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"New" bronchopulmonary dysplasia and chronic lung disease

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is the major cause of chronic lung disease and morbidity in preterm infants. Since it was first described fifty years ago, the epidemiology, pathogenesis, and treatment for BPD has changed dramatically. This review summarizes these changes and the clinical outcomes for infants diagnosed with BPD.

This year marks the 50th anniversary of Northway's description of bronchopulmonary dysplasia (BPD). BPD is the major cause of chronic lung disease and morbidity for preterm infants, affecting 10,000–15,000 infants per year in the US. The epidemiology and pathology of BPD have changed dramatically over the past 50 years. "Old" BPD occurred in preterm infants with surfactant deficiency (<34 weeks) following respiratory distress syndrome (RDS). These infants required ventilatory support and high concentrations of supplemental oxygen, therapies that induced a heterogeneous lung injury marked by regions of atelectasis and other regions of hyperinflation, severe epithelial injury, airway smooth muscle hyperplasia, fibrosis, and pulmonary vascular hypertensive changes [1]. Over the past 25 years, the introduction of two therapies, antenatal steroids [2,3] and intratracheal surfactant [4], significantly decreased the morbidity and mortality of RDS and BPD in this population, shifting the demographics of BPD to earlier preterm infants (<29 weeks gestational age). These extremely low gestational age infants may not have surfactant deficiency or RDS, but instead have early requirements for oxygen and ventilatory support due to multiple factors leading to "respiratory instability of prematurity" [5]. These infants may have an immature respiratory drive with hypopneas or apneas, increased pulmonary edema due to patent ductus arteriosus, pulmonary infections, lung injury due to oxygen and ventilator therapies, atelectasis and hypoventilation due to poor lung compliance, or secondary surfactant deficiency. The "new" BPD pathology for these extremely low gestational age infants is characterized by arrested alveolar-capillary development with larger, simplified alveoli, increased interstitial fibrosis, and abnormal pulmonary vasculature with decreased branching and precapillary arteriovenous anastomoses [6]. Importantly, preterm birth, BPD and early respiratory infections may result in dysanaptic growth with increased alveolar size but blunted airway growth. These changes result in fixed airflow obstruction into adulthood and constitute a cause of early life origins of chronic obstructive pulmonary disease [7].

Although BPD epidemiology and pathology have changed over 50 years, the diagnosis of BPD is still based on the level of support required by infants at 36 weeks post-menstrual age. Infants meet the diagnostic criteria if they require supplemental oxygen during the first 28 days of life and require supplemental oxygen at age 36 weeks post-menstrual age. Diagnostic criteria have been further refined by including a physiologic challenge test to determine the level of supplemental oxygen required at 36 weeks. However, we still face challenges in diagnosing BPD because of the lack of better biological or physiologic measures to define this disorder [8].

To understand the impact of BPD on developing pulmonary physiology, infants with BPD have had infant pulmonary function testing (PFT) performed during the first two years and over time to adulthood. The raised volume, rapid thoracoabdominal compression technique for infant PFTs is highly technically dependent but provides physiologic data that can be followed longitudinally. Several studies from single centers demonstrate that preterm infants with or without BPD have reduced small airway flows compared to full-term matched control infants [9,10]. However, infants with BPD have been reported to have more severe airflow obstruction [11]. Importantly in follow up studies, there is a trend for persistent airflow obstruction that is present in studies of young adults with the diagnosis of BPD [10,12].

The management of BPD has dramatically changed due to results from large clinical trials. Three large trials tested the impact of oxygen titration in different ranges, between 91% and 95% vs. 85% and 89%, on BPD, ROP, other comorbidities and mortality. Three studies, the Surfactant, Positive Pressure and Pulse Oximetry

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Randomized trial (SUPPORT), the Benefits of Oxygen Saturation Targeting (BOOST)-II, and the Canadian Oxygen Trial (COT) revealed that the lower range had a greater rate of mortality than the higher range [13]. Several other large trials have tested new modes of ventilatory support and the impact of permissive hypercapnia. Non-invasive modes of ventilatory support which have been tested in large prospective, multicenter trials include nasal synchronized intermittent positive pressure ventilation (siNIPPV), nasal continuous positive airway pressure (CPAP), and post-extubation high flow nasal cannulae [14–16]. The results from these trials have shifted the current standard of care to initial treatment with non-invasive ventilatory support in infants without cardiorespiratory failure at birth, and close monitoring of infants to expedite invasive support to less invasive modes of therapy.

Since the introduction of antenatal steroids and post-natal surfactant to reduce BPD occurrence, there have only been two therapies demonstrated to decrease the risk for BPD: caffeine [17] and intramuscular Vitamin A [18]. Although long term steroid use has been associated with increased morbidity due to gastrointestinal hemorrhage and poor neurocognitive outcomes, short term dexamethasone use to facilitate extubation may be better tolerated. Furthermore, one group, Yeh et al. [19,20], published two prospective, randomized, controlled clinical trials that demonstrate that in newborn infants with RDS requiring mechanical ventilation within 4 h of birth, intratracheal administration of a mixture of budesonide and surfactant compared to surfactant alone every 8 h until FiO2 was decreased to less than 0.4 or infant was extubated, reduced the incidence of BPD. Further investigation in a larger clinical trial will be required for universal acceptance of this approach.

To better understand the natural history of chronic lung disease in extremely low gestational age preterm infants, the NIH sponsored a multicenter (13 medical centers) observational study of preterm infants less than 29 weeks gestational age up to one year corrected age, the Prematurity and Respiratory Outcomes Program (PROP) [21] to obtain detailed NICU and post-NICU demographics, clinical features, and biomarkers to identify factors that predict chronic lung disease. Families or guardians were surveyed by questionnaires at 3, 6, 9, and 12 months corrected age for respiratory symptoms- cough or wheeze, use of cardiorespiratory medications, use of oxygen or requirement for tracheostomy, ventilator, or non-invasive ventilatory support or hospitalization. If questionnaires were positive at two time points, the infant met the diagnosis of prematurity respiratory disease (PRD). Severe disease was defined as requirement for home supplemental oxygen for greater than 3 months, multiple hospitalizations, systemic steroids or symptoms despite inhaled corticosteroids. Of the 724 infants classified for primary outcome, 68% of infants had PRD significant lung disease at 1 year of age and 38% had severe disease. Importantly, both perinatal factors and the diagnosis of BPD accurately predicted respiratory outcomes [22]. Each center is in the process of evaluating biomarkers for association with risk for PRD.

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