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The Impact of Neonatal Illness on Nutritional Requirements— One Size Does Not Fit All

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Abstract

Sick neonates are at high risk for growth failure and poorer neurodevelopment than their healthy counterparts. The etiology of postnatal growth failure in sick infants is likely multi-factorial and includes undernutrition due to the difficulty of feeding them during their illness and instability. Illness also itself induces fundamental changes in cellular metabolism that appear to significantly alter nutritional demand and nutrient handling. Inflammation and physiologic stress play a large role in inducing the catabolic state characteristic of the critically ill newborn infant. Inflammatory and stress responses are critical short-term adaptations to promote survival, but are not conducive to promoting long-term growth and development. Conditions such as sepsis, surgery, necrotizing enterocolitis, chronic lung disease and intrauterine growth restriction and their treatments are characterized by altered energy, protein and micronutrient metabolism that result in nutritional requirements that are different from those of the healthy, growing term or preterm infant.

Keywords

Preterm; Nutrition; Illness; Stress; Physiology; Protein; Macronutrients; Micronutrients; Bronchopulmonary Dysplasia; Neonatal Sepsis

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Conflict of Interest

Sara E. Ramel, Laura D. Brown, Michael K. Georgieff declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

A large amount of debate and research has centered on determining what constitutes optimal nutritional delivery for the preterm and term neonate. Long-standing recommendations for term infants stemmed largely from assessments of intakes of healthy breastfed babies growing along appropriate growth curves. The nutritional care of the preterm infant has different roots than term infants since they do not feed *ad libitum* and thus do not regulate their intake until the time of hospital discharge. A different approach was necessary to define optimal growth and to determine the amounts of macro- and micronutrients required to promote such growth. This alternative approach was based on the premise and on subsequent research observations that the physiology of the preterm infant differed from the term infant in fundamental ways. These differences include (generally) higher metabolic demands and immature metabolic and digestive/absorptive systems (1,2). A large literature from the 1960's, 70's and 80's was devoted to defining preterm infant nutritional requirements, developing nutrition support products and measuring outcomes. To a large extent, general consensus was reached in the early 2000's on the nutritional requirements of the healthy, growing term and preterm infant (3,4), such that most neonatal practitioners can recite the caloric and protein needs of these two groups of infants by memory. Smaller studies from the 1980's (5,6) followed by large multicenter studies (7) raised the stakes regarding the importance of nutrition in preterm infants by demonstrating that neurodevelopmental outcome was influenced by in-hospital nutritional status. As neonatology moved as a field from one of preventing mortality to one of minimizing morbidity, it became clear that nutrition was one mutable factor in the hands of the practitioner that could influence neurodevelopmental and other morbidities.

In light of the large amount of research that defined nutritional requirements in preterm infants, it is therefore somewhat surprising that consideration of the physiology of illness, whether it be prenatally, such as in the case of chronically reduced nutrient supply from the placenta and intrauterine growth restriction (IUGR), or postnatally, from neonatal sepsis, surgery, and chronic lung disease, has been given relatively short shrift when considering nutritional requirements *within* either the term or preterm population. While preterm and term infants spend most of their hospitalization days in "growth mode", ie, convalescing and preparing for discharge, a significant portion of their time is also spent being ill. Bodies of literature from adult and pediatric critical care demonstrate that illness significantly alters metabolism, and by definition, nutrient requirements (8, 9). Furthermore, recommendations for the nutritional management of the IUGR infant are not distinguished from appropriate for gestational age (AGA) preterm infants, yet metabolic rates and the capacity for nutrient utilization inevitably differ (10). Surprisingly little has been written about the effect of illness on macro and micronutrient status in newborns.

This article reviews the principles of stress physiology and its effects on nutrition as it is understood from the adult and pediatric literature, surveys the existing literature on the topic in neonates and highlights disease states where alterations to standard nutrient delivery designed for physiologically stable newborns can be reasonably proposed based on known physiologic alterations induced by the illness.

Does One Size Fit All?

Despite increasing attention toward providing more aggressive nutrition and in some cases providing preterm infants the same amount of nutrition as they would have received in utero (11), preterm VLBW infants continue to have growth failure. As many as 79% remain below the 10th percentile in weight at 36 weeks post-conceptual age (12). Additionally, linear growth failure that persists well into the second year of life is common (13, 14). What remains unclear is whether this unrelenting growth failure is due to continued inadequate nutritional delivery (due to insufficient goals or not meeting intended goals) or secondary to other processes such as inflammation leading to restriction of growth by non-nutritional mechanisms.

Critically ill neonates have slower rates of growth in weight and length than those who remain healthy (15). Additionally, those infants who are ill (and likely in a proinflammatory state) appear at even greater risk than their healthy counterparts to undergo disproportionate growth. Severity of illness is associated with poorer linear growth and also decreased fat free mass gains (13, 16). Fat deposition has also been noted to be altered according to illness severity, with those that are more critically ill having decreased amounts of subcutaneous fat and increased amounts of intra-abdominal fat (17). These findings are critical as poor weight gain and disproportionate growth are risk factors for worsened neurodevelopmental outcomes as well as for long-term metabolic disease (7, 13).

Unfortunately, there has been little research investigating the mechanisms behind the slowed and disproportionate growth in this population. Ehrenkranz et al report that the relationship between early critical illness and poor growth is largely mediated by decreased nutritional provision to this population (15). Fear of metabolic intolerance and necrotizing enterocolitis (NEC) lead practitioners to withhold nutrition from the smallest, gestationally youngest and sickest patients despite evidence that in most cases provision of aggressive nutrition is safe and, in fact, beneficial (18, 19).

Ultimately, the question is whether one “size” of nutritional support (ie, 120–130 kcal/kg and 3–4g protein/kg daily) fits all preterm infants. This basic formula for energy and protein has been recommended with relatively few modifications since the late 1970’s, with the exception that the amount of protein that is currently prescribed represents a significant increase over the past ten years. The question of whether “one size fits all” was addressed by two working groups in the 1990’s and early 2000’s. The Canadian Pediatric Society recognized that metabolism varies based on stage of development and illness (20). They proposed three phases of a preterm infant’s course, the first two of which occur while in the hospital. The first phase was termed “Transition” and represented approximately the first days (to weeks) of postnatal life when infants are typically ill, physiologically unstable and losing weight. This is a time period when preterm infants are receiving the least amount of calories, and when nutritional deficits begin to accumulate (21). Additionally, infants in this stage are often catabolic and insulin resistant (22). They have high levels of endogenous and exogenously administered counter-regulatory hormones (eg steroids, catecholamines) that, while critical for survival, do not promote tissue accretion and growth (23,24). The second phase was termed the “Growth” phase and extended until at least 34 weeks post-

conceptional age. The physiology of this phase contrasts with “Transition” in that it is characterized by anabolism, insulin sensitivity and growth, even though absorption and digestion may still be immature compared to term infants. To a large extent it was the metabolic requirements of this phase that drove the calculations of how much energy and protein was necessary to match expected intra-uterine growth rates and tissue accretion (25, 26). Yet, clearly “preemie growers” can become sick and the question remains open as to how postnatal illness alters their metabolism and nutritional requirements. The third phase occurs when the digestive and absorptive capacities of the preterm infant mature to term levels typically after 34 weeks post-conceptional age. This period extends from the last part of the hospitalization through the post-discharge period and is differentiated from the second phase by the ability of the infant to handle more complex nutritional substrates that the term infant can handle. That said, there remain significant growth and nutritional deficits that may take years to recover (13) and thus these infants cannot be considered the nutritional equivalent of the healthy term infant.

The LSRO also considered this question in 2002 but reported that there was not sufficient experimental evidence to advocate for different nutritional goals in sick vs. healthy preterm infants (4). ESPGHN has considered the question as recently as 2013 and concluded that more research on the question is needed (24).

Illness alters nutrient requirements in critically ill adults and children

The principle that illness alters nutrient requirements was first studied in adults. Critically ill children and adults undergo significant metabolic changes, including decreased absorption of nutrients and inability to utilize the nutrients provided (8,9). However there has been little research into the metabolic impact of illness on nutritional utilization in preterm infants. Adults who are septic or who have undergone trauma or surgery have increased cellular oxygen consumption and negative nitrogen balance, and therefore require higher energy delivery and more protein to remain in positive balance (8). Additionally, branched chain amino acid solutions have been utilized in critically ill children to improve nitrogen balance during illness (27). These metabolic changes appear to be mediated at least in part by elevated pro-inflammatory cytokines such as TNF-alpha and IL-6, insulin resistance and increased cortisol (28). The metabolic changes were quite different than simple starvation. Whereas starvation results in catabolism of stores with a reduction in metabolic rate (to reduce demand), sepsis, surgery or the combination of the two resulted in catabolism accompanied by a large *increase* in metabolic rate. Thus, a rapid mobilization of energy and protein stores is needed to meet this metabolic demand; a condition referred to as “auto-cannibalism” and driven by TNF-alpha (formerly known as cachexin) (28). The body makes these metabolic adaptations to increase the chance of survival. The adaptations produce additional fuel, primarily in the form of glucose from glycogen, de-aminated amino acids and triglycerides. Peripheral insulin resistance is prominent presumably as a mechanism to shunt glucose to organs necessary for survival such as the brain and the heart. The response is similar in critically ill children (9).

Do similar events occur in the critically ill newborn infant?

The metabolic stakes are higher in newborns than in adults because infants not only have to meet the goal of maintaining current nutritional status, but also must utilize additional substrates (eg, protein, energy, iron, zinc) to maintain growth velocity and tissue accretion through critical periods of development. Thus, it is likely that the need for altered nutritional plans during times of illness is amplified in this population. Ultimately, the question is: if neonates show similar catabolic responses to illness, can they continue to grow in the face of that illness?

In spite of the high stakes, data supporting the notion that nutritional delivery should be modified during illness are relatively sparse. The information that is available stems from studies in two populations, neonates that are sick from birth and neonates that become ill (eg, from sepsis, necrotizing enterocolitis) during their hospitalization. Neonates have similar, but more attenuated acute phase responses to sepsis than adults. Clinically, the degree of response appears highly variable among infants and it is unclear what roles, if any, gestational age and immune capability play in this variability. Nevertheless, as in adults, sepsis increases pro-inflammatory cytokines in critically ill neonates (29) suggesting that the potential for marked changes in energy and protein metabolism are there.

The effects of illness on individual nutrients in the neonate

Energy requirements are a function of the sum of the oxygen consumption rates of all of the organs in the body. Each organ has different energy requirements. For example the brain of the neonate consumes an astounding 60% of total body metabolism, far out of proportion to other mammals (30). The heart has a high metabolic rate, whereas the lungs and kidneys do not. Diseases of organs with high baseline metabolic rates disproportionately increase the total body oxygen consumption and thus total energy demand. Thus, heart failure (31) and recurrent or ongoing seizures increase energy requirements by approximately 30%, whereas the effect of respiratory distress syndrome (surfactant deficiency) is equivocal (32, 33) especially with assistant ventilator support. Chronic lung disease increases resting energy expenditure by 15% (34, 35), but this may be more a function of right heart strain than of the lung disease itself. Like adults, sepsis increases energy needs (36). In contrast to adults, surgery does not (37, 38). Intrauterine growth restriction (IUGR) is a condition that significantly alters the metabolism of the newborn. Preterm infants born small-for-gestational age (SGA), often due to insufficient placental nutrient supply, have higher metabolic rates, increased energy expenditure, and decreased fat absorption when compared to appropriately-grown (AGA) infants in the first month of life (39–41). However, increased energy expenditure was not shown to impair weight gain when adequate nutrition was provided (39, 41).

Protein status is also negatively influenced by illness in neonates. Protein breakdown is an essential part of stress physiology because deaminated amino acids are recycled through the liver as carbon sources for gluconeogenesis, particularly when the meager glycogen stores of the neonate have been utilized. The neonatal brain is highly dependent on glucose to support its high metabolic rate, although it can also utilize lactate, ketones and amino acids (42).

Protein catabolism occurs during neonatal sepsis (43), presumably driven by pro-inflammatory cytokines (29). In contrast to its negligible effect on energy status, surgery increases protein breakdown as does extracorporeal membrane oxygenation. The latter is a condition that is characterized by a massive increase in pro-inflammatory cytokines (44). Not only do illnesses increase protein breakdown, the treatment of illness can as well. While there are no studies demonstrating increased protein requirements in neonates with chronic lung disease, glucocorticosteroids that are used to treat the disorder cause massive protein breakdown and turnover (23).

IUGR compromises neonatal protein status. Promoting optimal growth of lean body mass in the IUGR infant is of particular importance, because they are at risk for lifelong reductions in muscle and lean mass growth, which in turn may influence long term metabolic health (45, 46). Very limited data are available to guide the optimization of protein balance in the IUGR infant, and studies are conflicting. Some studies show that SGA infants are more efficient at protein gain, suggesting that slightly higher protein intakes are appropriate (47, 48). However, other studies indicate that SGA infants have deficiencies in protein metabolism, including higher alpha-amino-nitrogen in both the serum and the urine and lack of urea production when protein delivery is increased, suggesting that additional protein supplementation may not be well tolerated (49, 50). Future research is clearly needed to determine optimal protein delivery for these high risk infants.

Micronutrients are also affected by neonatal illnesses and their treatment. The treatment of chronic lung disease frequently involves diuretics, which induce a hyponatremic, hypochloremic alkalosis. The sodium requirements of preterm neonates that are not on diuretics are 4 to 7 meq/kg/d; with diuretics this value may reach 10–15 meq/kg/d (51). Hyponatremic neonates exhibit poor growth (52). Calcium and phosphorus balance are difficult to maintain in the sick preterm neonate (53). In an effort to prevent neonatal hypocalcemia by loading TPN with calcium salts, phosphorus delivery is compromised with resultant hypophosphatemia. At the cellular level, there is a risk for inadequate substrate for important phosphorus compounds such as ATP. From a calcium and bone mineralization perspective, the treatment of chronic lung disease with calciuric diuretics (eg, furosemide) or simply fluid restriction compromises bone health.

The divalent metals iron and zinc are also at risk during neonatal illness. Certain subgroups of neonates, including infants of diabetic mothers and IUGR infants are born with low iron stores (54, 55). Postnatally, infants with cyanotic heart disease and secondary polycythemia have increased iron requirements (56). Treatment of anemia of prematurity/phlebotomy in preterm infants with recombinant human erythropoietin increases those infants' enteral iron requirements from the standard 2–4 mg/kg body weight daily to 6 mg/kg daily in order to have enough substrate to synthesize additional hemoglobin without compromising other tissues (57). Finally, it is likely that inflammation significantly alters iron absorption and trafficking in the sick newborn. The resultant anemia of inflammation, mediated by hepcidin, is characterized by reduced enteral iron absorption and iron sequestration in the reticulo-endothelial system where it is unavailable for red cell production and tissue growth (58). The consequence of true or functional iron deficiency is a risk of abnormal neurodevelopment (59). Zinc deficiency is also a risk, particularly in infants with NEC or

short bowel syndrome. Infants with low zinc status are at risk for poor growth (60). IUGR preterm infants may be at even higher risk than the AGA preterm infant for micronutrient deficiencies secondary to impaired placental transfer and low stores (61). For example, comparisons between IUGR and AGA cord blood have shown reductions in vitamin A and red blood cell folate (62). Bone mineral content was lower in SGA infants than in AGA infants, as was cord blood 1, 25 OH-dihydroxyvitamin D (63).

Beyond nutrient supply: The potential effect of illness on growth factors

Growth factors are essential for nutrients to exert their effects on cellular growth and differentiation. Complex intracellular signaling pathways such as the mammalian target of rapamycin (mTOR) that regulate protein translation rates, transcription rates, autophagy and structural complexity (ie, growth and differentiation) are in turn regulated by nutrients and growth factors (64). The mTOR pathway is regulated not only by oxygen, iron and nutrients, but also by growth factors like insulin and IGF-1 that signal through the PI3K pathway (64). Without growth factors, cells will not differentiate in spite of adequate nutrients, and conversely, without nutrients, growth factors cannot mediate growth. IGF-1 is the major growth factor for the fetus and neonate and its synthesis is suppressed by sepsis (65). This is not wholly surprising in light of the discussion of factors that promote anabolism or catabolism above. Growth and cellular IGF-1 sensitivity occur in a state of anabolism, where metabolic resources and tissue reserves are not being utilized for stress physiology to promote survival.

Ultimately, the question is whether poorly growing critically ill babies should be induced to grow simply by provision of greater amounts of nutrients. This remains an open and testable question. Current neonatal nutrition support strategy appears to use the rationale “if the baby is not growing, simply give more nutrients.” This supply-side approach may be appropriate for non-stressed, anabolic infants who simply have high metabolic demands because of the nature of their chronic disease (eg, chronic lung disease, heart failure, IUGR). On the other hand, providing extra or excessive nutrients during acute illnesses that are by nature catabolic (eg, sepsis, NEC, surgery) may not only be futile, but counter-productive. Cellular processing of substrates (ie, nutrients) has a metabolic cost. Each additional calorie delivered increases the oxygen consumption of the cell. Excessive caloric administration in a setting where such calories will not be utilized for storage (ie, weight gain) represents a metabolic load that the neonate may or may not be prepared to handle. Besides the absolute amount of fuel delivered, composition of the fuel can also affect metabolism. Each mole of carbohydrate that is cellularly combusted generates a mole of carbon dioxide that must ultimately be removed via the lungs. In contrast, each mole of fat generates only 0.7 moles of CO₂. The metabolic demand of a mixed or fat-dominant blend of calories may reduce respiratory load and this may be crucial during respiratory failure (66). Thus, manipulation of nutrition may have a significant impact positively or negatively on ventilation of the neonate with lung disease.

Conclusion

Ultimately, a judgment needs to be made on an individual patient basis as to whether the disease state of the infant influences how it deals with the nutrients that are provided. Acute and chronic neonatal illnesses have significant metabolic effects that in turn affect nutritional status and prescription of nutritional support. As in adults, illness changes nutrient demand and trafficking in addition to limiting the supply of certain nutrients for growth. The stress of illness changes the physiology of the baby, characterized by insulin resistance and the activation of counter-regulatory hormones such as cortisol that promote tissue breakdown rather than accretion. This in turn results in poor growth through the diversion of nutritional resources needed to address the acute illness. Supply side approaches alone (ie, giving more nutrients) are unlikely to achieve the goal of continued growth and neurodevelopment in preterm infants who are acutely ill. In fact, the best nutrition support for acutely ill infants may be non-nutritional; that is, an important “nutritional adjunct” might be to reduce episodes and duration of infection, reduce the incidence of chronic diseases characterized by a high degree of inflammation (eg, chronic lung disease) and reduce the amount of catabolic medications (eg, steroids) that are given to the neonate (13). In addition, customized attention to the specific nutritional needs induced by illness and/or chronic deficits in intrauterine growth may serve the compromised neonate better than a generic “one size fits all” approach. After all, the respiratory support world learned this lesson long ago. Clearly, not every infant is put on the same ventilator settings. Why would we do the same with nutrition support?

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