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The Natural History of Bronchopulmonary Dysplasia (BPD): The Case for Primary Prevention

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1. Introduction

Bronchopulmonary dysplasia (BPD) is the most common form of chronic lung disease in infancy.¹ "Classic BPD", described in 1967 by Northway *et al.*,² occurred in modestly premature infants with surfactant deficiency who were exposed to ventilator-induced volutrauma and high oxygen concentrations. BPD currently occurs primarily in extremely premature infants (23–28 weeks of gestation) born during the late canalicular / early saccular stage of lung development.³ In contrast to the inflammation, fibrosis and scarring that characterized classic BPD, the BPD today is conceptualized as a consequence of disrupted and impaired lung development ("new BPD").⁴ Importantly, a diagnosis of BPD carries the risk of significant clinical and functional respiratory abnormalities into adolescence and adulthood.⁵

As the epidemiology and pathology of BPD has changed and former premature infants reach adulthood, the life-course trajectory of BPD continues to be studied. It appears that the natural history of the "new BPD" may not be significantly different than the natural history of the "classic BPD". Both groups of individuals manifest with ongoing respiratory symptoms and reduced lung function, with pulmonary function tests (PFTs) showing expiratory flow limitation at school age, which may improve with bronchodilator treatment,⁶ and into adulthood.^{7,8} There is concern that BPD will predispose to chronic obstructive pulmonary disease (COPD) since infants are beginning life with reduced lung function, and

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longitudinal cohorts indicate that individuals track along their predetermined PFT percentiles throughout life.⁹ This emphasizes the important need for increased focus on the primary prevention of BPD.

Pathologic datasets from newborns and infants with BPD are limited and histologic examination of lung tissue from patients with the “new BPD” is rare. Therefore, the characterization of the natural history of BPD is mostly clinical, consisting of PFTs, respiratory symptoms, radiographic, evaluations, and exercise intolerance. In this article we will summarize the current knowledge of the life course of BPD by emphasizing recent or key articles notating its natural history from the newborn period through adulthood and building the case for a continued focus on its primary prevention.

2. Natural History of Pulmonary Function Testing Measurements

It is unclear when BPD begins, but likely many of its origins occur *in-utero*.⁴ Therefore, detailed assessment of neonatal pulmonary function after a premature delivery is important to understand the evolution of disease, and to identify potential windows of vulnerability and intervention. In preterm infants, lung development that would normally occur *in-utero* happens postnatally under altered mechanical and environmental conditions, including active tidal breathing with strain and stretch of immature intrathoracic structures, and a state of relative hyperoxia, even with room air.¹⁰ Lung development is also affected by conditions precipitating premature delivery, often including inflammatory and infectious processes.¹¹ While premature delivery impacts normal alveolarization and pulmonary vascularization, it can also affect respiratory mechanical processes.¹²

Neonatal pulmonary mechanics or PFTs have been useful to reproducibly quantify the newborn’s response to a variety of antenatal and postnatal exposures, therapies, or conditions, including preterm birth itself. These PFT results correlate with clinical outcomes. PFTs have given useful insights into normal and aberrant lung development in preterm infants and have strengthened the physiologic basis (or lack thereof) for therapies used for the prevention and treatment of respiratory distress syndrome (RDS) and evolving BPD. Antenatal steroids (AS) and surfactant which have been shown in randomized controlled trials (RCTs) to significantly decrease the incidence of death and RDS, have also been shown to significantly improve measurements of neonatal PFTs.^{13–17} Therapies unproven in large RCTs, such as inhaled nitric oxide (iNO) for BPD prevention, are not associated with improvements in neonatal PFTs.¹⁸ International guidelines are published regarding specific methodology, acceptance criteria and standardized equipment for PFT testing in neonates and young infants.^{19,20}

Neonatal PFTs are challenging because the patient is often not cooperative, but can be accomplished noninvasively, during quiet sleep and do not require sedation. Published studies examining the newborn mechanical properties of the respiratory system have primarily applied passive and dynamic techniques to measure respiratory compliance (Crs) and resistance (Rrs).^{12,15} Lung volumes have been measured by gas washout methods, helium dilution or body plethysmography.²¹ Table 1 summarizes PFTs that have been used

to monitor the natural history of BPD from the neonate through adulthood. (Table 1 to be placed here if possible)

Neonatal Studies

PFTs have been used to examine the effects of pharmacologic agents on the premature lung including those of AS,^{13–16} surfactant,^{17,22} and postnatal steroids.²³ Similar to results in animal models, studies have demonstrated a significant increase in Crs and FRC after a timely single course of AS,¹³ thereby supporting accelerated lung maturation with AS treatment (Figure 1). These PFT improvements correlated with improved clinical outcomes with less surfactant and supplemental oxygen need. Neonatal PFTs have been used to quantify the duration of the clinical effect of a single course of AS¹⁴ and to quantify the effects of a single rescue course of AS versus placebo given to women undelivered more than 14 days after their first course of AS.¹⁵ This study demonstrated a significantly increased Crs in the preterm infants (n=113) whose mothers received the rescue course of AS and provided a physiologic basis for a large randomized trial²⁴ showing improved clinical respiratory outcomes after a rescue course of AS. Clinical studies examined the effect of surfactant in preterm newborns with RDS and demonstrated an increase in functional residual capacity (FRC) prior to an increase in Crs.^{12,17}

Preterm delivery is the most common cause of abnormal lung development with BPD in the extremely preterm infant at one end of that spectrum. Studies have shown that even “healthy” preterm infants have a lower Crs and higher Rrs when compared to healthy term infants.^{25,26} Preterm infants with BPD have lower FRCs than preterm infants without BPD.^{27,28} Infants with BPD studied at 34–36 weeks had significantly lower Crs and FRC and higher Rrs when compared to matched healthy late preterm infants studied at comparable postmenstrual ages.^{29,30} A longitudinal study demonstrated Crs was 50% of predicted during the acute phase of BPD and was associated with abnormal Rrs values. These values normalized over the first two years of life but significant airway dysfunction persisted in many infants.³¹ This illustrates the importance of defining the trajectory of the “healthy” premature lung for an appropriate comparison or control for infants at risk for or diagnosed with BPD.³¹ Representative PFT studies in neonates and infants are presented in Table 2. (Table 2 to be placed here if possible)

Infants

Infant PFTs are perhaps more challenging than neonatal PFTs both because the patients are not cooperative and the techniques applied to this age group require sedation with normative values established during sleep induced with chloral hydrate, a drug no longer available in the United States. However, the period of lung growth during the first two years of life is the most rapid and therefore may be the most relevant to the investigations of the natural history of BPD. Infant PFTs have primarily been the measurement of forced expiratory flows (FEFs) and volumes with the raised or tidal volume rapid thoracic compression (RTC) technique and of FRC with the plethysmograph¹⁹ (Table 1).

Extremely preterm infants are born before the onset of alveolar formation leading to failed septation and a reduced number of alveoli. To understand the growth of the preterm lung, a

term reference lung is needed. Studies of infants with healthy term lungs show their lungs grow in concordance with somatic growth and their lung volume or forced vital capacity (FVC) increases faster than their airway flows.^{32,33} Lung growth can occur by two possible mechanisms: by increasing the number of alveoli or by increasing the size of existing alveoli. Studies measuring alveolar volumes and gas diffusion in healthy term infants between 3 and 23 months of age³⁴ have shown that the ratio of pulmonary diffusing capacity (DLCO) versus alveolar volume (V_A) is linear, indicating that lung growth that is increasing primarily by the addition of new alveoli rather than the expansion of existing alveoli, and that $DLCO/V_A$ is constant through the first 2 years of life. Infants with BPD have normal V_A but have lower DLCO for the same V_A when compared to term control infants (Figure 2A, B) supporting the premise that in BPD there are fewer (but larger) alveoli.³⁵ A study using aerosol-derived airway morphometry demonstrated that alveoli number remained constant from 6 years of age and up.³⁶

In infants with BPD there are fewer and larger alveoli and less tethering of the airways through the elastic components in alveolar walls¹⁰ which can affect both gas transfer and elastic recoil. Infants with BPD have lower FEFs when compared to reference values from healthy term controls.^{37–40} Infants with BPD who wheeze have lower FEFs than infants with BPD who don't wheeze.⁴¹ Infants with BPD studied at 6 and 12 months of age have decreased FEFs that remain subnormal and may worsen over time.⁴² Studies have shown that healthy preterm infants (minimal oxygen and ventilation need) have decreased FEFs compared to normal term infants and their FEFs do not appear to catch up over time.³² (Table 2).

Children and Adolescents

Studies evaluating the effect of BPD on school age children in general document measurements of airflow obstruction with decreased FEFs and forced expiratory volume at 1 sec (FEV1) compared to term controls.^{43–45} Measurements of residual volume/total lung capacity were suggestive of air trapping and diffusing capacity was decreased.⁴⁵ Baraldi *et al*⁴⁶ demonstrated that structural abnormalities in the small airways of children with BPD accounts for at least part of their manifested airflow obstruction. These investigators compared children with BPD to children with asthma with a similar degree of airflow obstruction and found those with BPD had lower levels of exhaled NO and were less responsive to beta agonists, supporting a structural abnormality. Vrijlandt *et al.*⁴⁷ applied forced oscillometry in 3–5 year olds with a history of BPD and found higher resonant frequency and lower mean reactance compared to children without BPD suggesting those with BPD had decreased peripheral airway patency.

Follow-up of extremely preterm infants from the EPICURE study at 11 years of age demonstrated that 56% of the children had significantly decreased FEFs and 27% had a positive bronchodilator response with reductions in lung function being more severe in the infants with a prior BPD diagnosis.⁴⁸ A subset of these patients were further tested showing lung function abnormalities in 78% of the extremely preterm children with evidence of airway obstruction, ventilation inhomogeneity, gas trapping, and airway hyperresponsiveness.⁴⁹

Several investigators^{50,51} demonstrated that as children, former very low birth weight (VLBW) infants with BPD have decreased lung function compared to former VLBW infants without BPD, while other investigators reported no differences in lung function or diffusing capacity in VLBW infants with and without BPD.⁵² Doyle *et al.* reported a decline in lung function measured at 8 and 18 years of age in BPD survivors.⁴⁴ Hospital readmissions in the first 2 years of life and FEV1 and FVC in patients between 8–15 years of age have been shown to be significantly associated with initial BPD severity.⁵³

Adults

Studies of BPD survivors in adulthood have utilized case control or prospective cohort study designs and have consistently reported significantly lower FEFs and FEV1 when compared to term controls. While several studies have demonstrated significantly decreased FEFs in adult survivors of BPD compared to adults who were preterm without BPD,⁷⁸ other studies have not demonstrated this difference.⁵⁴ A recent regional cohort study⁵⁵ reported respiratory outcomes of 26 extremely preterm survivors (< 28 weeks gestational age or 1000 grams birth weight) at 25 years of age compared to matched term-born subjects. Lung function was in the normal range in the majority of the extremely preterm survivors and few subjects reported respiratory symptoms, but methacholine responsiveness was more pronounced in the extremely preterm survivors than in the term born young adults.⁵⁵

3. Natural History of Respiratory Symptoms in Patients with BPD: Clinical Pulmonary Outcomes

A number of studies using various BPD definitions, study designs and reference groups have reported the persistent clinical respiratory morbidity of infants, children, adolescents and adult survivors of BPD.

Infants

An increased incidence of abnormal clinical pulmonary findings are reported in infants with both the “old” and “new” BPD when compared to era matched former premature infants without BPD as well as to contemporaneous term control infants. Greenough *et al.*⁵⁶ reported frequent rehospitalizations through 2 years of age in infants with BPD which then declined with age with rare hospitalizations by 14 years of age.⁵⁷ A single center birth cohort study followed the outcomes in preterm infants through 12 months of age and showed 80% had cough, 44% had wheeze, and 25% were rehospitalized with similar respiratory morbidity among preterm infants with and without BPD.⁵⁸ Follow-up at 12 months of age of 255 infants with birth weights < 1250 grams who had been randomized to iNO versus placebo after delivery revealed overall about 53% had wheezing and 22% required respiratory hospitalization.⁵⁹

Children

Hennessy *et al.*⁶⁰ reported follow-up of 308 extremely preterm infants (< 25 weeks gestation with and without BPD) at 30 months and 6 years of age compared to term controls. They reported increased respiratory symptoms and medication use in the premature infants compared to term controls, which was much higher in the premature group with BPD. The

EPICURE study⁴⁸ evaluated 219 of 307 survivors at 11 years of age compared to age-matched term infants. Children delivered extremely preterm were significantly more likely to have a current diagnosis of asthma (25% vs 13%; $p<0.01$), recent respiratory symptoms and medication use, and increased asthma-associated sleep disturbance than the term reference group. Those with BPD had significantly more respiratory morbidities. This contrasted an earlier study of outcomes at 8 years of age which reported preterm infants without BPD had a greater incidence of wheezing and asthma compared to preterm infants with BPD.⁶¹

A recent study⁶ of children at 9.5 years of age with a history of moderate to severe BPD demonstrated that patients with BPD had significantly increased rates of persistent respiratory symptoms compared to matched former VLBW infants without BPD (36% vs 7%; $p<0.05$). Significantly more patients with BPD received respiratory medications (21% versus 0%; $p<0.05$). There was no significant difference in the incidence of doctor diagnosed asthma, atopy or allergies between the groups. In this study, one half of the BPD patients and 25% of the non BPD patients demonstrated a positive response to bronchodilators. Limitations of this study include its relatively small size (28 infants in each group), absence of a term control group, and differences in the exposure to AS (29% vs 50%, respectively) and surfactant (68% vs. 40%, respectively) in the BPD and no BPD groups.

Adolescents and Young Adults

Northway *et al.*⁶² compared clinical findings in 26 BPD survivors (mean age of 18.7 years) to 26 age matched adults born at similar gestational ages but who had not developed BPD, and 53 normal term controls. Patients with BPD had more wheezing, episodes of pneumonia, exercise intolerance and long term medication use compared to either of the other two groups. More contemporary studies of survivors with BPD over the age of 18 continue to demonstrate increased respiratory morbidity. Gough *et al.*⁷ reported that BPD survivors at 24.1 years of age were twice as likely to report wheeze and three times more likely to use asthma medications than term controls. Vrijlandt *et al.* reported significantly more shortness of breath and wheeze during exercise at 19 years of age in female BPD survivors compared to term controls.⁶³

4. Evolution of Radiographic / High Resolution Computed Tomography (HRCT) Changes

Aquino *et al.*⁶⁴ correlated inspiratory and expiratory HRCT findings with pulmonary function in BPD survivors at 10 years of age and found that 92% had abnormal CT findings. There was a significant correlation between abnormal PFTs and abnormal CT findings including decreases in density, air trapping on expiratory CT, and architectural distortion. Northway *et al.*⁶² evaluated CT scans in young adults with BPD and found the patients with BPD had extensive bilateral areas of reduced lung attenuation and bronchial wall thickening.

Aukland *et al.*⁶⁵ found parenchymal abnormalities in the majority of extremely preterm survivors, and those with BPD had significantly more opacities and hypoattenuated areas

than those without BPD. The extent of these abnormalities was positively associated with the duration of oxygen therapy and degree of impaired lung function. In a study of 19 adult survivors of moderate and severe BPD, 84% had emphysema which was inversely related to low FEV1 scores.⁶⁶

The process and timing of the postnatal development of alveoli in the human lung remains poorly understood with controversy over the age (2–3 years of age versus 7–8 years of age) at which alveolarization is complete, with studies citing 2–3 years of age to as late as 7–8 years of age.⁶⁷ However, there is recent provocative evidence of ongoing alveolarization into adolescence or early adult life in humans. Narayanan et al^{68,69} recently reported the application of a new technique using hyperpolarized helium diffusion during a brief breath-hold and using magnetic resonance to measure alveolar dimensions. Using this technique, they reported measurements consistent with continued alveolarization through adolescence in 109 healthy patients aged 7–21 years.⁶⁸ They also demonstrated similar alveolar dimensions/size at 11–12 years of age in survivors of extreme prematurity and survivors with BPD compared to term and mild preterm survivors.⁶⁹ These data suggest that late alveolarization may be able to compensate for early impaired alveolar development. The implication of this finding, if validated, is a longer therapeutic window for interventions that stimulate catch-up alveolar growth than previously thought.

5. Evolution of Exercise Tolerance Through Adulthood

A recent meta-analysis⁷⁰ of 20 studies (685 preterm and 680 control subjects) showed that children and adults born preterm with or without BPD have a significantly lower oxygen uptake at maximal exercise than term born controls, although the effect size was small. Some individual studies have not shown differences in exercise capacity between children born preterm compared to those born full term. In adults with a history of extreme prematurity, Clemm *et al.*⁷¹ found only a minor reduction in exercise capacity that was primarily related to self-reported physical activity.

A recent⁷² study performed ventilatory and sensory measurements before and during exercise in three groups of adults 18–31 years old: 20 former premature without BPD; 15 former premature with BPD; 20 full term controls. The adults born very premature with and without BPD demonstrated severe dyspnea and leg discomfort which was associated with critical constraints on tidal volume expansion and reduced exercise tolerance. This occurred despite differences in expiratory flow limitation in the patients with and without BPD, emphasizing the potential limitations of spirometry alone in the assessment of very preterm survivors. In summary, continued research is needed to fully elucidate exercise capacity limitations in patients with BPD as they age.

6. Need for Primary Prevention of BPD

The development of BPD is closely related to gestational age with infants born at the earliest gestational ages at the highest risk. However, there are extremely preterm infants who do not develop BPD, supporting the premise that primary prevention of BPD is attainable. To accomplish this goal, many barriers must be overcome. Also, the refinement of BPD risk and diagnosis by endotypes, inclusion of BPD severity classifications in outcome measures,

improving the sensitivity and accuracy of a diagnosis of BPD as a modifiable outcome in future trials, and increased understanding of the molecular causal pathways that underlie the pathogenesis of BPD are required to design strategies to prevent BPD.

The recognition and refinement of BPD phenotypes is underway. An increasingly recognized extreme phenotype is BPD associated with pulmonary hypertension (PH). A recent longitudinal study⁷³ demonstrated that echocardiogram-derived risk factors at 7 days of age were associated with development of both BPD and PH.

The Challenge of Defining a “Healthy Lung” in the Premature Infant

To define the abnormal trajectory of a premature lung evolving to BPD, we must define “normal” lung growth, development and function in the “healthy” preterm infant who does not progress to BPD. This is challenging given that premature infants are born at various junctures of the late canalicular / saccular stage of lung development, and are exposed to a wide range of pre and postnatal circumstances contributing to lung injury and repair. It also necessitates a new paradigm with increased focus and research on the evolution of lung health in the well infant delivered at term, a group largely unstudied particularly in infancy.

BPD related research has focused on the etiology, risk factors, and interventions for this poorly defined and evolving disease. Several studies^{74,75} have documented the clinical pulmonary evolution in extremely preterm infants and offer insight into possible postnatal windows for BPD prevention. A study of 1,340 extremely preterm infants described three patterns of pulmonary disease over the first two weeks of life: 20% of infants had consistently low oxygen requirements and 17% of these infants developed BPD; nearly 38% had low initial oxygen needs that increased in week 2 of life and 51% developed BPD; 43% of the infants had initial and consistently high oxygen needs and 76% developed BPD.⁷⁴ Future studies examining risk factors and exposures in the first two weeks of life or earlier (including *in utero*), and collecting robust functional and molecular biomarkers associated with the different phenotypes of premature infants and their pulmonary dysfunction are crucial to the primary prevention of BPD.

Causal Pathways of BPD

It is critical to understand the causal molecular pathways that underlie BPD development if we are to prevent its occurrence. The current views on several of these pathways are detailed in other chapters of this publication. Other important areas of focus include genetic, epigenetic and environmental factors.

A number of studies have applied approaches including familial aggregation, twins, candidate genes, and genome-wide association studies to examine genetic factors in the development of BPD. A family based study⁷⁶ found a SP-B marker locus B-18 within the 5' UTR of SP-B was associated with susceptibility to moderate-severe BPD. Several twin studies have estimated heritability for moderate-severe BPD to be 50% to 80%.^{77,78} The SPOCK2 gene has been shown to have a strong association with BPD.⁷⁹ Investigators have evaluated specific alterations in the sequence of candidate genes that might be associated with a change in the risk of developing BPD. Although many genes have been investigated,

few studies have been replicated. Progress in this area will require robust prospective multi-center/international population cohort studies.

Although few studies have been done in premature infant, epigenetic changes may alter the expression of genes involved in prenatal and postnatal lung development and may increase BPD susceptibility. For example, in-utero smoke exposure has been shown to cause modification of methylation of specific genes and to be associated with changes in indices of global DNA methylation. At birth, DNA methylation of the repetitive element AluYb8 is decreased in smoker's placentas with a correlation between the degree of AluYb8 methylation and birth weight.⁸⁰ Breton *et al.*⁸¹ showed that AluYb8 methylation remains decreased in buccal epithelia of kindergarten-age children who had prenatal smoke exposure. The degree of Alu methylation has been found to correlate with lung function in adults.⁸² Maternal prenatal stress, cortisol, and obesity⁸³ have been shown to be independently associated with children's wheeze perhaps through programming mechanisms. Studies are needed to understand the relationship between epigenetic factors and lung outcomes in preterm infants at risk for BPD. We would like to put box 1 (see next page) here.

7. Future Goals and Research Priorities for BPD Prevention

BPD is categorized as a rare disease since there are an estimated 10,000–15,000 new cases per year in the United States. However, the significance of BPD spans the individual's life time which if estimated to be 65 years, places the estimated prevalence of BPD at 1 million.⁸⁵

Although adults with persistent symptoms of wheeze, breathlessness, and reduced exercise tolerance may have bronchial asthma, it is important to consider preterm birth as a potential etiology. Future progress will require longitudinal studies in large populations of well-phenotyped individuals born preterm (with and without BPD) and healthy term controls to follow the progression of respiratory disease in the context of lung injury, developmental disruption, environmental exposures and natural aging. Multifaceted physiologic and quantitative assessments will be needed to define specific phenotypes to facilitate targeted biologic and genetic interventions that may need to begin very early to accomplish primary prevention of BPD.

The holy grail is the prevention of prematurity which has proven elusive. Aside from prematurity prevention, perinatal interventions represent a unique opportunity in BPD prevention since longitudinal studies show small improvements in neonatal lung function translates into large improvements in childhood and adult respiratory health.

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Box 1. Barriers to Primary Prevention Research and Clinical Trials in BPD

A. Barriers related to the targeted patient population

- Vulnerable (immature, developing) population of very premature infants
- Need to balance risk/benefit of preventative strategies or interventions - some premature babies that would never get the disease will be exposed to an experimental therapy that could have side effects or cause harm
- IRB consent and ethical issues of dealing with children and vulnerable populations, including possible harm with no guarantee of benefit in a high risk population
- BPD is a rare disease necessitating multi-institutional collaborations:
 - De-regionalization of neonatal care
 - Need to organize academic centers into “consortiums” with the capacity to collect data and enroll patients in intervention trials for rapid scientific discovery
- Pharmaceutical companies are reluctant to study the neonatal population given limited numbers of patients and inherent risks of studying a critically ill pediatric population with high mortality and long statute of limitations
 - Best Pharmaceutical for Children Act: limitations in studying drug therapies in neonatal population⁸⁴

B. Barriers related to scientific knowledge gaps

- Limited understanding of normal lung growth and repair mechanisms; few tissue repositories for anatomic studies of lungs of babies who die from BPD or premature babies who recover from BPD and die of other causes
- Poorly understood pathophysiology - multiple pathways to BPD
- Unclear timing for primary prevention - does BPD start in utero; at delivery?
- Need for more information on how various BPD phenotypes evolve/mature over time
 - Limited BPD model systems: rodents may not be an ideal model for studying BPD prevention
 - Long standing primate model in San Antonio no longer funded
 - History of novel, promising therapies in rodent studies that have not been translated to early phase clinical trials
- Lack of validated early biomarkers that predict later disease onset
- No good surrogates for important long-term respiratory outcomes
 - Relatively poor correlation between a diagnosis of BPD and childhood respiratory disease

C. Systematic clinical and bureaucratic barriers

- Poor phenotyping/definition of BPD -Definition provides no information about pathophysiology, disease progression or variability in lung pathology.
- Failure to examine severity of disease; some interventions (i.e. iNO) may reduce disease severity but not incidence, as currently defined by O2 use at 36 weeks.
- Failure to identify subpopulations with distinct mechanisms of disease
- Clinical trials of combination therapies are hard to design and interpret but may be what is needed given the various mechanistic pathways and phenotypes
- Double standard for the evidence: High bar for new therapies but not for established approaches which may cause harm
- Need for redesign of the clinical research machine plagued with inefficiencies and bureaucratic barriers

Adapted from McEvoy CT, Jain L, Schmidt B, Abman S, Bancalari E, Aschner JL. Bronchopulmonarydysplasia: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases. *Ann Am Thorac Soc* 2014; 11 Suppl 3:S146-S153; with permission.

Key Points

- Premature birth alters lung growth and development and may predispose to pulmonary functional limitations and early chronic obstructive pulmonary disease as an adult.
- Measurements of lung function early in life can improve understanding of the determinants of lung growth and facilitate evaluation of current clinical strategies and new therapeutic interventions.
- Primary prevention of bronchopulmonary dysplasia is a critical research priority.

Figure 1.

Measurements of FRC in mL/kg in 40 preterm infants (20 treated vs. 20 untreated infants) and of respiratory compliance (Crs) in mL/cmH₂O/kg in 36 preterm infants (mean±SEM). FRC and respiratory compliance were significantly increased in the betamethasone-treated group compared to the untreated group.

(From John Wiley & Sons publications McEvoy C, Bowling S, Williamson K, Stewart M, Durand M. Functional residual capacity and passive compliance measurements after antenatal steroid therapy in preterm infants. *Pediatr Pulmonol* 2001;31(6):425–430; with permission.)

Figure 2.

A. Pulmonary diffusing capacity, DL_{CO} , versus alveolar volume, V_A . Individual data for subjects with chronic lung disease of infancy (CLDI) (*solid circles*) and control subjects (*open squares*) are presented, as well as the linear regressions for each group. DL_{CO} was significantly lower for subjects with CLDI compared with control subjects when adjusted for alveolar volume by analysis of covariance ($P = 0.0004$). **2B.** Ratio of pulmonary diffusing capacity to alveolar volume, DL_{CO}/V_A , was not related to body length. Individual data for subjects with CLDI (*solid circles*) and control subjects (*open squares*) are

presented, as well as the average data for each group. DLCO/V_A was significantly lower for subjects with CLDI compared with control subjects ($P = 0.0004$).

(Reprinted with permission from the American Thoracic Society. Copyright © 2015 American Thoracic Society..Balinotti JE, Chakr VC, Tiller C et al. Growth of lung parenchyma in infants and toddlers with chronic lung disease of infancy. Am J Respir Crit Care Med 2010;181(10):1093–1097.Official Journal of the American Thoracic Society.)

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Table 1

Pulmonary Function Tests That Have Been Used to Monitor the Natural History of BPD

<i>Neonates (Up to 44 weeks post menstrual age [PMA])</i>				
Measurement	Technique	What it tells us	Units of measure	Is sedation needed?
Crs = Passive respiratory system compliance	Single breath or multiple breath occlusion	Respiratory system mechanics (stiffness of lungs) Assess effectiveness of medications, i.e., prenatal and postnatal steroids, surfactant, and others Decreased in BPD	mL /cm H ₂ O; mL /cm H ₂ O/ kg	No
Rrs = Passive respiratory system resistance	Single breath or multiple breath occlusion	Respiratory system mechanics (flow in airways/airspaces) Assess effectiveness of medication as above Increased in BPD	cm H ₂ O/ mL/sec	No
Cdyn = Dynamic compliance	Least mean square analysis, and others. Uses a pneumotachograph	Dynamic respiratory system mechanics (stiffness of lungs) Assess effectiveness of medications as above Decreased in BPD	mL /cm H ₂ O mL /cm H ₂ O/ kg	No
FRC = Functional residual capacity	Nitrogen washout; Helium dilution; SF ₆	Volume in the lungs at the end of a normal expiration. Assess effectiveness of medications as above Decreased in "new BPD"	mL and mL/kg	No
Z_{rs} = Impedance of respiratory system	Forced oscillation technique	Describes the resistance, compliance, and inertance of the respiratory system, also resonance frequency		No
LCI = lung clearance index / mixing efficiency	Multiple breath washout	Measure of lung homogeneity		No
<i>Infants (Age 44 weeks PMA to 2 years of age)</i>				
<i>As above can measure Crs, Rrs, Cdyn, FRC, Zrs*, LCI*</i>	As above in neonatal tests	As above	As above	Yes
FEFs = Forced expiratory flows (FEF ₇₅ ; FEF ₅₀ ; FEF ₂₅₋₇₅ ; VmaxFRC)	Raised volume rapid thoracic compression (RTC) technique; Tidal breathing RTC (also called Vmax FRC)	Expiratory flow during forced expiration. Decreased in BPD	mL/sec	Yes
FVC = Forced vital capacity; FEV 0.5 = Forced expiratory volume in 0.5 seconds	Raised volume RTC; Tidal breathing RTC	Volume change between full inspiration and complete expiration Volume change in first 0.5 seconds. FEV0.5 decreased in BPD	mL	Yes
FRCp = Functional residual capacity	Plethysmography	Volume in the lungs at the end of a normal expiration. Assess effectiveness of medications as above Decreased in "new BPD"	mL	Yes
DLCO = Pulmonary diffusing capacity VA =Alveolar volume	Single breath hold	Used to assess lung growth and parenchymal lung disease DLCO decreased in BPD; VA normal in BPD	mLCO/min/mm Hg mL	Yes
<i>Children/Adolescents/Adults</i>				
FEFs = Forced expiratory flows (FEF ₂₅₋₇₅ ; FEF ₇₅ ; FEF ₅₀)	Spirometry	Expiratory flow during forced expiration Decreased in BPD	mL/sec	No
FVC = Forced	Spirometry	FVC as above	mL or Liters	No

<i>Neonates (Up to 44 weeks post menstrual age [PMA])</i>				
Measurement	Technique	What it tells us	Units of measure	Is sedation needed?
expiratory capacity FEV1 = forced expiratory volume in 1 sec		Volume change in first 1 second of expiration FEV1, volume change in first 1 second of expiration Decreased in BPD		
FRC ; RV =residual volume; TLC - total lung capacity; other volumes	Spirometry	FRC as above RV/TLC increased with air trapping	mL or Liters	No
DLCO = Pulmonary diffusing capacity	Single breath hold	DLCO as above	mLCO/min/mm Hg	No

Other techniques have been used in neonates but may require sedation;

* Studies are underway evaluating the ability to measure Zrs and LCI in infants without sedation. The above list is not comprehensive/inclusive; Peak oxygen consumption has also been measured during exercise tolerance in children and adults. Abbreviations used in table: BPD, bronchopulmonary dysplasia; CO, carbon monoxide; SF6, sulfur hexafluoride

Table 2

Representative PFT Studies in Neonates and Infants Reporting Response to Therapies and Elucidating Natural History of BPD

<i>Treatment Studies (antenatal steroids, surfactant, effects of PEEP, postnatal steroids)</i>					
Study/year	Aim	Study Design	Study Groups	Methods	Conclusion/Outcome
McEvoy (2001) ¹³	Document changes in Crs and FRC after single course of AS	Case control	20 preterm infants treated with AS vs 20 preterm untreated	SBOT; Nitrogen washout	A single course of AS within 7 days of delivery significantly increases Crs and FRC
McEvoy (2008) ¹⁴	To compare PFTs in infants born at different intervals after AS therapy	Case control	28 preterm infants born within 7 days of AS therapy vs 28 preterm infants born >7 days after AS	SBOT	Infants born > 7 days after AS therapy had a significant ↓ in Crs due to the dissipation of the beneficial effects of surfactant induced by AS
McEvoy (2010) ¹⁵	To evaluate whether a "rescue" course of AS improves PFTs in preterm infants	RCT	56 infants randomized to rescue AS vs 57 randomized to placebo	SBOT; nitrogen washout	Preterm infants who received a rescue course of AS had improved Crs and less oxygen need
Hjalmarson (2011) ¹⁶	To evaluate if AS induced lung changes persist	Case control	22 infants treated with AS but born at term vs 50 term infants untreated with AS	SBOT; nitrogen washout; gas mixing efficiency	No signs of a permanent effect of AS on lung function
Dinger (2002) ²²	To understand mechanisms of improved oxygenation after surfactant	Descriptive	90 preterm infants with severe RDS studied prior to and serially after surfactant	SBOT; SF6 washout	↑ in FRC within 1 hour of treatment with ↑ in Crs 3 to 24 hours after treatment depending on type of surfactant
Dinger (2001) ¹⁷	Effect of PEEP levels on lung mechanics	Descriptive	20 infants at 24–32 weeks of gestation and 72 hrs after surfactant	SBOT; SF6 washout	↑ in FRC with ↑ PEEP but ↓ Crs with increasing PEEP
Durand (2002) ²³	Compare 7 days of low vs high dose postnatal steroids on pulmonary function	RCT	24 preterm infants randomized to low and 23 to high dose dexamethasone	Cdyn	Similar ↑ in Cdyn with both doses by day 7 of treatment, no difference in BPD
<i>Studies in Neonates and Infants With BPD</i>					
Kavvadia (1998) ²⁷	Compare FRC in preterm infants with BPD vs preterm infants without BPD	Case control	16 infants with BPD at 28 days and 8 without BPD had FRC done at 14 and 28 days	Helium dilution	Decreased FRC in patients with BPD compared to those without BPD
Kavvadia (2000) ²⁸	Predictive value of FRC, Crs, Rrs on	Descriptive	100 consecutive VLBW infants	SBOT; Helium dilution	Decreased FRC (<19 mL/kg) best predictor of BPD at 28

<i>Treatment Studies (antenatal steroids, surfactant, effects of PEEP, postnatal steroids)</i>					
Study/year	Aim	Study Design	Study Groups	Methods	Conclusion/Outcome
	day 2 of life in 100 VLBW infants		ventilated within 6 hours of life and studied on day 2		days in patients 28 weeks of gestation
McEvoy (2014) ²⁹	Compare PFTs at 34–36 weeks in BPD vs healthy patients born at 34–36 weeks	Case control	20 patients with BPD and 20 matched healthy infants	SBOT; Nitrogen washout	Infants with BPD have significantly ↓FRC and ↓Crs compared to healthy infants studied at same PMA
Hjalmarson (2005) ³⁰	Compare PFTs of BPD and healthy preterm infants, all studied at term	Case control	50 infants with BPD and 19 healthy preterm controls	SBOT; nitrogen washout; gas mixing efficiency	Infants with severe BPD had lower FRC, less efficient gas mixing, ↑ specific conductance than those with mild, moderate BPD or healthy preterms
Baraldi (1997) ³¹	Follow PFTs through 2 years in infants with BPD	Longitudinal cohort	24 patients with BPD	SBOT; nitrogen washout; VmaxFRC	Pulmonary mechanics improve over first 2 years but low FEFs persist
Fakhoury (2010) ³⁸	Describe PFTs in BPD infants in the first 3 years of life.	Longitudinal cohort	44 patients with BPD	TVRTC	Persistent low partial expiratory flows through 24 months of age
Filburn (2011) ³⁹	Assess longitudinal changes in PFTs over first 3 years of life in relation to somatic growth	Longitudinal cohort	18 patients with BPD studied at a mean of 59 and 91 weeks of age	RVRTC	Children with BPD have significant and persistent airflow obstruction. Those with above average somatic growth had greater lung growth
Thunqvist (2014) ⁴⁰	PFTs at 6 and 18 months in relation to BPD severity	Longitudinal cohort	55 infants with BPD studied at 6 and 18 months	SBOT; FRC by plethysmography; TVRTC; RVRTC	Initial low Crs and high Rrs improved over time but FEFs low at 24 months indicating impaired expiratory flows
Balinnotti (2010) ³⁵	Compare DLCO V _A in patients with BPD compared to term controls	Case control	39 infants with BPD and 61 term infants studied at about 12 months of age	DLCO with single breath hold	Infants with BPD had lower DLCO but normal V _A compared to term controls consistent with ↓alveolarization
<i>Studies in Healthy Preterm or Term Neonates and Infants (needed as reference group or control group as BPD is studied)</i>					
Hjalmarson (2002) ²⁶	Compare PFTs in healthy preterm vs term infants	Case Control	32 healthy preterm and 53 healthy term infants studied at same PMA	SBOT; nitrogen washout; gas mixing efficiency	Preterm infants show signs of dysfunction of terminal respiratory units
McEvoy (2013) ²⁵	Compare PFTs in healthy LPIs at term PMA vs PFTs in healthy term infants	Case control	31 healthy LPI and 30 healthy term infants studied at 40 wks PMA	SBOT; nitrogen washout	Healthy LPI have ↓Crs, altered flow volume loops, ↑ Rrs compared to term infants

<i>Treatment Studies (antenatal steroids, surfactant, effects of PEEP, postnatal steroids)</i>					
Study/year	Aim	Study Design	Study Groups	Methods	Conclusion/Outcome
Balinotti (2009) ³⁴	To measure the ratio of DLCO to V _A in healthy term infants	Observational	50 healthy infants between 3 and 23 months of age	DLCO and V _A	Lung growth in this age mostly by addition of alveoli rather than expansion of current alveoli
Jones (2000) ³³	Establish reference values for FEFs for term infants	Observational/normative	155 healthy infants between 3 and 149 wk of age	RVRTC	FEFs increase with increasing length
Friedrich (2007) ³²	Compare longitudinal FEFs in healthy preterm vs healthy term infants	Prospective cohort	26 preterm (average GA of 32.7 wks) and 24 term infants studied in year 1 and 2 of life	RVRTC	Healthy preterm infants have persistently lower FEFs than term infants suggesting no catch up growth in airway function

List of above studies is not inclusive; Abbreviations used in above table: AS, antenatal steroids; BPD, bronchopulmonary dysplasia; CO, carbon monoxide; Crs, passive respiratory system compliance; DLCO, pulmonary diffusing capacity; FEF, forced expiratory flows; FRC, functional residual capacity; GA, gestational age; LPI, late preterm infants; PFT, pulmonary function test; PMA, post menstrual age; RCT, randomized controlled trial; Rrs, passive respiratory system resistance; RVRTC, raised volume rapid thoracic compression technique; SBOT, single breath occlusion technique; SF₆, sulfur hexafluoride; TVRTC, tidal volume rapid thoracic compression technique; V_A, Alveolar volume