Pathogenesis and Prevention of Chronic Lung Disease in the Neonate

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KEYWORDS

• Bronchopulmonary dysplasia • Chronic lung disease
• Neonate • Premature

Increased survival rates in infants born between 24 and 26 weeks gestation has resulted in larger numbers of neonates who require respiratory support at birth. Despite the use of antenatal steroids, exogenous surfactant, and a variety of modes of ventilation, a number of these neonates develop complications of prematurity, including the development of chronic lung disease (CLD). Often used interchangeably, CLD or bronchopulmonary dysplasia (BPD) develops primarily in extremely low birth weight infants (ELBW) weighing <1000 g who receive prolonged oxygen therapy and or positive pressure ventilation.[1] CLD, which occurs in as many as 30 percent of infants born weighing <1000 g, contributes significantly to the morbidity and mortality seen in very low birth weight infants.[2]

Despite extensive research aimed at identifying risk factors and devising preventative therapies, many questions about the etiology and pathogenesis of BPD remain. It is known that acute lung injury, resulting from a multitude of factors including the pressure, volume and oxygen associated with mechanical ventilation, initiates a cascade of inflammation, arrested lung development, and abnormal repair processes that ultimately damage the still-immature alveoli and result in prolonged oxygen dependency. This article reviews the embryologic development of the lung and the pathogenesis of CLD or BPD. The authors discuss some of the measures that have been used in an attempt to both prevent and treat BPD.

DEFINING BPD

BPD was first described by Northway and colleagues[3] in 1967. At that time, neonates with severe respiratory distress syndrome (RDS) were treated with conventional mechanical ventilation using high peak inspiratory pressures and high levels of inspired oxygen. These infants remained oxygen dependent beyond the expected resolution of their RDS, had acute episodes of bronchospasm, and demonstrated classic radiographic changes, including the presence of areas of atelectasis and cystic hyperinflation.[3] Northway and colleagues[3] developed a set of criteria for both defining and staging the severity of BPD. In this staging system, Stage I and II BPD occurred in the first ten days of life with the findings indistinguishable from RDS. Stage III marked the transition to chronic disease and Stage IV occurred in infants who, at one month of age continued to require oxygen or ventilatory support and who associated radiographic abnormalities.

Building on the work of Northway, Bancalari and colleagues[4] suggested additional clinical criteria to support a diagnosis of BPD: ventilation for a minimum of three days in the first week of life; and, at 28 days of life, the need for supplemental oxygen to maintain oxygen levels of at least 50 mm Hg, clinical signs of respiratory distress (tachypnea, retractions, adventitious breath sounds) and an abnormal chest radiograph.

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More recently, the introduction of antenatal steroids, exogenous surfactant therapy, synchronized modes of ventilation, and aggressive nutritional support have changed the course of the ELBW infant and of BPD. The classic or ''old BPD'' seen in both preterm and term infants, had been replaced by a ''new BPD'' seen almost exclusively in ELBW neonates. This new BPD is less severe and, in many cases, presents in infants who had mild lung disease and required little or no supplemental oxygen at birth.[5] The newer type of CLD highlights the need to re-examine the definition of BPD. Some studies done in the 1980s and 1990s used the need for oxygen at 28 days to define BPD;[6,7] however, this definition would include infants who may have an acute illness at that time and may exclude neonates who subsequently require supplemental oxygen.[5] Other criteria used to define BPD include the need for supplemental oxygen at 36 weeks postconceptual age[8] or the presence of chronic respiratory symptoms requiring treatment in the first year or two of life.[9,10]

In 2000, the National Institutes of Health (NIH) held a consensus conference for the purpose of identifying a common definition of BPD. The result was a list of diagnostic criteria that is based on the need for supplemental oxygen for a minimum of 28 days. The amount of oxygen needed is used to determine the severity of disease (**Table 1**).[11] Although this definition has become widely accepted, it has not yet been prospectively evaluated.[12]

INCIDENCE

Variable definitions and inclusion criteria make it difficult to determine the incidence of BPD. Even in multisite studies using a common definition, the incidence of BPD varies widely among sites.[12,13] Walsh and colleagues[14] identified an incidence of 35% in their study of 1598 low birth weight (LBW) infants (<1250 g), while Sahni and group[15] found that only 7.4% of infants in their study needed oxygen at 36 weeks postconceptual age.

When the NIH definition of BPD was applied in a retrospective review of 4866 ELBW infants done by Ehrenkranz and colleagues,[16] they found that 77 percent of the neonates met the NIH criteria for BPD with 16 percent having severe disease and 30% moderate BPD.

PATHOGENESIS

BPD has been associated with lung inflammation and fibrosis, and BPD was presumed to primarily reflect barotraumas secondary to mechanical ventilation. The lungs of infants who have BPD presented with signs of infection, inflammation, and parenchymal fibrosis; otherwise, areas devoid of fibrous changes were believed to be histologically normal. The presumed etiologies included oxygen toxicity and/or barotrauma. However, as management strategies have evolved, younger preterm infants have higher survival rates. As a consequence, the clinical picture of BPD, as well the understanding of the pathogenesis of this disease, has changed considerably.

As alluded to earlier, several authors now distinguish between ''old'' and ''new'' BPD.[1,17] The essential features of new BPD are alveolar simplification and enlargement, as well as vascular changes. Alveoli retain a saccular appearance; the distal microvasculature is dysmorphic; and capillaries are abnormally distributed and are generally further away from the air surface. Thus, both angiogenesis and alveolarization are altered in patients with BPD. The following discussion focuses on the authors' current understanding of pathogenesis of BPD, including what is known concerning the molecular mechanisms underlying alveolar and vascular dysfunction. As an introduction, the sequence of lung development is briefly reviewed.

OVERVIEW OF LUNG DEVELOPMENT: ALVEOLAR AND VASCULAR DIFFERENTIATION

Lung development spanning 40 weeks of gestation can be divided into five stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar (**Fig. 1**). Midway through gestation (week 20), the conductive airways are almost complete, but alveoli appear only after 32 weeks of gestation. Nonetheless, the period of viability for preterm birth is generally considered to begin after 23 weeks, by which point lung development is transitioning from the cannalicular phase into the saccular phase.

Vascular events are tightly linked to and partly controlled by alveolar development. Two mechanism of capillary growth can be considered: vasculogenesis and angiogenesis. During the early stages of lung growth (spanning the embryonic and pseudoglandular stages), the developing airways serve as a guide for the growth of new blood vessels via vasculogenesis; this process involves the formation of new blood vessels from mesenchymal progenitor cells. By week 17, or the beginning of the cannalicular stage, new blood vessels begin to be formed via angiogenesis, during which existing capillary endothelial cells give rise to new capillaries.

According the revised or new schema of BPD, both vascular and alveolar development appear