness. (63) The authors found that those who were less critically ill received increased amounts of nutrition in their first 3 weeks after birth, grew faster, had a lower incidence of chronic lung disease, sepsis, and death and improved neurodevelopment compared with those who were more critically ill. (63) They also found that these relationships were mediated largely by energy intake during the first week. They concluded that if more nutrition was provided to those infants who were critically ill, their growth and risk for other morbidities would be improved. (63)

Decreased nutritional provision to those infants may not completely explain the degree of long-term stunting these children experience. Uthaya et al found that the primary determinant of increased abdominal adiposity among preterm infants was degree of illness. (57) Multiple clinical surrogates of inflammation, including days requiring antibiotics, oxygen, and steroids, are negatively associated with linear growth up to 2 years of age. (50) Also, preterm infants with higher illness scores on the first day after birth have been shown to have decreased amounts of fat-free mass up to 4 months' corrected age. (50) The lasting impact of these non-nutritional factors, well beyond the period of malnutrition, suggests that alterations may be occurring in the growth hormone axis; however, further research on this is needed.

CONCLUSIONS

Many nutritional and non-nutritional factors influence physical growth in the NICU, are linked with measures of early brain development, and predict long-term functional outcomes. Weight gain is convenient to measure in the NICU and predicts neurodevelopmental outcomes in childhood and adulthood; however, linear growth and fat-free mass may be more specific than weight as indicators of nutrient accretion into organs and tissues including the brain. Large observational and randomized intervention studies are needed to further establish the best markers of nutritional status in the NICU and to inform interventions that optimize both short- and long-term outcomes. Such interventions may involve increased provision of macronutrients and/or micronutrients, or supplementation with non-nutrient bioactive factors discovered in maternal milk. In addition, future interventions might target biological pathways that influence nutrient accretion such as inflammation and the growth hormone axis.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know how body composition changes during postnatal growth and development and understand the effect of prematurity
- Know the caloric requirements for optimal postnatal growth of preterm and term infants, accounting for caloric expenditures needed for physical activity and maintenance of body temperature
- Know the consequences of feeding preterm infants too little or too much protein
- Know the importance of prenatal and postnatal nutrition on neurodevelopmental outcomes, including the importance of breast milk for brain development

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NeoReviews Quiz

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1. Preterm infants are particularly vulnerable to suboptimal growth and receiving inadequate nutrition in the NICU, which can lead to alterations in brain development. In randomized trials by Lucas and colleagues comparing various nutrition strategies, which of the following led to higher rates of weight gain, linear growth, and head growth during NICU hospitalization?
    A. Donor human milk.
    B. Mother's own milk with supplemental vitamins.
    C. Partially hydrolyzed formula with supplemental iron.
    D. Preterm formula enriched with calories, protein, and other nutrients.
    E. Standard term formula with cow milk–based protein.
2. A woman who just found out that she is pregnant is researching the optimal nutrition for herself and the fetus. She enquires about long chain fatty acids and whether she should supplement her diet. Which of the following statements regarding long chain fatty acids is correct?
    A. Docosahexaenoic acid is highly variable in human milk, and its content depends on maternal diet.
    B. Docosahexaenoic acid levels increase rapidly after birth for both preterm and term infants, whereas linoleic acid levels fall.
    C. Linoleic acid is preferentially transferred from the mother to fetus compared with docosahexaenoic acid.
    D. Long chain fatty acids only reach the fetus via passive transport across the placenta.
    E. Several studies have consistently shown a positive impact of docosahexaenoic acid on Bayley cognitive score for male preterm infants, but not for female infants.
3. A preterm infant is receiving both parenteral and enteral nutrition. Which of the following statements regarding zinc supplementation for this patient is correct?
    A. Altered zinc balance in the brain can contribute to neuronal and oligodendrocyte death.
    B. Infants with mild zinc deficiency present with severe skin rash, acute tubular necrosis, failure to thrive, and irritability.
    C. The potential for excessive zinc supplementation does not exist, because even preterm infants can easily filter out zinc through the kidneys.
    D. There is no naturally occurring zinc in human milk.
    E. Zinc is not compatible with parenteral nutrition intended for preterm infants.
4. An infant born at 28 weeks' gestational age is receiving fortified human milk. Which of the following describes a benefit of this approach compared with non–human milk preterm infant formula?
    A. Accretion of more lean mass.
    B. More head growth.
    C. More weight gain.
    D. Prevention of necrotizing enterocolitis.
    E. Reduced requirement for oxygen in the first week after birth.

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5. An infant born at 25 weeks' gestational age is transitioning from parenteral to enteral nutrition. The team is assessing growth and nutrition status. Which of the following statements regarding current standards of growth for preterm infants is correct?
    A. A strategy to be at the 10th percentile of age-matched fetal growth is optimal.
    B. A weight gain velocity of 20 to 30 g/kg per day while in the NICU may be necessary to optimize long-term neurodevelopmental outcomes.
    C. Because of the difficulty in measurement and variation in technique among providers, tracking linear growth has not been shown to be of any benefit in clinical practice or in research.
    D. Preterm infants with higher illness scores on the first day after birth have increased amounts of fat-free mass for several months.
    E. Slower head growth is usually associated with bronchopulmonary dysplasia, but has no association with neurodevelopment.

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