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Title

Nutrition and Growth in Infants with Established Bronchopulmonary Dysplasia

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Abbreviations: breast milk (BM), bronchopulmonary dysplasia (BPD), gastroesophageal reflux disease (GERD), parenteral nutrition (PN), nasogastric tubes (NG), necrotizing enterocolitis (NEC), neonatal intensive care unit (NICU), transcutaneous gastrostomy tube (GT)

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Abstract

Bronchopulmonary dysplasia (BPD) remains the most common late morbidity of preterm birth. Ongoing clinical care and research have largely focused on the pathogenesis and prevention of BPD in preterm infants. However, preterm infants who develop BPD have significant medical needs that persist throughout their neonatal intensive care unit course and continue post-discharge, including those associated with growth and nutrition. The objective of this manuscript was to provide a review on nutrition and growth in infants with established BPD after discharge from the hospital and to identify the knowledge and research gaps to provide direction for future studies.

Introduction

Nutrition plays a critical role in respiratory development of infants with bronchopulmonary dysplasia (BPD), whose saccular-alveolar stage of lung maturation occurs mostly or entirely in post-natal life.^{1,2} Infants with BPD have increased caloric needs, which continue after discharge from the hospital. These nutritional needs are often unmet, as evidenced by data showing that infants and young children with BPD are smaller than term controls, with greater deficits observed in weight than in height, and growth abnormalities might persist into adolescence and adulthood.³⁻⁵ Growth delay is also associated with severe and prolonged respiratory dysfunction, and nutritional status in former infants with BPD at 2 years of age is a predictor of pulmonary function later in childhood.⁶ Conversely, improvement in respiratory symptoms is associated with an accelerated growth rate.⁴ These data highlight the importance of growth and nutrition in affecting pulmonary outcomes in BPD. In this article, we will review the epidemiology of nutritional deficits in BPD, the mechanisms by which growth failure contributes to worse lung

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function, factors contributing to poor nutrition in BPD, and suggestions for nutritional management in BPD.

Epidemiology of nutrition in BPD

In the neonatal period, infants born preterm have greater nutritional needs to match the high rates of weight gain achieved by infants *in utero*. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Growth Observational Study⁷ demonstrated that, although the rate of weight gain was similar to the reported intrauterine rate of weight gain (15 g/kg per day), once birth weight was regained, most of the infants born at a gestational age between 24 to 29 weeks did not achieve the median birth weight of the reference fetus of the same post-menstrual age (PMA) at hospital discharge. In fact, at discharge from the neonatal intensive care unit (NICU) or at 36 weeks' PMA, most were less than the comparable 10th percentile birth weight for completed weeks of gestation.⁸ **Table 1** provides a summary of NICU morbidities and other factors associated with higher incidence of postnatal growth failure.⁹

Energy needs for an infant with BPD have been estimated to be 15% to 25% greater than for an infant without BPD, and thus, in the range of 140 to 150 kcal/kg/day.¹⁰ Often, increased calorie and protein delivery is required to meet the increased energy expenditures and metabolic needs of these vulnerable infants.¹¹ In addition, patients born prematurely may lack the ability to feed orally. The occurrence of gagging, choking, and vomiting, and other issues related to oro-motor coordination can contribute to the suboptimal nutrition of these patients. Increased metabolic demands can also cause growth failure.¹² Developmental delays, lower social economic status, tobacco smoke exposure, indoor air pollution can have further impact on growth and respiratory outcomes of patients with BPD.¹³⁻¹⁵

Pathophysiology

The effects of post-natal undernutrition on lung maturation have been characterized in animal models. Rodent models, which are at a saccular stage of lung development when born at term², suggest that early post-natal undernutrition affects the bronchiolar epithelium¹⁶ and disrupts alveolarization¹⁷, with a reduction of both epithelial cells division and conversion of club cells to ciliated cells. Lamb models have demonstrated that fetal growth restriction can induce changes to both the chest wall and lung which persistent and subsequently impair respiratory function early in life.¹⁸ Furthermore, post-natal growth restriction has been shown to augment oxygen-induced pulmonary hypertension in rat models.¹⁹ Additional studies have found that alveolar formation is dysregulated by restricted nutrition²⁰ and malnutrition can reduce lung weight, lung weight-to-birth-weight ratio, lung volumes, as well as the number of alveoli and elastic fibers and collagen deposition.²¹

Clinical studies have reported that infants with BPD have increased energy expenditure compared to preterm infants without BPD.²²⁻²⁴ Total daily energy expenditure has been found to be 16% greater in infants with BPD compared to match controls.²⁴ This is likely due to increased work of breathing, increased respiratory rate, and increased FiO₂ requirement.²⁴⁻²⁶ De Meer et al. found that infants with BPD require an additional 7.5 kcal/kg/day of energy intake for every additional 10 breaths/min greater than 60 breaths/min.²⁵ Additional contributing factors for increased energy expenditure include growth suppression from chronic stress and inflammation,²⁷ and chronic corticosteroid and/or diuretic use. Research has shown that infants with BPD who have received dexamethasone therapy have decreased weight gain, head circumference, length, and skinfold thickness during therapy.²⁸ However, at term and three months corrected age, there was no difference compared to controls.

Several studies have also demonstrated postnatal growth restriction in preterm infants, particularly in those with BPD, suggesting that these increased energy needs can have an impact on long term growth.^{7, 29, 30} It has been shown that by 2-4 weeks of age, infants with BPD have lower weight, length, and head circumference z-scores, as well as arm muscle area and arm fat area measurements, compared to infants without BPD matched for gestational age and birth weight.²⁹ Another study demonstrated that infants with BPD at 12 months post-term age, compared to healthy term infants, had a significantly lower weight, length, fat free mass, and total body fat, despite having energy and protein intake at or above the recommended daily intake for healthy term infants during the first six months.³⁰

Other factors that may contribute to growth retardation in BPD include intrauterine growth restriction, which is a risk factor for BPD, and NEC.^{31, 32} A history of NEC is associated with slower growth rates and growth delay.^{33, 34} Treatment of NEC can require bowel resection, potentially leading to short gut syndrome or other problems of gastrointestinal absorption. While there have been no studies directly assessing the impact of NEC on growth in BPD, it is likely that NEC can contribute to poor growth in this patient population

In summary, animal models provide a mechanistic rationale for the impact of nutrition on lung growth and development, and clinical data demonstrate that infants with BPD have increased caloric needs. An inability to meet these increased needs can result in growth failure and worse pulmonary outcomes.

Dietary Factors

Formula Selection

The nutritional support of infants and children with established BPD is focused on provision of appropriate calories to promote growth and avoid growth failure. To that end, nutritional support in BPD is similar to that provided to premature infants without lung disease. There is

limited and mixed data describing optimal oral or enteral nutrition in the setting of BPD; experimental design and formula/feeding choice vary between study and outcomes described also vary. The American Academy of Pediatrics (AAP) recommends³⁵ that mother's breast milk should be used through the first 6 months of life. Data suggests that use of breast milk may be associated with reduced emergency department visits and need for systemic steroids in young children with BPD,³⁶ while data on reduction in hospitalization³⁷ for lower respiratory tract infection is mixed.³⁷ Recent data has suggested that exclusive breastfeeding in infants may be associated with lower oxygen need in BPD infants following initial discharge.³⁸ Adequate protein intake is necessary to promote linear growth, lung growth, and repair of damaged tissue.³⁹ However, at present, there are no specific protein intake recommendations for infants with BPD. The AAP recommends 3.2 to 4.5 g/kg/d of enteral protein for preterm infants.⁴⁰ Although excessive calories may increase CO₂ production, the net caloric gain from higher protein intake improves growth of infants with BPD.

Following cessation of breast milk consumption, the selection of a specific infant formula is based on patient gestational age, postnatal age, and nutritional needs. Studies on the use of a fortified discharge formula have demonstrated improved length, lean mass, and bone mass.^{10, 41, 42} However, there is insufficient data to support the selection of a specific formula in infants with established BPD.

Role of Calorie Supplementation

Infants with established BPD may require caloric supplementation to avoid growth failure due to prematurity and an increase in total energy expenditure. Various caloric supplementation strategies have been investigated in the setting of BPD but definite evidence-based guidelines cannot be developed based on available evidence. After confirming appropriate protein delivery, caloric supplementation should focus on providing sufficient nonprotein calories to

promote appropriate weight gain and linear growth. It is common for infants with established BPD to require caloric supplementation (many require 22 to 30 calories per ounce (cal/oz) formulas or fortified BM).

Ready-to-feed toddler formulas are available with a standard 30cal/oz concentration. However, these formulas are more appropriate for children greater than 1 year of age. In infants, if concentration of infant formula to 30cal/oz is needed, attention should be given to how the formula caloric density is achieved. Infant formula caloric supplementation may be achieved with use of glucose or fat sources. Fat (compared to glucose) provides a concentrated energy source and has a lower respiratory quotient and thus a lower production of carbon dioxide.⁴³. Use of a high-fat infant formula was associated with lower carbon dioxide formula in one study, but the impact on growth was mixed. Adequate growth was seen with the high fat formula, but higher weight gain was seen with higher carbohydrate intake⁴⁴. While evidence is limited regarding optimal strategy of caloric supplementation, clinicians should be aware of the nuances regarding fat and glucose supplementation especially during caloric concentration of infant formula. Consultation with a dietitian who is knowledgeable and experienced in the care of preterm infants and children can be helpful.³⁹

Other Dietary Factors

Micronutrients and Vitamins

There is limited evidence with regards to use of specific micronutrient supplementation during nutritional management of infants with established BPD. Zinc is an essential micronutrient that is involved in multiple cellular processes including growth, tissue repair, carbohydrate tolerance, and the host immune response and healing. Zinc supplementation should be considered in infants with BPD and poor growth⁴⁵, especially if other symptoms of zinc deficiency are present including diarrhea or acro-oral rash. The role of Vitamin A has been examined as an

intervention to prevent BPD, however, it's nutritional value for patients with established BPD is not known. On the whole, there is no evidence to suggest that specific vitamin supplementation above recommended dietary intake has a role in treatment or management of infants with established BPD.

Parenteral Nutrition

Parenteral nutrition (PN) is typically a key component of early nutritional management in infants at risk for BPD. Continued need for PN in infants with established BPD may coincide with a diagnosis of short bowel syndrome or intestinal failure. Similar to formula concentration, provision of PN in the patient with BPD should be focused on delivery of protein to meet needs. Appropriate dosing and choice of PN lipid should allow for avoidance of glucose infusion above standard glucose infusion rates for age⁴⁶. PN Lipid restriction in the infant with BPD, and subsequent excess glucose infusion, should be avoided if possible due to risk of CO₂ production.

Other Contributing Factors

There are many other contributing factors which affect growth and nutrition in patients with BPD. Swallowing dysfunction is common in this population and likely contributes to chronic respiratory symptoms in children with BPD.⁴⁷ Lung disease has been shown to be a major independent determinant of delayed feeding skills and time to full oral feeds in premature infants born before 32 weeks gestation.⁴⁸ One study identified that infants with BPD had higher respiratory rates, more oxygen desaturations, and poor suck-swallow-breath coordination, as well as poor sucking endurance and performance compared to preterm infants without BPD while oral feeding.⁴⁹ The same study also identified that feeding problems were dependent on the severity of BPD, with infants with severe BPD having worse feeding efficiency.⁴⁹ Similar results have been reported by Wang et al who demonstrated significantly lower mean oxygen saturation levels during feeding at 2-6 months corrected age in very low birth weight infants

with severe BPD compared to very low birth weight infants with mild BPD and term infants.

Additionally, throughout the study period infants with severe BPD had higher rates of growth delay defined as weight less than the 10th percentile.⁵⁰

Once an infant is able to tolerate oral feeds, evaluation for aspiration (by an experienced occupational or speech therapist with further diagnostics tests if warranted) is needed to assure intact swallow mechanisms. If swallowing dysfunction is identified, often the next step is to explore alternative routes of enteral feeding such as nasogastric tubes (NG) or transcutaneous gastrostomy tubes (GTs). GT placement is common in preterm infants and low birthweight infants, particularly in infants with BPD.⁵¹ However, the frequency and timing of surgical intervention, such as GTs and/or Nissen fundoplication (if gastro-esophageal reflux is identified), varies widely by site and clinical practice. McGrath-Morrow et al. examined the association of the presence of a GT or Nissen/GT and respiratory outcomes of children with BPD in the first 2 years of life and found that compared to those without GTs, both children with GTs and children with Nissen/GTs took longer to wean off supplemental oxygen.⁴⁷ In the same study, there was no significant difference in reported respiratory morbidities among the three groups. However, children with Nissen/GTs did have higher re-hospitalizations after initial discharge.⁴⁷ Similar findings of increased hospital admissions in patients with GTs for the treatment of aspiration compared to patients with aspiration fed orally have been reported by McSweeney et al. Notably, however, their study was not restricted to only patients with BPD.⁵² In both of these studies, it was not possible to determine if GTs contributed to respiratory morbidity or were simply a marker for more severe disease.

In addition to swallowing dysfunction, feeding can also be impaired by oral aversion, feeding intolerance, and gastroesophageal reflux disease (GERD) which subsequently may contribute to worsening lung disease and impaired growth.^{47, 49, 53}

As noted above, poor growth can impact lung development. Conversely, lung disease can impact poor growth. Duration of ventilator therapy has been found to be a risk factor for poor growth in very low birth weight infants with BPD.⁵⁴ Furthermore, pulmonary function testing in childhood has shown correlation between airway obstruction and body composition. Studies have shown children with BPD and airway obstruction have lower fat mass and lower free-fat mass compared to controls.^{6, 55}

The multifactorial etiologies of feeding and swallowing dysfunction in this population emphasizes the importance of an interdisciplinary team approach to feeding in both the inpatient and outpatient setting for patients with BPD.^{56, 57} Additionally, more research is needed to evaluate best approaches to the work-up and management of feeding in this population.

Approach to Nutritional Management of Infants and Children with BPD

In spite of the increased number of patients with BPD, there is scarce evidence addressing how to optimize nutrition in patients with established BPD. Frequent assessments are critical to maintain optimal nutrition and growth in these patients.¹¹ Close monitoring of nutritional status and growth is important not only to ensure an adequate growth trajectory but also to monitor for excess in weight gain due to intensive nutritional support. Excess weight gain in early infancy may increase the risk of insulin resistance and adult onset metabolic disease.^{58, 59}

Optimal growth is essential for the infant with BPD to be successfully weaned from oxygen and to continue the delayed alveolarization that can occur during childhood. One of the criteria for weaning oxygen is adequate growth and weight gain (goal of 20 to 30 grams per day).⁶⁰

Although breastfeeding is encouraged, many of these infants will require additional fortified breastmilk or formula to maintain adequate caloric intake and mineral supplementation. Along with additional calories, maintaining adequate micronutrients and vitamins is essential for

adequate lung growth.^{39,61} As respiratory symptoms improve and growth velocity is maintained off oxygen, caloric intake is often weaned around 1 year of life. Some children with severe BPD will require additional calorie drinks (Pediasure, Carnation Instant Breakfast) into early childhood to maintain adequate growth.

Nutritional management in BPD can benefit from an interdisciplinary team approach that includes pulmonologists, gastroenterologist, dietitians, and speech pathologists. At every follow-up visit, nutritional history should be obtained including type and frequency of feeding, nutritional supplements, food allergy or intolerance, chewing and swallowing problems, vomiting, diarrhea or constipation, gagging, choking or gastroesophageal reflux, behavioral problems related to eating, and current and past medications.⁶² Body measurements (weight, length, and head circumference) should be obtained at every follow up visit and plotted on appropriate growth charts. Blood tests can help in further assessment of nutritional status. Electrolytes should be monitored if the patient is receiving diuretics. Liver function tests are necessary to assess parenteral nutrition related cholestasis. Other mineral levels (calcium, phosphorus, magnesium, and alkaline phosphate) may indicate ongoing metabolic bone disease. If an iron deficiency is suspected, complete blood count and serum ferritin levels may be obtained. Albumin and prealbumin levels can aid in assessing energy and protein intake over a longer period of time. Specific vitamins, including vitamin A, and minerals, including zinc and selenium, can be determined if deficiency is suspected. The nutritional plan for infants should be individualized before discharge and should be reviewed regularly by a nutritionist with specific training and skills in the management of patients with established BPD.

The early recognition and management of swallowing dysfunction, oral aversion, and gastroesophageal reflux is essential to ensure feeding adequacy. Follow up by a pediatric gastroenterologist is recommended for infants with associated gastrointestinal problems, such

as GERD, short gut syndrome, or intestinal motility disorders. Chronological age may not be a good predictor for initiation of solid food as infants with BPD may achieve these developmental skills later due to prolonged hospitalization. Foods with thicker consistency may be swallowed more easily. If there is food aversion or respiratory compromise, a speech pathologist or occupational therapist should be consulted for supervised feeding. Oro-motor stimulation should be initiated early on for infants needing prolonged tube feeds. Some feeding problems may be related to psychosocial issues and referral to behavioral psychologist may be required.

Summary

Growth and nutrition play a key role in long-term pulmonary outcomes in infants with BPD, and the multiple factors can contribute to growth failure in this group of patients. Frequent monitoring and an aggressive approach to growth failure, feeding problems, and inadequate nutrition should be essential elements of the care of infants with BPD, and an interdisciplinary approach will help achieve optimal outcomes.³⁹ Despite the importance of nutrition in BPD, there is a paucity of high quality evidence to help guide selection of feeding regimens or use of interventions such as GTs that will result in optimal nutritional outcomes in BPD. While randomized controlled trials may be unethical or impractical, well-designed prospective cohort studies may identify practices associated with better nutritional outcomes, and these studies are urgently needed.

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Table 1. NICU morbidities and other factors associated with a higher incidence of postnatal growth failure
Bronchopulmonary dysplasia
Necrotizing enterocolitis
Severe intracranial hemorrhage
Late-onset sepsis
Male gender
Need for assisted ventilation on the first day of life
Need for respiratory support at 28 days of age
Treatment with postnatal steroids