Nutrition in Bronchopulmonary Dysplasia

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Bronchopulmonary dysplasia (BPD), also named chronic lung disease of prematurity, is a lung disease that causes dependence on oxygen for an extended period of time.

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1. Introduction

Bronchopulmonary dysplasia (BPD), also named chronic lung disease of prematurity, is a lung disease that causes dependence on oxygen for an extended period of time [1][2][3]. The “new BPD” seen today results from a reparative process in alveolar and vascular compartments of the lung, after injury caused by ante- and postnatal pathogenic factors leading to reduced, large, thin-walled alveoli, and less fibrosis when compared to the “old BPD” [2].

The definition of BPD has been a challenging issue. In 2001, a workshop sponsored by the National Heart, Lung, and Blood Institute defined BPD as the persistence of oxygen requirement at 28 days of life and 36 weeks postmenstrual age (PMA) [4]. A more recent Eunice Kennedy National Institute of Child Health and Human Development workshop proposed some refinements to the 2001 definition of BPD [5].

The overall incidence of BPD in infants delivered below 28 weeks’ gestational age is about 30–68% and is inversely proportional to the gestational age [6]. The large variability in rates among centers is partially related to differences in clinical practices, such as the criteria used for the management of mechanical ventilation [7].

Among postnatal factors, nutrition plays a central role in lung growth and repair [1][8][9]. After preterm birth, several problems associated with extreme immaturity result in difficulty in achieving sufficient energy and nutrient intake [10]. A retrospective cohort study reported that, in extremely preterm infants, high fluid intake containing low energy during the first postnatal week is associated with the severity of BPD [11]. Along the same lines, other studies have described the association of postnatal deficit in energy and nutrient and postnatal growth restriction with the development of BPD [12][13][14][15].

2. Fluid Management in Infants at Risk for and with Established BPD

Compared to full-term neonates, very low birth weight (VLBW) and extremely low birth weight (ELBW) infants have a higher proportion of body water, more immature renal function, and a limited capacity to eliminate excess of fluids [16]. A physiological contraction of extracellular fluid, with a negative water and sodium balance, occurs during the first postnatal week [16]. Excessive fluid intake will impair this physiological mechanism and is associated with a significant risk of hemodynamically significant patent ductus arteriosus [17]. Moreover, an early fluid overload (150–190 mL/kg/day) [18] may cause pulmonary edema, with reduction of lung compliance, increased airway resistance, and the need for more aggressive respiratory support [19][20][21].

A meta-analysis of randomized controlled studies determining the effect of fluid intake on morbidities and mortality in premature infants concluded that the risk of BPD was not significantly affected by water intake, although fluid restriction was associated with a trend toward reduced risk of BPD [22]. Thus, it seems prudent to employ a strategy of fluid restriction in preterm infants considered to be at high risk for BPD. In this regard, fluid restriction should be within the clinically acceptable limits of fluid intake, since reduction of free water intake may lead to an increase in renal solute load with the risks of renal dysfunction and nephrocalcinosis [23]. When fluid restriction is prescribed, evaluation of net fluid balance is mandatory, which includes the monitoring of body weight, urine output, plasma sodium, blood pressure, and functional echocardiographic assessment [23][24].

Body temperature and environmental humidity influence the fluids policy [25][26][27][28][29]. The temperature of the abdominal skin should be kept between 36.0 °C and 36.5 °C, and the inspired air temperature (hood, CPAP, or ventilator) between 34.0 °C and 41.0 °C at the Y-piece, with a relative humidity of 100% [25][26][27][28][29]. A survey on incubator humidity practices in the management of preterm infants found a wide variation in humidification practices, but the majority of the surveyed centers used a starting humidity higher than 80% [28]. A systematic review including 12 studies assessing preterm infants' outcomes related to incubator humidity concluded that 60–70% humidity in the first postnatal week was enough to reduce the transepidermal water loss in infants born at 26 weeks or older; however, more research is needed regarding more immature infants [27].

Phototherapy may increase insensible water loss and addition of 10–20 mL/kg/day to the total fluids may be needed, although this seems unnecessary when using the newer phototherapy lamps with light-emitting diodes [30].

3. Nutritional Requirements in Infants with BPD

Nutrition plays a critical role in the prevention and management in infants with BPD, and a vicious cycle may occur. Growth failure in BPD infants is predominantly due to malnutrition. Malnutrition, in turn, seems to worsen BPD probably by compromising lung development and function, and feeding difficulties in these infants can further affect nutrition [8][31].

As BPD is not typically diagnosed until 28 days of life or 36 weeks PMA, attempts to prevent postnatal growth failure cannot be made soon enough, as this condition can result in nutrient deficits that may be difficult to recover from [8].

In BPD infants, a status of increased respiratory work and inflammatory response, along with the lung damage/repair process, is characterized by higher energy consumption [25]. This energy should be provided in restricted fluid intake, since fluid overload may cause pulmonary edema, which can decrease lung compliance and increase airway resistance [32].

Uberos et al. [31], in a cohort study, found that infants who developed BPD, compared with those who did not, received a lower total intake of energy (76.1 vs. 91.1 kcal/kg/day), carbohydrate (11.6 vs. 12.6 g/kg/day), and fat (2.5 vs. 3.4 g/kg/day) during the first 14 days of life. Klevebro et al. [33] examined the effect of early nutritional intake on growth and the risk of BPD in 296 extremely preterm infants and found that, between days 7 and 27, every additional 10 kcal/kg/day in energy intake was associated with a 9% reduction in the risk of BPD.

Improved nutritional strategies have enhanced postnatal growth in infants at high risk of growth restriction [34]. In infants with chronic lung disease, a high-fat diet theoretically produces lower rates of carbon dioxide production than a diet with a lower fat and higher carbohydrate content [35]. However, pulmonary function test results were found to be equivalent in infants receiving high-fat or high-carbohydrate feedings [36]. In addition, 65% of nonprotein energy supplied as carbohydrate was found to be more effective than energy supplied as fat in sparing protein oxidation in enterally fed LBW infants [37].

In healthy preterm infants receiving adequate nutrition support, an optimal weight gain velocity of 15–20 g/kg/day is expected [38].

4. Functional Nutrients with Potential Beneficial Effects on BPD

The preterm infant's inability to down-regulate and maintain control of the inflammatory immune response may facilitate ongoing lung damage, leading to a chronic inflammatory state [39]. Some functional nutrients with antioxidant effects could play a role in reducing lung inflammation [39][40][41]. Despite the lack or limited evidence of their protective effect against BPD through an antioxidant effect or other mechanisms, their use with this purpose, as supplements in parenteral and enteral nutrition, is revisited.

In a historical cohort study of preterm infants with less than 30 weeks of gestation, a rapid decline in DHA and arachidonic acid levels in the first postnatal week, with a concomitant increase in linoleic acid (LA) levels, was observed [42]. Based on data from preterm infants and animal studies suggesting that docosahexaenoic acid (DHA) serves as a general preventive agent against inflammation, observational and interventional clinical studies were developed to improve DHA delivery in preterm infants to reduce the risk of BPD [39]. This effect was not observed in other clinical trials of breast milk-fed infants born at less than 29 weeks' gestation to mothers who were given DHA during the neonatal period, compared with the placebo. A meta-analysis including 14 randomized controlled trials that involved 3531 preterm infants investigated the efficacy of intervention with n-3 polyunsaturated fatty acids on the incidence of BPD and found no evidence (risk ratio 0.99; 95% CI 0.84–1.18) to support this intervention [43].

Glutamine during oxidative stress can reduce cell injury by increasing glutathione [44]. This finding motivated supplementation of this amino acid in preterm infants. However, a meta-analysis of 11 randomized controlled trials including 2771 preterm infants concluded that parenteral and/or enteral supplementation with glutamine did not decrease BPD [45].

N-acetylcysteine is a precursor of cysteine and is itself a free radical scavenger [23]. A multicenter, double-blind trial showed that a six-day course of intravenous N-acetylcysteine infusion during the first postnatal week did not prevent BPD in ELBW infants [46].

ELBW infants have low plasma and tissue concentrations of vitamin A, and vitamin A deficiency may predispose to BPD [47]. Clinical trials showed that intramuscular administration of vitamin A decreased the risk of BPD in ELBW infants [47][48]. Meanwhile, a systematic review and meta-analysis of four studies including 1011 preterm infants concluded that vitamin A supplementation for ELBW infants benefited oxygen dependency at 36 weeks PMA in survivors (pooled risk ratio, 0.88; 95% CI 0.77–0.99) Another systematic review and meta-analysis of three studies including 612 preterm infants assessing the effect of enteral vitamin

Vitamin E is another radical-scavenging antioxidant that protects cell membranes from oxidative injury [49]. Tocopherol deficiency worsens the effect of oxygen toxicity on lung tissue and its supplementation may have a protective effect on premature lungs [23]. A strong correlation of BPD with low plasma vitamin E and selenium levels measured in cord plasma and on the third postnatal day was reported in premature infants [41]. However, in preterm infants it was not demonstrated that supplemental vitamin E during the acute phase of therapy for respiratory distress syndrome modified the development of BPD [50].

Inositol, as a member of the vitamin B complex, is involved in surfactant synthesis and maturation, and its serum levels are low in preterm infants [23]. A meta-analysis evaluating the effect of inositol supplementation in preterm infants found a trend toward the reduction of BPD at 28 days, but this did not reach statistical significance [51].

Copper, zinc, selenium, and manganese act as co-factors of antioxidant enzymes, such as the copper–zinc superoxide dismutase and manganese superoxide dismutase [23][52]. However, in ELBW infants, an association between BPD and decreased antioxidant enzyme activities related to trace elements was not demonstrated [53].

In a prospective study including 83 preterm infants, it was found that BPD was independently associated with significantly lower serum zinc levels at term age than those who did not develop the disease [54]. A randomized controlled trial including 193 VLBW infants determined the efficacy of zinc supplementation in reducing morbidity. No difference was observed in the rate of BPD, necrotizing enterocolitis, sepsis, periventricular leukomalacia, or retinopathy of prematurity between the group receiving zinc supplementation and that not supplemented. However, the risk of developing at least one of these morbidities was significantly reduced (OR 0.513; 95% CI 0.280–0.939) in the supplemented group [55].

The reduced stores of selenium in preterm infants motivated supplementation, but a meta-analysis of three trials found no benefit of selenium supplementation in the development of BPD [56].

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