Disease Phenotyping of Infants with Severe Bronchopulmonary Dysplasia

The most common complication of preterm birth is bronchopulmonary dysplasia (BPD) (1), widely referred to as the chronic lung disease of prematurity. This disease was first described over 50 years ago in moderately preterm infants (~34-wk gestation). At the time, the most cutting-edge therapies were supplemental oxygen and nascent mechanical ventilation techniques used to treat respiratory distress syndrome—for which the mortality rate was >50% (2). Since this initial report by Northway and colleagues in 1967 (2), extensive efforts by basic and translational researchers have dramatically changed the BPD landscape. Today, we enter the sixth decade since the initial BPD description, over 90% of preterm infants survive their neonatal ICU course with the use of antenatal corticosteroids, improved delivery room...
management, noninvasive respiratory techniques, surfactant, and more sophisticated mechanical ventilation techniques (1).

Although the rate of BPD has not changed dramatically (1), the babies who develop BPD have changed. Today, the babies with the highest risk for the development of BPD are those born between 22- and 28-weeks’ gestation and those born with extremely low birthweight (<1,000 g). There is growing recognition that extremely preterm infants who lack a BPD diagnosis at 36 weeks are still at increased risk for respiratory morbidities and abnormal lung function during late childhood and early adulthood (3). This concept was highlighted in the PROP (Prematurity and Respiratory Outcomes Program) cohort, for which about 50% of infants with persistent respiratory disease at 1 year of life had no or mild BPD at 36-weeks' postmenstrual age (4). This has led to a plethora of reports in recent years trying to better define BPD. Thus, to better predict outcomes and to identify those infants at greatest risk for poor outcomes, there is a need to identify antenatal factors and postnatal mechanisms that drive airway and distal lung growth and repair after preterm birth.

More than 30 years after BPD was defined by Shennan and colleagues (5), and even since the publication of the 2001 NHLBI workshop report (6), the definition of BPD has become more challenging, as more immature infants are surviving the neonatal period. How well the diagnosis of BPD can predict pulmonary outcomes in infancy and childhood, and how those long-term pulmonary outcomes should be defined, remain primary research and clinical questions (7). Until most recently, BPD was defined solely by supplemental oxygen requirements; however, the increased use of high-flow nasal cannula and continuous positive airway pressure has made these definitions insufficient. In the PROP cohort, 359 infants (47%) younger than 29 weeks of age were treated with nasal cannula flow at 36-weeks’ postmenstrual age, including 95 infants (12%) on flow with room air (8). The NHLBI 2018 revision, which established grade 3 BPD for infants receiving positive pressure or nasal cannula >3 L/min in addition to oxygen, has attempted to address the use of these new modalities of respiratory support (9), and recent studies have shown that this classification scheme is useful for prediction of long-term morbidity (10). Despite the prognostic implications of the existing definition for BPD, all current definitions rely on defining a disease based on the level of respiratory support and do not provide insights into the underlying cardiopulmonary pathophysiologic disease components. Stratifying infants with severe BPD into subgroups based on their predominant disease phenotype is likely the next step in improving care for the severely affected infants with BPD.

Perinatal and postnatal injury to a premature lung can affect any number, it not all, of the three main lung compartments, including airways, alveoli and adjacent lung parenchyma, and the pulmonary vasculature. Clinical manifestations of airway disease in BPD can take the form of bronchomalacia or tracheomalacia, or increased airways reactivity (11, 12). Disruption of distal lung growth with impaired alveolarization can lead to decreased surface area for gas exchange, resulting in hypercarbia, hypoxemia, and need for supplemental oxygen and/or positive-pressure support. Decreased or abnormal growth of the pulmonary microvasculature resulting in pulmonary vascular disease, most commonly manifests as pulmonary hypertension (PH) in some children with BPD (13). The complex pathophysiology of BPD can lead to significant pulmonary phenotype variability among infants with severe BPD and may be influenced by prenatal and postnatal exposures. Physiologic phenotyping of infants with BPD can discern the relative contributions of lung, airway, and vasculature to help better inform prevention, treatment, and long-term outcome prognostication.

In this issue of the Journal, Wu and colleagues (pp. 1398–1406) present exciting new work that helps define the frequency of three critical disease components in BPD (14). In a referral cohort of preterm infants with severe BPD, the authors in this study used frequency of parenchymal lung disease, PH, and large airway disease to predict outcomes. Although there have been efforts by this group and other investigators to identify individual pathophysiologic disease components in BPD to predict outcomes and mortality, this current report suggests that disease components in isolation may not fully convey the burden of severe BPD. Their focus was on understanding the potential interactions of three predominant clinical components of BPD, and they found that less than one-third of infants in their cohort were found to have only one predominant pathophysiologic component. Nearly three-quarters of infants were diagnosed with at least two or more disease components, suggesting that the presence of a single, predominant pathophysiologic disease component in BPD may be true for only a minority of patients. Of the 73 infants classified, 78% had moderate-to-severe parenchymal lung disease, 66% had PH, and 60% had large airway disease. Presence of all three disease components was the most common phenotype observed in 32% of infants with severe BPD.

This group reports the rate of their primary outcome of death before neonatal ICU discharge, tracheostomy, or the use of a systemic pulmonary vasodilator at discharge increased with greater counts of disease components. Specifically, 91% of infants with all three disease components developed the primary composite outcome compared with 45% of infants with only one disease component. In this cohort, PH was the primary predictor of mortality, and tracheomalacia was most closely associated with the eventual placement of a tracheostomy tube. Surprisingly, the severity of parenchymal lung disease was not independently correlated with any outcomes evaluated. These results highlight the potential importance of phenotyping BPD for predicting outcomes and monitoring response to therapies.

Advancements in the care of BPD over the next decades are dependent on improved understanding and use of disease phenotyping in infants with BPD to enable better risk stratification and targeted therapeutic interventions. Improved BPD phenotyping with better objective measurements and biomarkers of lung, airway, and pulmonary vascular injury, along with incorporating antenatal risk factors, will help better refine the approach to defining BPD disease severity for both clinical care and research.

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Pulmonary arterial hypertension (PAH) is a disease that is typically fatal within 5–7 years of diagnosis for most subjects and occurs in all ancestral populations (1). Since the initial discovery of BMPR2 (bone morphogenetic protein receptor type 2) mutation as a cause of PAH, countless publications have further expanded the genetics of PAH, including discoveries of other causative genes and the role of common gene variant associations (2–4). Yet, few studies have comprehensively explored how ancestry, race, or ethnicity plays a role in PAH development and response to therapy. The lack of such studies is striking given the intense focus on providing personalized care to patients with PAH. Of course, studies of discrete populations, such as minority groups, are challenging to perform in rare diseases given the small numbers of subjects.

Nearly a decade ago, Gabler and colleagues conducted a pooled analysis of data from placebo-controlled trials of the use of endothelin receptor antagonists in >1,000 participants with PAH, and uncovered variations in response to endothelin receptor antagonists related to sex and self-reported race (5). Race-based comparisons focused on black versus white individuals showed a difference in placebo-adjusted beneficial treatment response, favoring white individuals by considerable effect sizes. However, this difference did not meet statistical significance. Although other racial groups were not explored, the study was an important reminder that variations in treatment response may occur among individuals of different racial and ethnic groups. A few subsequent studies reported the impact of self-reported African ancestry; overall, there appears to be a higher degree of severity and perhaps a reduced treatment response among those who self-report as black (6–10).