

Bronchopulmonary Dysplasia: Development and Progression in the Neonatal Intensive Care Unit

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Advances in neonatology have led to increased survival at younger gestational ages. These advances have included the ability to provide and titrate oxygen, improved modalities of assisted ventilation, improved nutritional and environmental support, and surfactant therapy. As a result of increasing survival of these immature infants, bronchopulmonary dysplasia (BPD) has become a consistent outcome despite improvements in technology. Varying definitions of BPD have emerged in an effort to best identify infants at risk for long-term adverse outcome and those who might benefit most from preventive therapies. Underlying abnormal pulmonary development of extremely preterm infants in the face of exposure to oxygen, assisted ventilation and inflammation make this a complex, multifactorial disease. Recent focus has been directed at preventing and treating inflammation. Efforts to minimize the inflammatory process include avoiding hyperoxia, minimizing injury from assisted ventilation, and preventing and treating postnatal infections. Additional therapies to modulate inflammation, such as steroid therapy or inhaled nitric oxide, need further investigation of both short- and long-term outcomes before routine use can be recommended.

Defining Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) emerged as an entity in the 1960s as a result of the new-found ability to provide assisted ventilation to small infants by way of pressure controlled ventilation. Originally described by Northway in 1967, a subset of surviving infants treated with oxygen and assisted ventilation developed characteristic chest X-ray changes and a persistent oxygen requirement at 28 days of life. Chest X-rays demonstrate alternating cystic and fibrotic areas.¹ The population described by Northway was, on average, 33 weeks gestation with birth weight 1,900 g, a population who in that era had significant mortality risk from respiratory distress syndrome. With ongoing improvement in the ability to support preterm infants, such as providing parenteral nutrition and neutral thermal environments, survival of increasingly smaller, more immature infants improved such that by the 1980s, the limit of viability dropped to 500 g and 25 weeks gestation.² Surfactant was introduced as a therapy for respiratory distress syndrome in the early 1990s and resulted in a significant reduction of mortality in preterm infants.^{3–5} The hope for a concomitant reduction of BPD did not materialize; the incidence of BPD remained the same.^{6,7} It is likely that surfactant resulted in a shift of the mortality and BPD to a more immature population. Infants who would have died before surfactant therapy were surviving with BPD, whereas those who previously may have survived with BPD had significant amelioration of

their lung disease with surfactant and recovered without BPD. Additional strides occurred with the advent of prenatal betamethasone therapy, further reducing neonatal mortality and respiratory distress syndrome.⁸

Since BPD tends to be an outcome in extremely low-birth-weight infants (ELBW; those with birth weight less than 1,000 g), Northway's original definition of oxygen requirement at 28 days of life became less useful. Approximately 80% of ELBW infants will still require oxygen at 28 days of life with less characteristic chest X-ray findings, thus making this definition less helpful in distinguishing which infants have more significant lung disease. To account for this phenomenon, BPD was redefined as persistent oxygen requirement at 36 weeks postmenstrual age. Using this definition, BPD still affects over 20% of infants with birth weights less than 1,500 g. The incidence is significantly influenced by degree of immaturity, with BPD affecting one-third of infants with birth weight 750–1,000 g, and half of infants with birth weight less than 750 g.⁹

Oxygen requirement unfortunately can be variable and dependent on the prescriber. A physiologic test for defining BPD was developed to allow standardization of oxygen needs, especially in research settings assessing therapies across multiple centers. At 36 weeks postmenstrual age, infants requiring more than 30% oxygen to maintain oxygen saturations of 90%–96% clearly meet the definition of BPD. For infants requiring less than 30% oxygen, if saturations are greater than 96%, the oxygen is weaned to its lowest level to

maintain these saturations, and if able to be maintained in room air with saturations greater than 90% for 30 min, is considered not to have BPD, regardless of the clinical decision of the provider to continue oxygen supplementation.^{10,11}

Defining BPD becomes important for a number of reasons. In addition to being an important outcome measure of therapies used in the first weeks of life, it is well documented that infants in whom BPD is diagnosed have significant long-term adverse outcomes.¹² These infants have increased late mortality, increased hospitalization rates, long-term pulmonary sequelae, and increased adverse neurodevelopmental outcomes. To further capture the highest-risk infants, the National Institute of Health developed a consensus definition. Infants with an oxygen requirement at 28 days that resolves by 36 weeks postmenstrual age have mild BPD, those with oxygen requirements of less than 30% at 36 weeks have moderate BPD, whereas those requiring more than 30% oxygen or require positive pressure [positive pressure ventilation or nasal continuous positive airway pressure (CPAP)] have severe BPD.¹³ Using this definition for infants with birth weight less than 1,000 g and surviving to 36 weeks, 30% of infants had moderate BPD and 16% had severe BPD.^{13,14}

Changing Clinical Risk Factors

Although the clinical concepts originally proposed by Northway implicated high supplemental oxygen and barotraumas from assisted ventilation in the face of respiratory distress syndrome and moderate prematurity, it is increasingly clear that BPD is a disease of multifactorial etiology. A large number of clinical risk factors have been identified and include inflammation,¹⁵ infection,¹⁶ modes of ventilation, nutritional factors such as vitamin A deficiency,¹⁷ ureaplasma,^{18,19} patent ductus arteriosus,²⁰ and possible genetic factors.²¹ The clinical risk factors and their treatments have changed over time, with respiratory support remaining important. However, the increase in survival of extremely premature infants has shifted in the pathological changes of the lung. The original BPD was characterized by damage and fibrosis: alveoli had alternating atelectasis and over inflation; airways demonstrated epithelial lesions and smooth muscle hyperplasia; and vasculature showed arterial thickening with pulmonary hypertension. The exposure of increasingly immature lungs to the extrauterine environment results in abnormal development and impaired alveolarization. Pathology reveals fewer, larger, simplified alveoli, with fewer, dysmorphic capillaries. Airways continue to show epithelial lesions and smooth muscle hyperplasia. Early inflammation and persistent inflammation have increased prominence.²²

Mechanical Ventilation

Since the advent of BPD occurred with the ability to provide mechanical ventilation to these vulnerable infants, much attention has been drawn to the pathophysiology of damage from conventional ventilation and how it might be minimized while still providing the necessary support for infants with respiratory disease. Traditional conventional ventilation consists of time-controlled, pressure-limited intermittent mandatory ventilation with positive end expiratory pressure. Although an effective method to deliver small

tidal volumes to lungs with high compliance, this method results in volutrauma from over distension due to high peak inspiratory volume and atelectotrauma from repeated collapse and reopening of alveoli. Advances in technologies have focused on techniques to minimize these injuries. Synchronizing breaths, assist control, pressure support, and flow cycling all allow maximal synchrony with the patient and may decrease total time on the ventilator.²³ Although providing a gentler mode of ventilation, no trials have documented reduction in BPD. With improvement in the ability to deliver small tidal volumes more effectively, a volume limiting strategy has become available for ELBW infants. Although 1 study has suggested that this method results in a decrease in BPD (4% versus 25%), it has not been replicated.²⁴

High-frequency ventilation delivers rates of 10–15 breaths per second with very low tidal volumes that are less than the physiologic dead space. In animal models, high-frequency ventilation has demonstrated decreased lung injury. Multiple studies comparing conventional with high frequency have not shown a consistent advantage in either treatment of respiratory distress syndrome or in reduction of mortality or BPD at 36 weeks.²⁵ Although early studies suggested a possible increase in intraventricular hemorrhage and periventricular leukomalacia,²⁶ subsequent studies have not confirmed this.²⁷ One study suggests the difficulty in finding a difference between outcomes of conventional mechanical ventilation compared to high-frequency ventilation may be a result of improved outcomes with conventional ventilation over time due to standardization of its use.²⁸

Knowing the resultant damage of any mechanical ventilation strategy, there has been ongoing interest in using nasal CPAP as a mode of respiratory support. CPAP allows inflation to be maintained without excessive over-distension and helps avoid atelectasis. Early CPAP was shown to decrease the need for ventilator support in the presurfactant era. Several institutions have adopted the use of CPAP as their primary mode of ventilation, tolerating extreme physiologic variability and higher carbon dioxide levels, and have reported reduced incidence of BPD compared with national averages.^{29,30} Additional trials have attempted to tease out whether the improved outcome is an institutional phenomenon or a more generalizable therapy.^{30,31} Infants born at less than 28 weeks gestation were randomized to receive either CPAP or intubation with surfactant administration in the delivery room. The primary outcome, death or BPD, was not different between the groups, although infants with CPAP had fewer days of mechanical ventilation and less frequently required intubation. Both studies concluded that CPAP is an equivalent alternative to intubation and surfactant in preterm infants.

Oxygen

Providing supplemental oxygen is another essential mode of support in preterm infants with respiratory distress syndrome, yet excessive oxygen can cause injury via promotion of oxygen free radicals³² and impair ongoing alveolarization.³³ It additionally promotes abnormal vascularization of the immature retina, known as retinopathy of prematurity (ROP), which leads to impaired vision and possibly blindness. In studies attempting to regulate oxygen support to ameliorate the progression of ROP, it was noted that

targeting lower oxygen saturations resulted in lower rates of BPD.^{34,35} The definition of “low” saturations varied widely in the studies from low 90s to the 80s. Developmental follow up of infants maintained at lower saturations did not demonstrate any adverse impact in neurodevelopmental outcomes.³⁶

The SUPPORT trial also examined targeted oxygen saturations, comparing saturations of 85%–89% to saturations of 91%–95%, and found no difference in the combined outcome of severe ROP or death.³⁷ When separated, severe ROP occurred less often in the low-saturation target group (8.6% versus 17.9%), but death before discharge was increased (19.9% versus 16.2%). Rates of BPD were not different between groups, but all infants avoided hyperoxia. The optimal target range is still controversial and will require further investigation, examining broader outcomes in addition to the incidence of BPD.

Inflammation

There is a clear role for inflammation in lung injury and the development of BPD. Maternal chorioamnionitis and postnatal infections have been associated with higher rates of BPD.^{38–40} Additionally, infants born to mothers with chorioamnionitis have impaired response to surfactant administration.⁴¹ Even in the absence of an infectious etiology, inflammation as a result of oxygen toxicity and volutrauma results in inflammatory infiltrates, release of cytokines, and pulmonary edema. Preterm infants with documented chorioamnionitis on placental pathology had elevated cytokines in cord blood, which correlated with the severity of placental inflammation.⁴² Cytokine levels decreased after day 1 of life. In infants with no evidence of inflammation on placental pathology, cytokine levels increased after birth. For all infants, elevated interleukins-8, -10, and granulocyte colony stimulating factor on day 1 of life were associated with an increased risk of BPD. The authors suggest that the lack of inhibition of early inflammation from chorioamnionitis led to the increased risk of BPD. Other studies have found an association of BPD and death with elevated interleukins-1 β , -6, -8, and -10 and decreased interleukin-17 and tumor necrosis factor- β , suggesting the increased risk may be related to the impairment in transition from an innate immune response mediated by neutrophils to the adaptive immune response mediated by T lymphocytes.⁴³

To address the excess inflammatory response that is an integral component of BPD, steroids have been used as both treatment and preventive therapy. High-dose steroids decrease inflammation, inflammatory infiltrates, and cytokine damage; accelerate lung maturation; improve surfactant and antioxidant production; and stabilize capillary wall permeability. High-dose dexamethasone therapy was shown to significantly decrease oxygen requirements and promote extubation, and it became commonly used in the neonatal intensive care unit (NICU) setting as treatment for BPD.^{44,45} Although infants often had a remarkable response while on steroid therapy, mortality or need for supplemental oxygen at the time of discharge was not improved. Numerous side effects became evident such as hyperglycemia, hypertension, gastrointestinal bleeding and perforation, and poor weight gain and head growth. It was subsequently noted that the accelerated lung maturation in these immature infants led to premature alveolarization before septation with resulting

larger but fewer alveoli and, thus, reduced surface area.²² Despite this, steroid use became commonplace, until late neurodevelopmental sequelae, especially cerebral palsy, were noted. Infants with BPD are at high risk for adverse neurodevelopmental outcomes, but those treated with high-dose dexamethasone had a disproportionate increase in cerebral palsy.^{46,47} A large meta-analysis controlling for poststudy steroid contamination revealed a relative risk of 2.86 for development of cerebral palsy, with a number needed to harm of 7 and a relative risk of 1.66 for neurodevelopmental impairment (including mental disability, blindness, and deafness) with number needed to harm of 11.⁴⁸ Further evaluation of outcomes at 8 years of age revealed that although infants with BPD had poorer outcome than infants of similar birth weight and gestational age, those infants with BPD treated with steroid therapy had lower full-scale IQ (77.0 versus 85.2), increased participation in special education (78% versus 48%), need for occupational therapy (71% versus 44%), and physical therapy (71% versus 41%) compared with infants with BPD who were not exposed to steroids.⁴⁹

The American Academy of Pediatrics (AAP) released a statement in 2002 recommending that steroid therapy should be used only in trials or in extreme circumstances, and after discussion with the parents regarding the risks and benefits.⁵⁰ No definition was provided for the circumstances in which steroids could be considered. Although routine use of high-dose dexamethasone for BPD has decreased, steroid use remains common in the NICU, with increasing use of hydrocortisone for blood pressure support.⁵¹ A revised AAP statement was released in 2010, again reinforcing the need to avoid high-dose dexamethasone exposure, while stating that there is still insufficient evidence to recommend other glucocorticoid doses and preparations.^{52–54}

In vitro, glucocorticoid receptors promote apoptosis of neuronal cells, whereas mineralocorticoid receptors inhibit apoptosis.⁵⁵ High-dose dexamethasone provides a significant glucocorticoid stimulus while suppressing adrenal function and, thus, lowering mineralocorticoid exposure. This suggests that a more physiologic steroid preparation may allow the benefits of modulating inflammation without adversely impacting neurodevelopmental outcomes. In critically ill adults, symptoms such as hypotension and electrolyte imbalance have been associated with low normal cortisol values when clinical condition would dictate an elevated cortisol response to the stress of illness.⁵⁶ This condition, known as relative adrenal insufficiency, responds to physiologic replacement of hydrocortisone. These are common symptoms among preterm infants, raising the possibility of relative adrenal insufficiency as the etiology. Infants with low cortisol values early in life have increased incidence of BPD.⁵⁷ Confounding this observation is the fact that low cortisol values can be a normal developmental finding in preterm infants,⁵⁸ with *in utero* cortisol values remaining low.⁵⁹ To improve the inflammatory response by providing physiologic cortisol replacement, a large randomized, double-blinded multicenter trial was undertaken to evaluate the efficacy of physiologic hydrocortisone treatment (1 mg/kg/day) in the first 2 weeks of life for the prevention of BPD.⁶⁰ The study was terminated due to an increase in gastrointestinal perforations in babies receiving hydrocortisone (10% versus 2%). Most infants with perforations also

received indomethacin, and, thus, may have been related to the drug combination rather than the hydrocortisone alone. No impact was found in the incidence of BPD between groups. A secondary analysis of cortisol values was unable to identify a target population for this therapy: those infants with low cortisol values at either day 1 or 7 were not more likely to develop BPD or benefit from the hydrocortisone therapy.⁶¹ Neurodevelopmental assessment of the study participants at 18 months of age showed no difference between groups, showing that hydrocortisone was not associated with the adverse outcomes seen with high-dose dexamethasone.⁶² A similar study of early hydrocortisone prophylaxis was also halted early due to concerns of gastrointestinal perforation and, thus, had much smaller numbers, but suggested some benefit in the reduction of BPD in those infants with lower cortisol values.⁶³

In light of reassuring neurodevelopmental outcomes after treatment with hydrocortisone, increasing interest has risen for the use of hydrocortisone for a treatment of established BPD. Higher doses (5 mg/kg/day) followed by a 3 week taper have been shown to be equally as effective as high-dose dexamethasone in reducing oxygen and days on the ventilator, with less adverse short-term effects and less adverse long-term neurologic outcomes.⁶⁴ This was a retrospective, nonrandomized report reflecting on clinical experience with this regimen. High-dose hydrocortisone has not been submitted to the rigors of a randomized trial to address both short- and long-term outcomes.

Nitric Oxide

Inhaled nitric oxide has been shown to cause pulmonary arterial smooth muscle relaxation and pulmonary vessel vasodilatation, resulting in improved pulmonary blood flow in term infants, and has been shown to improve outcomes in persistent pulmonary hypertension.^{65,66} Additional actions of inhaled nitric oxide include a decrease in neutrophil accumulation and cytokine release, resulting in less inflammatory damage. There is also suggestion that nitric oxide may enhance surfactant production and prevent neomuscularization and airway remodeling.⁶⁷ This broad potential range of pulmonary effects has resulted in interest in using inhaled nitric oxide to prevent BPD. In a single center, infants treated with nitric oxide had decreased mortality and BPD, and this resulted in improved neurodevelopmental outcomes.⁶⁸ Subsequent multicenter, randomized trials have shown variable differences in survival without BPD, with follow up in 1 study with no difference in neurodevelopmental outcomes.^{69–72} Each trial varies in dose, timing of initiation, and length of treatment with nitric oxide and vary in the population targeted by the studies. A recent meta-analysis concluded that the routine use of inhaled nitric oxide in preterm infants with respiratory failure did not alter mortality or the subsequent development of BPD at 36 weeks postmenstrual age and is, therefore, not recommended.⁷³

Conclusion

As a result of improving survival of increasingly immature infants, BPD has become a consistent outcome despite improvements in respiratory support through surfactant therapy and improved technology of modes of respiratory support. Underlying abnormal pulmonary development of

extremely preterm infants in the face of exposure to oxygen, assisted ventilation, and inflammation make this a complex, multifactorial disease. Efforts to minimize the inflammatory process include avoiding hyperoxia, minimizing injury from assisted ventilation, and preventing and treating postnatal infections. Additional therapies to modulate inflammation, such as steroid therapy or inhaled nitric oxide, need further investigation of both short- and long-term outcomes before routine use can be recommended.

Author Disclosure Statement

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