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Review

Potential Nutrients for Preventing or Treating Bronchopulmonary Dysplasia

Liya Ma [1,‡,*], Ping Zhou [1,‡], Josef Neu [2], Hung-Chih Lin [3,*]

[1] Department of Neonatology, Shenzhen Baoan Maternal and Child Health Hospital, China
[2] Department of Pediatrics, University of Florida, U.S.A.
[3] Department of Pediatrics, Children's Hospital and School of Chinese Medicine, China Medical University, Taichung, Taiwan

EDUCATIONAL AIMS

Through this review, we hope the readers could understand the following points.

- Nutritional deficiency might interact with other well-accepted etiologic factors that lead to BPD.
- Current evidence shows that vitamin A and n-3 LCPUFA can prevent BPD, although the optimal dose, route, and duration of administration need to be further studied.
- L-citrulline might be a promising strategy for treating chronic pulmonary hypertension associated with BPD in premature infants.
- Other nutrients, including glutamine, cysteine or NAC, inositol, and selenium, either showed no effects in preventing or treating BPD or need to be further studied.

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SUMMARY

Bronchopulmonary dysplasia (BPD) is a frequent complication occurring in extremely preterm infants. Despite recent advances in newborn medicine, the incidence of BPD does not appear to have changed markedly, and specific treatments and prevention strategies are still lacking. Nutrition plays an important role in normal lung development and maturation. Malnutrition may delay somatic growth and new alveoli development, thus aggravating pulmonary injury involved in the pathogenesis of BPD. However, few nutrients have been investigated for their potential to mitigate the pathogenesis of BPD. In this article, we reviewed the recent progress in research on potential nutrients useful for the prevention or treatment of BPD, including glutamine, cysteine and N-acetylcysteine, L-arginine and L-citrulline, long chain polyunsaturated fatty acids (LCPUFAs), inositol, selenium, and some antioxidant vitamins including vitamin A. Current evidence shows that vitamin A and LCPUFA can prevent BPD, and that L-citrulline might provide a new method to treat chronic pulmonary hypertension associated with BPD in premature infants. The effects of other nutrients on BPD prevention need to be further studied.

INTRODUCTION

Despite recent advances in newborn medical care, the incidence of BPD appears to not have changed markedly. Numerous risk factors for BPD development have been identified, including immaturity, oxygen exposure, mechanical ventilation, infection, and inadequate postnatal nutritional support. Several mechanisms, such as inflammation, oxidative stress, and abnormal vascular growth, have been implicated in the pathogenesis of BPD (Figure 1).

* Corresponding authors.
E-mail addresses: maliya226@qq.com (L. Ma), xianggalao@126.com (P. Zhou), neuj@peds.ufl.edu (J. Neu), d0373@cmuh.org.tw (H.-C. Lin).

‡ Liya Ma and Ping Zhou contributed equally to the manuscript.

Abbreviations: BPD, Bronchopulmonary dysplasia; RDS, respiratory distress syndrome; VLBW, very low birth weight; ELBW, extremely low birth weight; NAC, N-acetylcysteine; RCT, randomized controlled trial; PN, parenteral nutrition; GSH, glutathione; NO, nitric oxide; GPx, glutathione peroxidase; LCPUFAs, Long chain polyunsaturated fatty acids; DHA, docosahexaenoic acid; ROP, retinopathy of prematurity.

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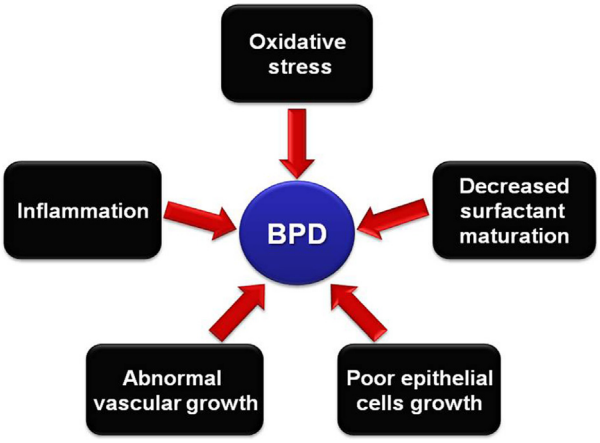

Figure 1. Possible mechanisms involved in the pathogenesis of BPD.

On the other hand, nutrition is a vital factor for normal lung development and maturation. Specific nutritional deficiency might interact with other well-accepted etiologic factors that lead to BPD. Malnutrition can delay somatic growth and new alveoli development. Premature infants who experience malnutrition and growth failure after birth are more likely to have BPD [1]. Owing to fluid restriction, diuretic use, mechanical ventilation, and increased oxygen expenditure, the nutrient needs of BPD infants compared with those of non-BPD infants may be much harder to meet. However, few nutrients have been investigated for their potential to mitigate the pathogenesis of BPD. In fact, vitamin A supplementation is the only nutrient-based therapy to have been extensively studied and recommended for BPD [2,3]. Some nutrients are potential candidates. In this review, we aimed to present information about the nutrients that are potentially useful for preventing or treating BPD (Tables 1 and 2).

NUTRITIONAL DEFICIENCY AND BPD

The current nutritional guidelines for preterm infants, including energy, protein, lipid, and carbohydrate needs, are not specifically tailored, and therefore may be insufficient, for those with high risk of BPD. Additionally, BPD infants might have higher energy expenditure than those without BPD, [4] suggesting that BPD infants may require a higher energy intake to achieve sustained growth. This is supported by a non-randomized interventional cohort study that showed enteral energy intake was positively associated with weight gain velocity during enteral nutrition in BPD infants, and inversely associated with the severity of BDP [5].

Although there is no consensus with respect to optimal nutritional management for BPD infants, studies have demonstrated that insufficient nutrition provision is associated with higher incidence of BPD in preterm infants [6]. Martaloun et al. reported that nutritional restriction and hyperoxia each interfere with alveolarization of the preterm rabbit lung and that nutritional restriction intensifies changes in the pulmonary architecture caused by hyperoxia [7].

BPD infants usually experience nutrient deficiency and malnutrition mainly because of delayed or insufficient nutritional support following delivery. Nutritional support of extremely low birth weight (ELBW) infants receiving intensive care is particularly

Table 1
Mechanism of nutrients to prevent or treat BPD.

Nutrients	Anti-inflammation	Anti-oxidant stress	Smooth muscle relaxation	Promoting maturation of surfactant	Improving lung cell growth
Glutamine	+	+	-	-	+
Cysteine,NAC	-	+	-	-	-
L-Arginine, L-citrulline	+	+	+	-	-
LCPUFAs	+	+	-	-	-
Inositol	-	-	-	+	-
Selenium	-	+	-	-	-
Antioxidant vitamins	-	+	-	-	-

Table 2
Evidence of nutrient supplementation on prevention or treatment strategy in BPD.

Nutrients	Animal models (Authors, Reference NO.)	Clinical trials (Authors, Reference NO.)	Outcomes
Glutamine	Perng WC et al, 2010. [13] Ma L et al, 2012. [14]	Poindexter BB et al,2004. [15]	Decreasing hyperoxia-induced lung injury in animal models. No effects on days of ventilation in VLBW infants.
Cysteine or NAC	Nagata K et al, 2007. [19] Langley SC et al, 1993. [20]	Sandberg K et al, 2004. [21] Ahola T et al, 2003. [22]	Decreasing hyperoxia-induced lung injury in animal models. No effects on prevention of BPD in ELBW infants.
L-Arginine or L-citrulline	Vadivel A et al, 2010. [28] Grisafi D et al, 2012. [31] Sopi RB et al, 2012. [32]	No clinical trials reported.	L-citrulline supplementation attenuated arrested alveolar growth and pulmonary hypertension and impaired relaxation of airways in newborn animal model of BPD.
LCPUFAs	Kinniry P et al,2006. [35] Rogers LK et al, 2011. [36] Ma L et al, 2012. [14]	Manley BJ et al, 2011. [38]	Effective in decreasing hyperoxia-induced lung injury in animal models. DHA supplementation reduced the incidence of BPD in male infants born at <33 weeks' gestation and in all infants with birth weights <1250 g in one RCT study.
Inositol		Hallman M et al, 1992. [43] Howlett A et al, 2012. [44]	Meta-analysis of inositol supplementation in preterm infants does not demonstrate a statistically significant reduction in the rate of BPD. A larger RCT has just been completed.
Selenium	Kim HY et al, 1992. [48]	Mentro AM et al,2005. [49] Darlow BA et al, 2000. [50]	Cochrane review shows selenium supplementation had no effect on oxygen dependency at 28 days or total days of oxygen dependency in preterm infants.
Antioxidant vitamins	Albertine KH et al, 2010. [53] Babu TA et al, 2010. [55]	Darlow BA et al, 2011. [3] Gadhia MM et al, 2014. [26] Watts JL et al, 1991. [57] Manzoni P et al, 2013. [58]	Intramuscular supplementation of vitamin A in extremely premature infants decreases the incidence of BPD. Other vitamins show no effects on BPD prevention.