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Review

Pulmonary sequelae and functional limitations in children and adults with bronchopulmonary dysplasia

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Educational aims

- To review the current data demonstrating long-term pulmonary and physical functional limitations in survivors of bronchopulmonary dysplasia (BPD).
- To emphasize the importance of active surveillance by physicians for respiratory and physical functional impairments in survivors of BPD.
- To promote consideration of structured exercise rehabilitation programs for these patients, begun in early childhood, to optimize adult functional capacity.

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ABSTRACT

Preterm infants with bronchopulmonary dysplasia (BPD) often suffer from life-long pulmonary impairments in pulmonary physical function. This review summarizes our current understanding of the chronic pulmonary impairments and physical functional limitations associated with BPD from preterm birth to adulthood. It also identifies opportunities for intervention in children and adults living with chronic lung disease (CLD) after preterm birth.

Introduction

Preterm birth can result in long-term impairments of pulmonary function and exercise capacity [2–6]. Infants born before 28 weeks' gestation or with a birth weight less than 1500 g may have altered lung development [7] resulting from complex interactions between immaturity, maldevelopment, perinatal insults and environmental stresses (Table 1) [8]. Prenatal injuries relate primarily to maternal health and placental conditions and include chorioamnionitis, placental insufficiency and intrauterine growth restriction [1]. Postnatal insults relate mostly to environmental insults such as mechanical ventilation, high oxygen exposure, infections and inflammatory responses [1]. Oxidative stress resulting from toxins, infection, inflammation, oxygen toxicity and an immature antioxidant system can interrupt distal lung growth and repair mechanisms and contribute to the development of BPD. Genetic and epigenetic susceptibilities are thought to play a role, but specific mechanisms have yet to be elucidated [9].

Bronchopulmonary dysplasia

In 1967, when most surviving preterm infants were born after 30 weeks gestation, Northway and colleagues described a disease generated by ventilator-induced lung injury and oxygen exposure in infants born preterm [10]. Wide-spread surfactant use resulted in the emergence of a second phenotype, "new BPD", in infants born at earlier gestational ages (Table 2) [11]. As viability decreased to <28 weeks gestational age, insults resulting from medical treatments occurred in the context of a more immature lung, causing dysmorphic growth and interrupted maturation. Affected lungs displayed less regional heterogeneity and scarring, but mild airway smooth muscle thickening and fibroproliferative changes, fewer dysmorphic arterioles and fewer but larger alveoli [1,12]. As the phenotypes of BPD evolved so did attempts to better classify the disease. In 2001, the National Institute of Child Health

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Table 1
Etiologic factors in BPD.

Prenatal	Perinatal/postnatal	Developmental	Environmental
Intrauterine Growth Restriction	Prematurity	Immature antioxidant system	Prenatal, perinatal, postnatal toxin exposure
Maternal chronic disease	VLBW	Dysfunctional repair mechanisms	Tobacco smoke (maternal, second-hand, first-hand)
In utero infection (chorioamnionitis)	Oxidant injury	Genetic/epigenetic susceptibility	Environmental pollution
Poor maternal nutrition, obesity	Mechanical ventilation	Interrupted distal lung and vascular growth	
Placental pathology	Hypoxia		
Maternal stress	Infection/inflammation		
Steroids	Surgery		
Ethanol	Congenital disease (CDH, CHD, PPHN, pulmonary hypoplasia)		
	Aspiration		
	Poor nutrition		
	Steroids		

VLBW, very low birth weight; PDA, patent ductus arteriosus; CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; PPHN, persistent pulmonary hypertension of the newborn.

Table 2
Comparison of "old" and "new" BPD.*

"Old" BPD	"New" BPD
Growth disruption in late saccular to early alveolar development	Growth disruption in late canalicular to early saccular development
Disruption of established lung structure	Interrupted, decreased alveolar development
Distorted and obliterated alveoli, atelectasis	Fewer, larger, simplified alveoli, atelectasis
Intense inflammation and fibrosis	Mild inflammation and less fibrosis
Airway distortion and airway collapse	Smaller airways and airway collapse
Emphysematous change, bullous lesions	Little emphysematous change
Hypertensive lung microvascular remodeling, PH	Reduced, dysmorphic lung microvasculature, PH
Lifelong lung structural changes and airway obstruction	Lifelong lung structural changes and airway obstruction

PH, pulmonary hypertension.
* Adapted from Baraldi and Filippone [1].

and Human Development (NICHD) established consensus criteria for diagnosing and grading the severity of BPD [13]. The consensus definition required supplemental oxygen use for 28 postnatal days and incorporated the gestational age at birth. For infants born <32 weeks' gestation, severity was assigned at a postmenstrual age of 36 weeks or upon discharge home. Infants breathing room air were classified as having mild BPD, those requiring <30% oxygen as moderate BPD and those requiring ≥30% oxygen, positive pressure or both as severe BPD. Infants born >32 weeks' gestation followed the same severity criteria but were assessed at >28 but <56 postnatal days or discharge home. This classification system has not proven sensitive or specific for long-term outcomes [14], and lacks specificity for respiratory morbidities and health-care utilization in the first year [9,15]. In particular, the classification system, based on the degree of support rather than pathophysiology, was not designed to predict life-long impairment in pulmonary function or functional factors such as physical performance and exercise tolerance, muscle weakness, and postural changes [6,16].

Long-term pulmonary effects

Respiratory system compliance (C_{RS}) is the ability of the lungs and chest wall to expand, and respiratory system resistance (R_{RS}) is airway resistance to airflow during inspiration and expiration [17]. Both C_{RS} and R_{RS} are adversely altered in BPD. Initially in BPD, C_{RS} is decreased and R_{RS} is increased [18]. However, during the first two years after birth, extremely low birth weight (ELBW, <1000 g) children with BPD show improvements in respiratory system compliance (C_{RS}) and resistance (R_{RS}) [18]. In these former ELBW infants, values for C_{RS} (15.96 ± 0.65 ml/kPa/kg) and R_{RS} (3.0 ± 0.2 kPa/L/s) at 2 years approximate values obtained from healthy, term and preterm-born 2-year-olds (C_{RS} 9.2–18.4 ml/kPa/kg and R_{RS} 2.2–4.1 kPa/L/s) [19]. However, the forced expiratory flow at functional residual capacity (an indicator of airflow in peripheral airways) in most of these children is reduced by more than 40% of expected, indicating the persistence of airflow limitation [18]. Bronchodilator therapies are commonly used to relieve airflow limitation but with limited success in this population. On average, only one third of childhood survivors of BPD respond to bronchodilator therapy (ranging from 25 to 60%), as measured by pulmonary function testing (PFT) [20–23], and the response can diminish over time. For example, the number of bronchodilator responders can decrease from 30% at the initial trial of therapy to 20% within 24 months [24]. One explanation for the poor response to bronchodilator therapy may be the nature of the airway disease. Compared to term-born, school-aged and adolescent peers with asthma, children with BPD have a distinct pattern of airway obstruction and inflammation [20,25,26]. The airflow limitation experienced by BPD survivors is more often a fixed obstruction, likely due to a combination of irreversible, structural airway changes and neutrophilic inflammation [2,23,27]. This contrasts with the reversible obstruction and eosinophilic inflammation characteristic of many asthmatics [28–30]. Despite biopathological differences, children and adults with BPD are often diagnosed with asthma because their overt symptoms (wheezing, cough, increased work of breathing) are similar. However, emerging pathogenetic differences may influence future treatment choices, possibly tailored more specifically to non-eosinophilic inflammatory mechanisms [30–32].

While circumstances accompanying preterm birth contribute to the development and progression of BPD, adolescents born extremely preterm continue to experience oxidative airways stresses

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