

Long-term respiratory outcomes

Key points

- Bronchopulmonary dysplasia (BPD) is the most common chronic lung disease of infancy, accounting for about 40% of survivors of very preterm birth.
- Prematurity, especially when associated to BPD, is a cause of frequent hospitalization, over the first two years of life, most commonly due to respiratory infections (such as from respiratory syncytial virus, RSV).
- Typical symptoms that can be experienced in pre-school and school age are cough, wheezing, and later on asthma-like symptoms with reduced exercise tolerance. The pulmonary picture may be worsened by the presence of pulmonary arterial hypertension (PAH), which, however, tends to progressively resolve with lung growth.
- Preterm infants with or without BPD present an airflow limitation from early years up to mid-adulthood, showing a tracking of lung function over time. However, those without BPD usually fare better than the affected. This characteristic is regardless of the type of BPD ("old" vs. "new") and raises concerns for the potential development of a COPD-like phenotype in adult age.

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Background

Chronic lung disease of infancy (CLDI) comprises a heterogeneous group of disease entities that evolve as consequences of prematurity and neonatal respiratory disorders. The most common form of CLDI is bronchopulmonary dysplasia (BPD). Advances in obstetric and neonatal management have led to an increase in survivors of preterm birth. The widespread use of antenatal corticosteroids and exogenous surfactant administration, together with the growing use of non-invasive ventilation have determined better over-all outcomes of preterm infants. Nevertheless, as a result, BPD still accounts for a high rate of prematurity-related morbidity, affecting up to 40% of very preterm infants <28 gestational weeks (GW). Although BPD was originally described as a consequence of prolonged oxygen exposure and mechanical ventilation (MV), sadly this condition may now also be found in survivors of preterm birth who have never received MV.

The most commonly adopted definition of BPD is the one developed by Jobe and Bancalari in 2001, which classifies BPD as mild, moderate, or severe according to the amount of supplemental oxygen (<30% versus $\geq 30\%$) and the mode of respiratory support administered at 36 weeks post-menstrual age (PMA) to very preterm infants treated with supplemental oxygen for at least 28 days. However, these widely-used criteria may not reflect contemporary neonatal respiratory care, which include the use of the increasingly popular application of high flow nasal cannula. For this reason, in October 2016 the National Institute of Child Health and Human Development (NICHD) suggested a refined definition of BPD, as shown in *Table 1*.

Thus, it has been recognised that commonly used criteria for diagnosing BPD may not adequately predict later childhood respiratory outcomes. A recent analysis of 18 pre-specified BPD definitions identified BPD as treatment with respiratory support at 36 weeks PMA (no support; nasal cannula $\leq 2\text{L/min}$; nasal cannula $> 2\text{L/min}$ or non-invasive positive airway pressure; invasive MV), irrespective of level of oxygen therapy, to be the best predictor of death or serious respiratory morbidity at 18-26 months corrected age. Given the long standing respiratory impairment of preterm infants with BPD, future studies should assess the validity of new diagnostic criteria able to predict respiratory

symptoms and lung function in later life in order to optimise medical and ancillary support systems for those who need it most.

Table 1. Refinements to BPD definition for premature infants (<32 gestational weeks of age) with BPD as persistent parenchymal lung disease on radiographic confirmation, and **at 36 weeks PMA** requirement of one of the following FiO₂ ranges/O₂ concentrations (%) for ≥ 3 consecutive days to maintain arterial oxygen saturation in the 90-95% range (From Higgins RD, et al. Bronchopulmonary Dysplasia: Executive Summary of a Workshop. J Pediatr. 2018;197: 300-308.)

Grades	Nasal cannula flow <1L/min	Hood O2	Nasal cannula flow 1-3 L/min	nCPAP, NIPPV or nasal cannula ≥3 L/min	Invasive IPPV
I	22-70	22-29	22-29	21	-
II	>70	≥30	≥30	22-29	21
III				≥30	>21
III (A)	Early death (between 14 days of postnatal age and 36 weeks) owing to persistent parenchymal lung disease and respiratory failure that cannot be attributable to other neonatal morbidities (eg, necrotizing enterocolitis, intraventricular haemorrhage, redirection of care, episodes of sepsis, etc).				

Abbreviations: IPPV, intermittent positive pressure ventilation; N-CPAP, nasal continuous positive airway pressure; NIPPV, non-invasive positive pressure ventilation.

Morbidity associated with BPD

Oxygen requirement

About one third of infants with BPD may require oxygen supplementation on discharge from neonatal intensive care units. Lower gestational age, as well as gastrostomy tube feeds or Nissen fundoplication may be associated with later weaning of oxygen. However, very few individuals remain oxygen dependent beyond 1 year of age, the median age of weaning usually lying between 5.5–8.0 months. To date, the most commonly employed safety method for weaning supplemental oxygen remains overnight polysomnography.

In the most severe cases, however, when chronic respiratory insufficiency impedes growth and psycho-motor development, chronic invasive ventilation via a tracheostomy may help facilitate neurodevelopmental progress and can lead to an improved long-term outcome.

Hospitalization

Approximately one in three infants born preterm (<32 GW) will be hospitalized with respiratory problems in the first 2 years of life, mainly due to symptoms like cough, wheeze, food aversion predominantly in concomitance with infections. This rate may vary between 40 and 25% in the first and second years of life, respectively. Respiratory morbidity (primarily caused by respiratory syncytial virus (RSV) infection) accounts for the majority of these hospitalizations. This is thought to be due to preterm infants' immature humoral and adaptive immunity. However, since the introduction of prophylaxis with monoclonal antibody (palivizumab), studies have shown a reduction in RSV-related hospitalizations. Prevention of RSV infection is of utmost importance for highly selected population to avoid respiratory morbidity and mortality. RSV vaccines, as well as antivirals and new monoclonal antibodies are currently under investigation.

Respiratory symptoms

Compared with term-born infants, infants born prematurely, and survivors of BPD in particular, experience more respiratory symptoms in childhood. In a large meta-analysis from 2014, preterm birth was associated with a 1.7-fold higher risk of childhood wheezing disorders, this risk increasing up to three times when very preterm children were considered. RSV-related lower respiratory tract infections, again, represent an important risk factor for childhood recurrent wheezing.

Although cough and wheeze are very common at preschool age (up to 80% and 44%, respectively), the clinical condition of BPD survivors generally improves with time, but respiratory symptoms may still remain very common even at school age.

Asthma-like symptoms due to a component of reactive airway disease may as well be present. It has been speculated that for children born <26 GW the incidence of asthma at 11 years of age is approximately 25%. Nevertheless, children with BPD and asthma-like symptoms are less likely to demonstrate airway hyper-responsiveness or response to bronchodilators, as they appear to suffer from fixed peripheral airway narrowing and may show an exacerbated wheezing with the use of bronchodilator therapy due to co-morbid broncho- and tracheomalacia. Data on defined lung pathology are scarce, but studies on exhaled nitric oxide and high-resolution computer tomography (HRCT) have documented differences in both biomarkers and morphology in the lungs of children with asthma and of those with BPD. Thus, patients with BPD should not be diagnosed as asthmatics, and they may require different treatments.

Encouragingly, symptoms progressively subside in most survivors of BPD in adolescence, and most of them will lead apparently normal lives. The relationship between clinical symptoms and lung function fades, and even patients with severe airway obstruction, detected by spirometry, may not have any clinically significant respiratory symptoms.

Exercise intolerance and response to hypoxia

Survivors of BPD may experience exacerbation of pulmonary morbidities with exercise. Indeed, these subjects may present exercise-induced bronchoconstriction, altered ventilatory response and aerobic capacity during exercise compared to healthy children. Follow-up studies have demonstrated lower maximal oxygen consumption and minute ventilation, decreased running time, as well as a ventilator pattern characterised by lower tidal volumes in BPD survivors, with consequent hypoxemia and alveolar hypoventilation. The larger drops in FEV₁ and abnormal ventilatory reserve during exertion may lead to exercise intolerance relating to reactive airway disease and compromised gas exchange with physical activity. These, in turn, may be attributed to long-term derangements in pulmonary structure or residual right ventricular dysfunction affecting cardiac output.

Preterm-born adults with or without BPD may show an abnormal response to hypoxia-exposure as well, due to a dysmature function of carotid chemoreceptors. Specifically, normal responses of increased ventilation with hypoxia or decreased ventilation with hyperoxia may be altered. Interestingly, the infants with the most severe disease seem to experience the smallest change in ventilation in response to **acute hypoxia hyperoxia**. The picture may be worsened by the co-existence of central airway disease, bronchomalacia, and abnormal respiratory muscle function. Furthermore, these underappreciated abnormalities in ventilatory control may have important clinical consequences, for instance an increased risk of disordered breathing during sleep and in response to high altitude and anaesthesia.

Pulmonary arterial hypertension

The clinical course of extremely preterm infants with BPD can be worsened by concomitant pulmonary arterial hypertension (PAH). A recent systematic review and meta-analysis has shown a pooled incidence of PAH of 17% in BPD of any severity and of 24% in moderate-severe cases, with higher odds of mortality in those affected. PAH in BPD subjects arises from the combination of an altered vascular development (pulmonary angiogenesis disrupted by premature birth), function (hypoxia-related increases in vascular tone and reactivity) and structure (vascular remodelling with smooth muscle cell proliferation). However, preterm infants *per se* exhibit abnormal right ventricle performance (measured by pulmonary artery acceleration time (PAAT)) at 32 weeks PMA,

suggesting a less developed intrinsic myocardial functional response following preterm birth. While preterm infants subsequently show a progressive increase of PAAT to 1 year corrected age, reflective of the physiologic postnatal drop in right ventricular (RV) afterload, BPD and PAH have a negative impact on PAAT measures.

To address the lack of consensus care guidelines and marked differences regarding optimal diagnosis, evaluation and management of BPD-PAH, in 2017 the Pediatric Pulmonary Hypertension Network (PPHNet) published a report presenting consensus recommendations for the care of children with BPD-associated PAH. *Table 2* shows the report's summary of recommendations on diagnosis, management, follow-up and treatment of PAH in BPD infants.

Table 2. Summary of the consensus recommendations on diagnosis, management, follow-up and treatment of PAH in BPD infants by the 2017 Pediatric Pulmonary Hypertension Network (PPHNet) (From Krishnan U, et al. Pediatric Pulmonary Hypertension Network (PPHNet). Evaluation and Management of Pulmonary Hypertension in Children with Bronchopulmonary Dysplasia. J Pediatr. 2017;188: 24-34.e1.)

Patients who should be screened for PAH by echocardiogram	<ul style="list-style-type: none"> • Preterm infants with severe hypoxemic respiratory failure shortly after birth attributed to PPHN physiology • Preterm infants with continued need for ventilator support at postnatal day 7 • Preterm infants with sustained need for significant respiratory support at any age • Preterm infants at 36 weeks PMA (time of BPD diagnosis)
Echocardiogram evaluation	<ol style="list-style-type: none"> 1. Complete anatomic evaluation for structural abnormalities, shunts and pulmonary veins; 2. Right and left ventricular size, hypertrophy, systolic and diastolic function; 3. Systolic and diastolic interventricular septal position; 4. Tricuspid and pulmonary regurgitation jet velocities (when present); 5. Simultaneous systemic blood pressure documentation
Indications for cardiac catheterization	<ul style="list-style-type: none"> • Confirmation of diagnosis • Determine disease severity • Evaluate contributions of shunt lesions • Define the need for combination drug therapy
PAH definition and severity	<ul style="list-style-type: none"> • Absent PAH: estimated sPAP <1/2 SAP • Mild-moderate PAH: estimated sPAP <1/2-2/3 SAP • Severe PAH: estimated sPAP >2/3 SAP with septal flattening or right-to-left shunt across the ductus arteriosus
Treatment options	<ul style="list-style-type: none"> • Supplemental oxygen for oxygen saturation target 92-95% to decrease pulmonary artery resistance • iNO for acute PAH crisis • Sildenafil (phosphodiesterase-5 inhibitor) • Bosentan (Endothelin receptor antagonist) • Milrinone (phosphodiesterase-3 inhibitor) <p><i>Important: wean Oxygen and iNO only gradually and after stabilization</i></p>
Follow-up	Baseline and serial BNP or NT-pro-BNP to monitor disease progression/regression and response to therapy, in conjunction with echo evaluation

Abbreviations: BNT, brain natriuretic peptide; BPD, bronchopulmonary dysplasia; NT-pro-BNP, N-terminal-pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PMA, post-menstrual age; sPAP, systolic pulmonary artery pressure; SAP, systemic arterial pressure.

Infants with PAH and BPD should be cared for by a multi-disciplinary team (involving respiratory, cardiac, and nutritional care, as well as physiotherapy) and have outpatient follow-up at intervals of 3-4 months, including echocardiography, biomarkers, hemodynamic studies, and sleep studies

when indicated, depending on disease severity and clinical progress. By the time BPD patients with PAH reach school age, pulmonary vascular resistance and pulmonary arterial pressure appear to return to normal in most cases, although pulmonary vascular reactivity to hypoxia may often persist into adolescence and adulthood. Currently, there is limited evidence on the appropriate duration of PAH therapies in this population. If the PAH gradually resolves with lung growth, medications can be gradually tapered. However, continued monitoring for new respiratory signs, exercise intolerance, or reduced activity will be necessary. A repeat echocardiogram is recommended after stopping PAH medications, usually within 1-2 months.

Lung function

Lung function measurements can be obtained from infants with evolving or established BPD up to adulthood (*Table 3*).

Early studies highlighted that lung compliance and functional residual capacity (FRC) improved with increasing age, such that by two years of age these had reached the normal range. In contrast, airflow limitation appears to be a persisting issue in preterm subjects with and without BPD. The analysis of forced expiratory flows (obtained with infant forced expiratory manoeuvres) has revealed substantial airflow limitation in BPD survivors during the first 3 years of life, with no significant improvements on serial measurements. Furthermore, the degree of airflow limitation in early years of life seems to predict pulmonary function later on: in a small cohort of BPD survivors followed from birth, forced expiratory flow at 2 years (measured by V_{maxFRC}) correlated with pre- and post-bronchodilation $zFEV_1$ at 15, 20 and 24 years of age, indicating a tracking of lung function over time and a negligible “catch-up” in lung growth. In addition, no differences were found between infants treated with or without surfactant. This finding is suggestive of an irreversible early airway remodelling process, which characterises both “old” and “new” BPD survivors. However, a trend towards an obstructive spirometry pattern seems to exist even in very low birth weight children who do not develop BPD, raising concern that prematurity *per se* may impair lung maturation and growth with life-long detrimental effects on pulmonary function. This has been recently confirmed by two longitudinal respiratory follow-up after preterm birth in the surfactant era. The first, conducted in survivors born in 1991-1992, showed an increased small airway obstruction between 8 and 18 years in extremely preterm/low-birthweight survivors compared with controls, with greater increase within those who had BPD and those who were smokers at 18 years. The second study, conducted in a cohort of infants born between 1997 and 2003, similarly demonstrated that preterm children, with and without bronchopulmonary dysplasia, had declines in spirometry z-scores over time (from 4-8 years to 9-12 years) and compared with term controls, with FEV_1 , forced expiratory flow at 25–75% of FVC ($FEF_{25-75\%}$) and FEV_1/FVC declining by at least 0.1 z-score per year in children with BPD. Interestingly, preterm children with bronchial wall thickening on chest CT (suggestive of inflammation) had bigger decreases in spirometry outcomes through childhood.

Significantly lower FEV_1/FVC ratio and $FEF_{25-75\%}$ than controls are indeed other characteristics of BPD survivors in their second and third decades.

Given the results of longitudinal studies into early adulthood and the well-known physiological decline in respiratory reserves with ageing, these individuals may reach a critical threshold for significant respiratory symptoms in mid-adulthood, and it is possible that a new phenotype resembling chronic obstructive pulmonary disease (COPD), but related to premature delivery, will emerge over the coming years.

These findings emphasise the need of novel therapies to reduce the long-term pulmonary effects of extremely premature birth, as well as of follow-up protocols to monitor these subjects and limit their exposure to risk factors associated with a faster decline of lung function, such as cigarette

smoking. Emerging strategies, such as mesenchymal stem cells-based therapies, have recently come into the focus of neonatologists.

Table 3. Suggested lung function tests to be performed in subjects with evolving or established BPD (newborn period and infant age) and to follow up (childhood, adolescence and adulthood).

Lung function test Suitable age group	Description	Advantages	Disadvantages
Newborn period and infant age			
Ventilator graphics (Ventilated newborns and infants)	Real-time display of continuous measurements of pressure, flow, and volume change on cot side (flow-volume and volume-pressure loops)	Pattern recognition is used to identify specific pathophysiological situations (airway obstruction or excessive inflation pressure, changes in lung compliance)	It does not yield exact numerical values
Tidal flow-volume loops (TFV loops)	Time to peak tidal expiratory flow to expiratory time (Tptef:Te)	Sedation is not required	Variability
Inert gas washout (Helium He, sulfur hexafluoride SF6, nitrogen N2) or multiple breath washout	Measurement of FRC and gas mixing efficiency (lung clearance index, LCI), which is a mark of ventilation inhomogeneity	Can be applied in intubated infants with or without sedation; SF6 less susceptible than helium to leaks	It may underestimate the FRC if insufficient time is allowed for complete equilibration; N2 washout impractical for ventilated infants receiving high FiO ₂
Whole-body plethysmography	Measurement of FRC and Total lung volume;	If used in conjunction with a gas dilution technique, can provide an assessment of hyperinflation and gas trapping	Systems depend on electronic manipulation to close the pressure flow loop (possible erroneous results); Not suitable for cot side measurements; Possible overestimation of lung volume
Passive mechanics, Single breath occlusion	Measurements of resistance and compliance of the lung or the entire respiratory system	Can be used in both spontaneously breathing and in ventilated neonates and infants	Require airway occlusion, but the small endotracheal tubes may invalidate attempts to detect small changes in resistance
Raised volume-Rapid Thoracoabdominal Compression Technique (RV-RTC)	Most commonly used method to assess airway function in infants measuring V _{max} FRC	Possible more sensitive mean of discriminating changes in airway function in infants with respiratory disease	Dependent on lung volume; Requires sedation
Forced Oscillation Technique (FOT)	<i>See further</i>	Can be applied during invasive and non-invasive ventilator support	Few data available
Pre-school age (2-5 years of age)			

Forced Oscillation Technique (FOT)	Measurements of the respiratory system mechanics (impedance, resistance and reactance)	Non-invasive technique performed during tidal breathing requiring minimal cooperation; The within-breath analysis can detect airway obstruction	
Interrupter technique (Rint)	Measurement of respiratory resistance during tidal breathing	Quick, non-invasive; can be performed in pre-schoolers not enough collaborative to perform spirometry; It can assess bronchodilator response	It does not give prediction of the development of asthma at school age
Children (>5 years of age), adolescents and adults			
Spirometry >5 years for reliable results	Measurement of volumes (TV, TLC), airflow limitation (FEV ₁ , FVC, FEV ₁ /FVC, FEF _{25-75%}), diffusing capacity (DLCO) and static lung compliance	It can assess bronchial obstruction and Bronchodilator response can be assessed	Highly dependent on patient cooperation and effort in order to obtain valuable measurements

Abbreviations: FRC=Functional Residual Capacity; VmaxFRC=maximal expiratory flow at FRC; FEV1=Forced Expiratory Volume in 1 second; FVC=Forced Vital Capacity; FEF25-75%= forced expiratory flow at 25-75% of the pulmonary volume; TV=Tidal Volume; TLC=Total Lung Capacity

Imaging

Imaging has played an important role in the clinical assessment of BPD since its first recognition. The roles of chest radiography and computed tomography (CT) are well documented but numerous recent advances in imaging technology have paved the way for newer imaging techniques including structural pulmonary assessment via magnetic resonance imaging (MRI), functional assessment via ventilation and perfusion MRI and quantitative imaging techniques using both CT and MRI. New applications for lung ultrasound have also been suggested.

Traditional chest radiograph findings in survivors of BPD include reticular opacities and cystic lucencies, and late-stage findings of pulmonary interstitial emphysema, characterized by scarring and hyperinflation (*Figure 1*). These images seem to be milder in new BPD survivors compared to those with old BPD. The sensitivity of radiography in diagnosing minor lung abnormalities, however, is limited.

Lung ultrasound seems to be a promising tool to evaluate BPD diagnosis and severity. A prospective study has recently suggested that in BPD subjects a lung ultrasound score (defined as a semi-quantitative score representing the aeration (0-3) in three different areas of each lung) remains high until 36 weeks PMA. Further research is needed to assess the validity of this non-invasive technique. Although chest CT is not routinely performed in BPD survivors, studies of CT scans can reveal structural abnormalities in >85% of BPD patients, providing important information of airways and parenchymal structural changes. Several CT scoring methods have been used to evaluate chest CT scans of BPD patients, as summarised in a recent review in 2016. The most common findings being scored are patterns of:

- Hypo-attenuation on inspiratory and/or expiratory scans (representing either hypoperfusion and/or hypoventilation at inspiratory scans and possibly trapped air in expiration);
- linear or sub- pleural opacities (probably reflecting alveolar septal fibrosis);

- bronchial wall thickening (likely reflecting peri-bronchial fibrosis or inflammation) and collapse
- consolidation or atelectasis.

Lower pulmonary function and increased respiratory symptoms have both been associated with chest CT abnormalities. The most sensitive structural abnormality associated with BPD severity appeared to be low attenuation on inspiratory or tidal breathing CT scans, but these in- and expiratory scans are not possible before the age of 4–5 years, unless anaesthesia is used. Both the presence of hypo-attenuation and opacities can be consistent with the hypothesis that the predominant abnormality in BPD is in the peripheral lung. Furthermore, taken together, all studies included in the review indicated persistent abnormalities in the lungs of patients born preterm irrespective of when in the evolutionary path of preterm neonatal care these patients were born (“old” vs. “new” BPD) and regardless of age at the time of chest CT imaging.

MRI studies have been performed on quiet-breathing, non-sedated BPD survivors allowing tomographic quantification of lung volumes and densities. These have shown that MRI can quantify hyperinflation in neonatal BPD with lung volumes significantly increased according to disease severity. In addition, with hyperpolarized Helium diffusion-weighted MRI, children with BPD have higher apparent diffusion coefficient and similar lung volumes when compared with age-matched healthy subjects, suggesting the presence of enlarged alveoli that are reduced in number.

Ideally, non-invasive and feasible imaging techniques should be applied for the diagnosis and monitoring of these patients following standardised protocols.

Treatment of BPD survivors

While several therapies and modes of ventilation have been proposed and studied for the management of early and evolving BPD, the treatment of infants and children with established BPD is still an under-investigated matter and many pharmacological treatments are routinely used with a limited evidence base. The recent European Respiratory Society guideline on long term management of children with bronchopulmonary dysplasia indeed highlights the lack of research based on randomised controlled trials on the use of the most commonly prescribed drugs in infants and children with BPD. In particular, inhaled and systemic bronchodilators may improve pulmonary resistance during acute bronchospasm, although some subjects may benefit more from this therapy. There has been an increased use of inhaled steroids compared to the systemic ones due to the possible limitation of adverse effects. Nevertheless, no studies have explored their benefits compared to placebo in BPD subjects alone. Finally, there is a wide variation in regimens, frequency, indications and duration of outpatient diuretic use, and this therapy may be more useful in infants with severe BPD or with pulmonary artery hypertension. The article by Bhandari and Panitch (see proposed readings) suggests drugs, dosing and weaning of post-NICU therapies in patients with BPD, which however might be discussed on a case by case given the paucity of evidence.

Conclusions

Chronic lung disease of infancy, in particular BPD, still claims a high disease burden of preterm birth, associated with increased hospitalizations in the first two years of life and more frequent respiratory symptoms up to adolescence. These may be worsened by the presence of pulmonary arterial hypertension, for which preterm infants with evolving BPD or certain worrisome characteristics should be screened and then eventually monitored. The fact that persistent airway obstruction and correlating pulmonary structural changes can be identified in these subjects, up to their adolescence and early adulthood, highlights the importance of further research to prevent BPD development, as well as the necessity for standardised recommendations to monitor these patients through time. A European Respiratory Society guideline on long term management of children with

bronchopulmonary dysplasia has been recently developed by a Task Force of experts, which highlights the gaps of knowledge and guides towards evidence-based care of these patients in the long term.

Further readings

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