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Review Article

Bronchopulmonary Dysplasia (BPD) Long-Term Pulmonary Sequelae in Premature Infants: A Review of the Literature

Talal Alzahrani*, Esmail Alzahrani, Maysoon Fageer, Omar Muttar and Oneza Ahmareen

King Faisal Specialist Hospital and Research Centre, Medina, Saudi Arabia

***Corresponding Author:** Talal Saleh Alzahrani, King Faisal Specialist Hospital and Research Centre, Medina, Saudi Arabia.

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Abstract

Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease in infancy which was first described in 1967 by Northway., *et al*. It occurs mainly in premature infants who require respiratory support, and O_2 supplementation up to 36 weeks of corrected gestational age. Advances in neonatal care have resulted in improved survival rates of premature infants with BPD raising concerns regarding the long-term complications of the disease.

In this review article, we aim to discuss the long-term pulmonary complications of BPD such as pulmonary hypertension, home O_2 therapy, increased risk of viral respiratory infections, pulmonary dysfunction, asthma-like symptoms, exercise intolerance, obstructive sleep apnoea (OSA) and other possible structural morbidities.

We also discussed the possible implications of this diagnosis on health system, new modalities in screening, novel experimental preventive interventions, as well as the best practices to improve the pulmonary outcome of BPD survivors.

Keywords: *Bronchopulmonary Dysplasia (BPD); Pulmonary Sequelae; Premature Infants*

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease mostly seen in premature babies who required respiratory support, oxygen therapy up to 36 weeks of corrected gestational age. BPD was first reported in 1967 by Northway., *et al*. in a group of premature with respiratory distress syndrome [1]. Advancement in antenatal and peri-neonatal care improve the survival rates of premature infants with low and very low birth weight, in which BPD remains the most common adverse outcome [1]. It is also the most frequent chronic lung disease in infancy in general [1].

The most updated definition of BPD stratified the patients to mild, moderate, and severe subgroups taking into account total duration of oxygen supplementation, positive pressure requirements and gestational age, in addition to oxygen dependency at 36 weeks post menstrual age (Table 1) [1].

Gestational Age	Less than 32 weeks	More than 32 weeks
Time points of assessment	36 wk PMA or discharge to home, whichever comes first	> 28d but < 56d postnatal age or discharge to home, whichever comes first
Treatment with oxygen > 21% for at least 28d plus		
Mild BPD	Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56d postnatal age or discharge, whichever comes first
Moderate BPD	Need * for < 30% oxygen at 36 wk PMA or discharge, whichever comes first	Need * for < 30% oxygen at 56d postnatal age or discharge, whichever comes first
Severe BPD	Need * for ≥ 30% oxygen and/or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need * for ≥ 30% oxygen and/or positive pressure (PPV or NCPAP) at 56d postnatal age or discharge, whichever comes first

Table 1: *NCPAP = Nasal Continuous Positive Airway Pressure; PMA = Post Menstrual Age; PPV = Positive Pressure Ventilation. Definition of Bronchopulmonary Dysplasia: Diagnostic Criteria. Copyright © 2016 American Thoracic Society. Jobe, A.H.; Bancalari, E. Bronchopulmonary Dysplasia. Am. J. Respir. Crit. Care Med. 2001, 163, 1723–1729. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.*

BPD is the result of a multiple pre- and postnatal factors that compromise normal development in the premature lung. Prematurity, respiratory support, oxygen toxicity, pre- and postnatal infection, inflammation, and growth restriction or nutritional deficits can all contribute to disruption of alveolar and pulmonary vascular development [1]. It is well known that BPD influences both pulmonary and neurodevelopmental outcomes as well as risk of mortality [1].

In this review article we will focus on the long-term pulmonary complications of BPD, which constitutes a great burden on the health system and its consequences continue into adulthood. In a recent study of a health care burden of BPD, rates of readmissions (due to pulmonary-related or non-pulmonary -related causes) to the hospital were significantly higher in infants with BPD compared with those without. Emergency room visits due to respiratory illness were also higher in infants with BPD [2]. The use of pulmonary medications during the first year after index hospitalization was reported in 16.7% infants with BPD compared to 15.4% infants without BPD [2].

Methods

A comprehensive search limited to English language was performed using PubMed applying the following search terms: (bronchopulmonary dysplasia) and (Premature) and (pulmonary sequelae) in various combinations. The search was conducted using these terms in the keywords, titles, and abstracts.

The articles were first scanned based on the title and abstract and were classified into three groups (include, exclude, or unclear). The full-text version of all unclear articles was checked and subsequently classified in one of the two other groups (include or exclude). All manuscripts were assessed for inclusion criteria written in English, included premature babies' cohorts, published in the 2010 - 2023 period and covering the scope of this literature review.

The literature search identified a total of 1071 articles. Sixty articles were included as they fulfil the above-mentioned inclusion criteria. Some articles from adult data are used for the sake of completion of this review.

Results

Home oxygen therapy

Home oxygen therapy is among the earliest complications in some premature babies with moderate-severe BPD upon discharge from neonatal intensive care unit (NICU). According to our review of articles, around 47% of cases with BPD were discharged on home O_2 [3]. Home O_2 may be considered to facilitate early discharge of clinically stable infants, without apnoea or other significant medical concerns and who are established on oral feeds with consistent weight gain. Parental education and confidence are critical in the efficacy and safety of a home oxygen programme. The American Thoracic Society guidelines suggest target SaO_2 > 93% [4] and the European Respiratory Society suggesting SaO_2 ≥ 90% [5].

Pulmonary hypertension (PH)

Birth of premature infants during the canalicular and saccular stages of lung development appears to disrupt the normal program of alveolar and vascular development, resulting in alveolar simplification, dysmorphic capillaries, and increases in vascular and airway smooth muscle cells. Patients with BPD have a reduced expression of proangiogenic factors such as: vascular endothelial growth factor-B (VEGF-B), VEGF receptor-2 and angiopoietin receptor Tie-2. Furthermore, premature infants receiving mechanical ventilation have increased expression of anti-angiogenic factors (endoglin and thrombospondin 1) [6], all of which will lead eventually to increased vascular tone and PH.

The pooled incidence of PH in patients with BPD (any severity) is 17% and 24% in moderate-severe BPD [13].

In a systemic review and meta-analysis study done by Nagiub M., *et al*. Nine risk factors to develop PH in infants with BPD was identified: lower gestational age at birth, lower birth weight, small for gestational weight, prolonged duration of mechanical ventilation, use of high frequency oscillatory ventilation, length of stay in the hospital, oligohydramnios, sepsis, severity of BPD and multiple births [7]. Other studies included the association of persistent ductus arteriosus as another important risk factor due to increased pulmonary flow [8].

In 2015, the pediatric arterial hypertension consensus by the American Heart Association (AHA) and the American Thoracic Society (ATS), recommended universal PH screening by echocardiography in patients with BPD [9]. Different echocardiography-based screening protocols are proposed in the literature, articles by Nagiub M., *et al*. and Savoia M., *et al*. [7,10,11] and further research work needed to validate the suggested cut-offs values that were included in those protocols. AHA and AST defined PH as a mean pulmonary arterial pressure equal or more than 25 mmHg in children more than 3 months of age at sea level with a pulmonary artery wedge pressure less than 15 mmHg and a pulmonary vascular resistance index of more than 2 WU/m^2 [9].

Several biomarkers were studied as a screening marker for PH in neonates with BPD: Brain-type Natriuretic Peptide (BNP), N-terminal pro-BNP (NT-proBNP), asymmetric dimethylarginine, angiopoietin-1, endostatin. A significant increase in 3 proteins (MUC5B, BPIFB1 and IGLL1/IGLL5) was observed in tracheal aspirations of preterm infants with BPD and PH. As such, they were proposed as potential markers of PH in BPD patients who were intubated, but further studies are needed to clarify their utility. More investigations are needed to confirm its validity and accuracy in neonatal population [6,12].

A predictive model combining the clinical data and the genotype of the BPD patients was developed by Trittmann JK., *et al*. and the primarily findings were that patients - with larger birthweight and gestational age and who are positive for single nucleotide polymorphism (SNP) in the arginase-1 gene (ARG1 rs2781666) and dimethylarginine dimethylaminohydrolase-1 (*DDAH1* rs480414) gene- can be stratified as low risk for developing PH [14]. By identifying the high versus low-risk patients, a more accurate screening programs can be developed.

While classical PH medications such as sildenafil (Revatio) can improve the pulmonary arterial pressure and respiratory score and decrease the mortality rate without serious adverse effects in patients with BPD and PH [15,16], more refractory cases can benefit from a combination of oral tadalafil and Bosentan [17] or prostaglandin I2 analogues (Epoprostenol and Treprostinil) [18]. In the severe irreversible BPD-PH cases extracorporeal life support (ECLS) or even lung transplant could be considered [19,20].

Finally, it is important to mention that experimental studies on rats models of BPD showed several interventions- (such as IL-1 receptor antagonist, serotonin 2A receptor antagonist, genipin, riociguat, L-citrulline, endothelial colony-forming cells conditioned media and Mesenchymal stem cell (MSC) extracellular vehicles (EVs))-that are able to attenuate the effects of hyperoxia-induced lung injury and prevents the end result of PH [21-27].

Viral respiratory infections

As type II cells in lung contributes to innate immune system and alveolar repair, their lost as in BPD patient will expose them at risk of being sensitive to viral respiratory illness [28].

BPD patients are susceptible for RSV infection and can have further impaired lung function in future, immunizing them with palivizumab is recommended and accepted principle universally. In pre palivizumab era BPD was associated with increase rate of hospitalization due RSV infection by twelve folds [29].

On the other hand, rhinovirus which is one of known triggers of asthma exacerbation can lead to increase in cytokine secretion in BPD patient's and can increase the rate of hospitalization [30]. As the influenza virus infection is a known public health issue, it has great burden in patient's with chronic lung disease like BPD patient's, a large cohort study found 5 folds increase in hospitalization rate for patient's with chronic lung disease in comparison to healthy population [31]. Furthermore, there are some reported cases of acquiring candida infection, with BPD patient's likely being on inhaled corticosteroids for long therapeutic courses [32].

Abnormalities in lung function test (LFT) and high-resolution CT (HRCT)

Several meta-analysis studies, like Kotecha., *et al*. showed impaired lung function in BPD patient's, and several objective predictors with spirometry can be used to follow patient's with BPD which show that these will not achieve optimal lung value's by their adulthood [33]. ELBW infant's can have lower lung function especially observed in pre surfactant era in comparison with infants with normal birth weight, however having BPD with ELBW can put a burden in lowering lung function [34].

Pulmonary function test (PFT) monitoring during infancy, childhood, adolescence and adulthood for whom born preterm less than (32 weeks) has been showed reduced spirometry outcomes with obstructive pattern in form of low FEV1 and normal FVC (35). FEV1 was further reduced in infants who have BPD in top of prematurity [35]. Severity grading of BPD from mild, moderate to severe wouldn't change the lung function outcomes, though it can affect the need of supplemental oxygen [36]. In conclusion spirometry objectives can be used early in life for patient's with BPD to track possibility of having obstructive airway disease in adulthood [36].

Oppenheim., *et al*. compared chest x-rays and HRCTs scans in survivors of BPD and concluded that HRCTs are much more sensitive in visualizing structural changes in the lungs. Wong., *et al*. described emphysema, linear densities, and sub-pleural triangular densities in a group of young adults with a history of BPD. Other studies showed that presence of abnormalities on CT scans was significantly associated with abnormalities of lung function, and a higher HRCT score was associated with reduction in FEV1, suggesting that radiological abnormalities correlated well with extent of pulmonary function abnormalities [37].

Newer modalities such as hyperpolarized gas magnetic resonance imaging scans and arterial spin labelling (ASL) may provide an alternative mode of evaluation without the radiation exposure of CT scans. Screening protocols with less radiation exposure will help evaluate and prognosticate lung function of survivors as they age [37].

Airway hyperreactivity and obstructive pulmonary diseases

Many theories link the pathogenesis of BPD with hyperoxia and proinflammatory state from volutrauma and barotrauma in the neonatal period. For instance, the effect of hyperoxia in newborn mice exposed to high percentage of oxygen, showed more hyperreactive airway and inflammation in adult mice than the control group on room air oxygen [38,39]. Moreover, Raffay., *et al*. discovered that hyperoxia raises the level of S-nitrosoglutathione reductase (GSNOR) which catalyse the endogenous bronchodilator S-nitrosoglutathione (GSNO) leading to increased bronchial hyperreactivity in experimental mice [39].

Preterm children with and without BPD have more respiratory symptoms of cough and wheeze that may improve with age, while some studies showed progression into adolescence and adulthood [40,43,44]. Specifically, studies on preterm children showed increased asthma symptoms in the group with BPD compared to the matched-control group without BPD [41,42]. However, there is no difference between the markers of atopy between the two groups, which points to hyperreactivity mechanism rather than atopy [41].

Despite the previous mentioned details, still the specific association between BPD and asthma is not conclusive in most studies as shown in a large systematic review, in which the authors advised conducting prospective studies with long-term following plans of population at risk [45].

Of note emphysema was the main finding in high resolution CT (HRCT) in both adults and pediatric patients with a history of BPD regardless of severity [40,41].

Aerobic capacity

Many recent studies have been addressing aerobic capacity of children with BPD [40,46,47], for instance, a cross sectional study published in 2019 concluded that school children who were born preterm have the same aerobic capacity as term children. However, the development of BPD and obesity was associated with an increased percentage of maximum heart rate for age (%HR max) [46]. On the other hand, reduced exercise capacity has been manifested in adults born preterm regardless of the presence and absence of BPD [48].

A randomized control trial looked into the effect of exercise programs on children with BPD, found that the programs had significant clinical and statistical improvement of functional exercise capacity in the test group compared to their matched control group who did not participate in any physical activity during the study period [47].

Anatomical and structural long-term complications

Tracheobronchomalacia (TBM)

TBM is excessive airway collapsing especially during air expiration and it can be congenital or acquired [49]. It is one of the comorbidities of BPD as seen in a large multi-centre cohort study, and eventually it can increase the hospitalization rate. BPD patient's who have airway malacia may not benefit from bronchodilators and it can cause paradoxical effect on them [50]. The long-term treatment for patient's with malacia is PEEP, other treatment choices are still under investigation [51].

Bronchoscopy though widely used for the diagnosis of tracheobronchomalacia, in patients with BPD other modalities like tracheobronchography has been used with more sensitivity for diagnosis as it not affected by airway distortion or narrowing [49].

Pneumothorax

Spontaneous Pneumothorax during the neonatal period can happen due to multiple factors like low birth weight, prematurity, meconium aspiration and one of the pneumothorax ramifications is developing BPD. The pathophysiology behind developing BPD with pneumothorax is possibly secondary to alveolar collapse that might lead to unresolving inflammation [52].

Large cystic pneumatocele

Large cystic pneumatocele in extreme preterm newborns with severe BPD, although rare, can happen because of ventilator-induced lung injury. Despite spontaneous regression, it had been associated with high mortality and extended-spectrum beta-lactamase (ESBL) *Klebsiella pneumonia* in tracheal aspirate [53].

Pulmonary venous stenosis

It is reported in the literature review that pulmonary venous stenosis has been associated with BPD medically, radiologically and at autopsy. Further research is needed for clear correlation [54].

Obstructive sleep apnoea (OSA)

In general, sleep disordered breathing has been more common in preterm children with BPD [43,55] with no significant improvement following adenotonsillectomy. Literature review confirmed that there is a delay in diagnosis of OSA in this subgroup of patients, as the mean age at diagnosis was 19 months. Some authors postulated that symptoms of snoring, failure to gain weight, and inability to wean night-time oxygen are also present as general complications of prematurity and BPD [55].

The role of oxygen therapy is described clearly in a large cohort involving 41 infants with BPD. It concluded that home oxygen supplementation significantly improved sleep disordered breathing (improve apnea-hypopnea index (AHI) - P value < 0.001) [56].

Chronic respiratory failure

Chronic respiratory failure although it is rare in preterm infant's with severe BPD, it can be managed successfully with chronic ventilation via tracheostomy [57].

Prevention and improvement of the pulmonary outcome

Socioeconomic factors such as combustible sources of indoor air pollution (gas stoves, fireplaces, and tobacco smoke exposure), living in affluent or disadvantaged areas were associated with increased respiratory symptoms and rate of hospital admissions in those high-risk infants born prematurely with BPD [58,59]. Governmental and public efforts to limit BPD survivors' exposure to indoor air pollution and enhancement of health access to the disadvantaged subgroups are important contributing factors in reducing the pulmonary morbidity in patients with BPD.

Enhanced patient-centred medical care is an important aspect that can improve the outcome of BPD patients. In a unique study, disease-specific parent-proxy questionnaire to measure the health-related quality of life (HRQL) in children with BPD between 4 - 8 years of age was developed and validated. Such an instrument would be very useful in long-term follow-up of these children, since it would better address clinically important problems in this age group and consequently help to determine therapeutic goals [60].

Conclusion

BPD survivors are at risk of pulmonary hypertension and other long-term pulmonary complications such as requiring home O_2 therapy, increased frequency of viral lung infections, impaired PFT and chronic structural changes of lung parenchyma and airways. Asthma-like symptoms and sleep breathing disorders is another aspect of lung dysfunction in this subgroup of patients.

Preventive practices of BPD and BPD related PH, long-term follow up, development of sensitive and specific screening protocols as well as raising ~~of~~ the families' awareness and the limitation of environmental insults to those patients are the most important outcome improving factors.

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