Nutritional problems of children with bronchopulmonary dysplasia after hospital discharge

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Abstract

The last decades have seen significant improvements in the care of premature infants. The introduction of new approaches, especially in the ventilatory management, have led to significant increase of survival rate of low and extremely low gestational age infants. These populations of neonates, however, often experience prolonged mechanical ventilation, which is widely recognized to be closely related to bronchopulmonary dysplasia (BPD) development.

The management of BPD, which is a multifactorial disease, requires a multidisciplinary approach and remains challenging for all the physicians involved. In fact, short and long-term sequelae are not only related to pulmonary performances but include neurological impairment and growth deficiency.

A proper nutrition management since the very first days has shown to significantly contribute to the optimal maturation and functionality of the lung.

In this paper, we aim to give an overall of the main principles of nutrition in infants born prematurely, with specific regard to the interventions, which could be relevant in infants affected by BPD.

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Introduction

Bronchopulmonary dysplasia (BPD) is widely recognized as a multifactorial disease. Extreme prematurity, genetic susceptibility, low birth weight at birth, pre and post-natal infections, the persistence of patent ductus arteriosus, postnatal fluid overload and prolonged mechanical ventilation are the main factors associated with BPD development.

Preterm infants, especially those of very low birth weight (VLBW, <1500 gr) and of extremely low birth weight (ELBW <1000 gr), often undergo mechanical ventilation for a prolonged period, and thus are at high risk to develop BPD.

In the last decades, the pathophysiology and the treatment of BPD have changed considerably,[1] in particular as consequence of significant improvements in obstetrics and neonatal care. In fact, nowadays antenatal steroids, gentle ventilation at birth and during NICU stay and surfactant replacement therapy are all part of standard routine clinical practice in the treatment of Respiratory Distress Syndrome (RDS), with the aim to reduce the risk of lung injury.

Although these interventions have increased survival rates in extremely preterm infants, short and long-term neurological and respiratory sequelae are still problems clinicians have to face with.

The management of children with BPD, particularly during the first two years of life, remains a challenge for parents and physicians. Thus, a multidisciplinary team is mandatory to manage this severe disease properly.

Nutrition in the development of BPD

Nutrition plays a crucial role in the normal lung's development and maturation. For this reason, an overall malnutrition can worsen the vulnerable preterm lung and favor oxidative damage.

Fluid

Neonatal lung function is influenced by fluid overload since pulmonary edema can decrease compliance and increase airway resistance. Therefore, weight, urine output and electrolytes serum levels[2,3] need to be strictly monitored. In a recent systematic review of 5 randomized clinical trials, it has been shown that a restricted fluid intake compared to a liberal one during the neonatal period could determine a trend toward less BPD and a marked reduction in patent ductus arteriosus (PDA) and necrotizing enterocolitis (NEC).[4] Hence, infants at high risk for BPD should not exceed 80-100 ml/kg/day of initial fluid intake with a gradual increase during the first seven days up to 120-150 ml/kg/day.

Carbohydrates

Carbohydrates are the primary source of energy for neonates and, in the first days of life, they are administered with intravenous glucose solutions. Preterm infants with severe RDS or BPD have much higher resting energy expenditure (REE) and could experience ineffective wash-out of CO_2. For this reason, increasing intravenous glucose up to 10-12 mg/kg/min in these patients results in about 20% increase in O_2 consumption and REE.[5,6]

Protein

There is no clear data regarding the correlation between the use of high or low intake of proteins and long-term respiratory outcomes. Neonates receiving high nutritional support during the first three weeks of life, seem to show a low incidence of moderate and severe BPD.[7] These findings are confirmed by a recent Italian study,[8] showing that an increase in the enteral energy intake of preterm infants with mild and moderate BPD, with a similar protein intake (3.2 vs 3.1 g/kg/die in the two groups of preterm infants), leads to a better post-natal weight gain velocity. Moreover, this study showed a correlation between this hypercaloric enteral feeding and the severity of BPD or NEC. Nowadays, it seems that a protein intake of 3.5-4 gr/kg/day should be adequate for preterm infants, irrespectively of whether they are affected by BPD or not.

Triglycerides and fatty acids

Long-chain polyunsaturated fatty acids (LCPUFA) have both pro-inflammatory (n-6) and anti-inflammatory (n-3) role. Animal studies show that administration of docosahexaenoic acid (DHA) can increase surfactant production.[9,10] It is well known that ELBW infants at birth have low levels of DHA, which further decrease during the first weeks of life. The deficiency is mainly due to prolonged administration of intravenous lipid solution free from DHA.

Moreover, the DHA concentration is lower in infants who develop BPD.[11] There is evidence that maternal supplementation with tuna oil, increase DHA in human milk and reduce the risk of BPD in infants with a birth weight under 1250 g.[12] However, to date, there is still debate about the role of DHA in reducing BPD development.[13]

Calcium, phosphorus, and magnesium

Careful monitoring of calcium, phosphorus, and magnesium serum levels, as well as adequate supplementation, are essential to maintain the normal neonatal lung function. Hypocalcemia has been associated with apnea episodes and laryngospasm in preterm infants.

A retrospective study of ELBW infants demonstrated a correlation between hypocalcemia in the first 48 hours of life and BPD development.[14] An inadequate intake of calcium, phosphorus and vitamin D can cause a severe chronic alteration of bone mineralization with subsequent thoracic instability and negative impact on the respiratory pattern. VLBW infants, especially those with intrauterine growth restriction (IUGR), frequently develop hypophosphatemia immediately after birth or in the first seven days of life, and this is associated with higher risks for sepsis, prolonged ventilation and BPD.[15,16] Moreover, pulmonary surfactant's phospholipids are made, among others, of phosphorus. Children with BPD are at higher risk for calcium and phosphorus deficiency, particularly due to low enteral intake, fluid restriction and the frequent use of diuretic drugs.

For these reasons, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend calcium intake of 120-140 mg/kg/day and 60-90 mg/kg/day of phosphorus. These levels are reached using fortifiers of human milk or in preterm formulas or post-discharge formulas.

Vitamin A

Vitamin A deficiency is associated with decreased lung growth and repair. Preterm infants have lower serum and tissue concentration of retinol, and this condition is associated with high risk of chronic lung diseases. A randomized clinical trial has demonstrated that intramuscular administration of 5000 UI of vitamin A three times a week for four weeks, starting in the first days of life, reduces the risk of BPD by about 7%, with a number to treat needed to treat of about 14 infants.[17] The benefits of vitamin A administration seem to be limited only to the neonatal period, without reduction of pulmonary disorders at 8-22 months of follow-up. Despite these results, the supplementation of vitamin A has not been widely adopted.

Nutrition at discharge

In the last decades, the increasing rate of survival in VLBW and ELBW infants has unfortunately led to the onset of several neurological and growth adverse outcomes. Moreover, particularly during the first two years of life, these children (especially infants with BPD) are at high-risk of re-hospitalization.

BPD patients show higher mortality risk,[18] obstructive respiratory symptoms and frequent airway infections (especially caused by respiratory syncytial virus), often until the age of 8.[19] They also have lower cognitive abilities and performances at school;[20] they suffer from reduced motor skills gastroesophageal reflux disease,[21] hearing loss and ROP.[22] Moreover, these patients frequently experience problems in height and weight growth and a reduced fat storage.[23]

For all these reasons, a careful plan at discharge is fundamental and should be decided in agreement with a multidisciplinary team, consisting of neonatologist, pulmonologist, nutrition specialists and qualified neonatal nurses.

Growth and nutrition

Growth faltering is quite common among BPD patients, and it is mainly due to an increase in energy expenditure and nutrient and caloric needs. Moreover, feeding could be impaired by oral aversion, intolerance, and gastroesophageal reflux disease. Often a misdiagnosed hypoxia, particularly during night hours when oxygen saturation physiologically decreases, could explain a poor weight gain. Consequently, BPD patients do not achieve adequate weight and height during their first year of life, even if protein and energy intake are similar to those recommended for healthy term infants.

During the first years of life, preterm infants are smaller and lighter when compared to healthy infants, with a catch-up growth between 8 and 14 years of life. Considering the relevant effects of malnutrition on brain development and cognitive ability,[24] a strict growth monitoring and the evaluation of nutritional aspects are mandatory. The aim would be to achieve a growth rate and percentiles comparable to those of term infants.[25]

At 40 weeks post-menstrual age, weight, length, head circumference and length/weight ratio, should be monitored on standard growth charts like CDC-WHO 2010. An optimal target for weight gain should be about 20-30 g/day. Head circumference growth has to be strictly monitored since it's known that a small head circumference at one year of age is related to low cognition ability and

learning difficulties during school age.[26] Regarding head circumference, an optimal growth target should be 0.4-0.6 cm/week and 0.7-11 cm/week for linear growth.

Although weight assessment is quite easy to perform, this could be affected by body fluid balance and does not reflect changes in lean body mass. Length measurement, instead, even if it could be more difficult to perform, reflects more accurately the nutritional intake and the lean mass storage, as well as organs' development and growth.[27]

Several studies showed that energy needs of BPD children are 15-25% higher than those of healthy infants, due to a higher metabolic rate.[28] The European Pediatric Society of Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends a daily energy intake of 110-130 kcal/kg for an adequate growth of healthy preterm infants, while for BPD patients an higher intake up to 140 kcal/kg/day[29] is preferable. According to current recommendations, the growth of ELBW and VLBW infants should be as close as the one of the babies of the same gestational age. Therefore, it is necessary to use adequate fortifiers of human milk or specific preterm or post-discharge formula milk, which have higher protein content than standard ones. Several studies confirm that infants fed with higher protein intake showed a better weight gain without any consequences regarding metabolic or uremic acidosis.[30,31] Breast milk feeding should be encouraged for long-term beneficial effects especially on cognitive abilities; however, a milk fortification is still needed to ensure adequate caloric intake. Fortification should occur when enteral feeding reaches 80 ml/kg/day, and more than 50% of the total amount is breast milk. Available fortifiers contain variable amounts of proteins, carbohydrates, calcium, phosphate, electrolytes, vitamins and other minerals. The fortification can be standard or individualized. This last one should be preferred since it can prevent protein deficiency; it can be adjusted according to milk analysis and the infant's blood results.

If breastfeeding is not possible, preterm or post-discharge formulas contain higher energy (72-74 Kcal/100 ml) and an increased amount of proteins (1.8-1.9 g/100 ml) in respect to the formulas especially produced for healthy infants, and they should be taken from 3 to 12 months after discharge. They are also enriched with vitamins, minerals and other elements.

To meet the energy needs of children with BPD, these formulas should be taken at very high doses (180-200 ml/kg/day); however, considering the difficulties in feeding that these children often show, more concentrated formulas are preferable (also over 80 kcal/100 ml). However, excessive energy density could increase osmolality, causing diarrhea or malabsorption. For this reason, the formulas should not be excessively caloric (> 80 kcal/100 ml), even if it is possible to gradually increase their density (*e.g.*, 3 kcal/30 ml) up to 100 kcal/100 ml[32] through the supplementation of medium-chain triglyceride or glucose polymers.

Particular attention should also be paid to proper supplementation of vitamins, folate, minerals, iron and other elements. In fact, BPD infants are frequently at risk for anemia, especially because of low iron storage. It is, therefore, necessary to provide these children supplemental iron (2-4 mg/kg/ day) between four and eight weeks of life and to continue this therapy for 12-15 months.

If the infants affected by BPD do not achieve adequate nutrition promoting an optimal catch-up growth despite improvement in oral feeding, enteral feeding should be considered. This modality of nutritional support could increase caloric intake, reduce gastric distension that worsens respiratory movements and ensure better digestion as well as intestinal absorption.

In patients with milder disease, this enteral diet can be administered with nasal or gastric tubes, while in the most severe patients gastrostomy may be used.

Conclusions

Available data suggest that in preterm infants full maturation of pulmonary alveoli and growth recovery occur in the first two years of life, but 10-25% of preterm infants affected by BPD are malnourished after this time. It is also widely shown that the nutritional status of these children at two years of age influences nutrition and respiratory outcomes in the second childhood.[33,34]

For all these reasons, it is essential to pay particular attention to the feeding of VLBW and ELBW preterm infants, especially if they have developed BPD, both during the recovery phase in neonatal intensive care unit and after discharge at home, in order to minimize the possible consequences of malnutrition.

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