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The New Bronchopulmonary Dysplasia

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Abstract

Purpose of Review—BPD remains the most common severe complication of preterm birth. A number of recent animal models and clinical studies provide new information about pathophysiology and treatment.

Recent Findings—The epidemiology of BPD continues to demonstrate that birth weight or gestational age are most predictive of BPD. Correlations of BPD with chorioamnionitis are clouded by the complexity of the fetal exposures to inflammation. Excessive oxygen use in preterm infants can increase the risk of BPD, but low saturation targets may increase death. Numerous recent trials demonstrate that many preterm infants can be initially stabilized after delivery with CPAP and then be selectively treated with surfactant for RDS. The growth of the lungs of the infant with BPD through childhood remains poorly characterized.

Summary—Recent experiences in neonatology suggest that combining less invasive care strategies that avoid excessive oxygen and ventilation, decrease postnatal infections, and optimize nutrition may decrease the incidence and severity of BPD.

Keywords

Ventilation; oxygen; prematurity; lung injury

INTRODUCTION

BPD remains the most common complication of very preterm birth. New research published within the last 2 years provides new insights into the pathophysiology of BPD, primarily using animal models. New clinical trials have not provided the clinician with new treatment strategies, but do provide some guidance. The NHLBI recently funded grants to explore childhood outcomes of lung diseases in infants and has established a 5-center consortium to better characterize BPD and to identify useful biomarkers of disease progression. These research programs should benefit very preterm infants in the future.

Epidemiology of BPD

New information about populations of infants with BPD has appeared. Stroustrup and Trasande (1) report the incidence and resource use of infants with BPD, using a US nationwide data base. They conclude that the incidence of BPD decreased by 4.3% per year for the years 1993–2006. There was an associated increase in noninvasive ventilation, but costs and length of hospitalizations for infants with BPD increased. We also learned more about the pattern of disease progression from the initial 14 days of oxygen exposure for 1340 infants born at 23 to 27 weeks gestational age in 2002–2004 (2) (Table 1). By

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multivariant analyses, the major predictors of BPD were not surprising: lower gestational age, and mechanical ventilation on day 7. However, 33% of the persistent lung disease population (receiving 49% oxygen and 84% ventilated at 14 days) **did not** develop BPD while 17% of the infants in room air at 14 days of age developed BPD. BPD is multifactorial in causality and our abilities to identify infants at risk are imperfect. I am surprised that 81% of this population was receiving conventional or high frequency ventilation at 7 days of age, suggesting that the investigators did not subscribe to noninvasive ventilatory support strategies. In a second report these investigators identify fetal growth restriction in infants 23 to 27 weeks gestation as a risk factor for BPD (3).

The National Institutes of Child Health – Neonatal Research Network also has provided us with information on 9575 infants of 22–28 weeks gestation born from 2003–2007 (4). The incidence of BPD did not decrease over the 5 years in this population of well-studied infants. The BPD outcomes are categorized for each gestational age according to the 2000 classification of BPD as mild (oxygen use for 28 days), moderate (oxygen need at 36 weeks), or severe (ventilatory support at 36 weeks) (Fig. 1). These curves are a useful visual reminder of the very high risk for severe BPD at the earliest gestational ages. However, overall, the numbers of infants with severe persistent BPD have decreased.

Chorioamnionitis and BPD

The clinical research on relationships between antenatal infection (chorioamnionitis) and RDS or BPD remains unsettled. Chorioamnionitis induced in sheep by pro-inflammatory mediators such as E.coli LPS, IL-1, or live Ureaplasma induce both lung maturation and a phenotype of fetal lung inflammation (5). Chorioamnionitis in fetal mice stimulates angiogenesis and an inflammatory profile comparable to the inflamed lungs of infants developing BPD (6). The infants in the ELGANS study had extensive evaluations for histologic chorioamnionitis; and just over 50% were exposed to chorioamnionitis, but there was no correlation of chorioamnionitis with severity of early respiratory disease or BPD (2) (Table 1). A multicenter study from the Canadian Neonatal Network found that clinical chorioamnionitis associated with increased risks for intraventricular hemorrhage and early-onset sepsis, but not respiratory outcomes (7). The simple associations of chorioamnionitis with RDS and BPD are confounded by the unknowns – duration of fetal exposure, extent of fetal responses, and the organisms inciting the responses, factors that are important based on animal model literature (5). Clinical examples of the complexity of the relationships were provided by Been and colleagues (8, 9). Chorioamnionitis isolated to the placenta and chorion was associated with decreased RDS while chorioamnionitis with fetal involvement increased the risk of RDS in early gestational age infants (9). Infants exposed to severe chorioamnionitis had decreased clinical responses to surfactant treatment and those less favorable responses correlated with longer mechanical ventilation and more BPD (8). Thus, simple evaluations of a clinical or histologic diagnosis of chorioamnionitis may mask populations of infants at either increased or decreased risks of outcomes such as RDS and BPD. The future will be in the use of molecular microbiological techniques to better characterize the organisms causing fetal exposures and to better define the fetal or newborn responses. An example is the report by Payne (10) demonstrating that the presence of Ureaplasma parvum in tracheal aspirates increased the odds ratio for BPD or death by 4.8.

Inhaled Nitric Oxide

The use of inhaled NO (iNO) to prevent BPD remains controversial. A new large trial demonstrated that the early use of low dose iNO had no beneficial effects (11). The NIH held a Consensus Conference on iNO for preterm infants in the fall of 2010, and a summary of their conclusions is available (12). Research on how iNO treatments might help preterm infants is continuing. McCurnin and colleagues (13) demonstrated in preterm baboons that

postnatal estriol supplementation improved pulmonary outcomes, possibly by upregulating nitric oxide synthase. iNO decreases the alveolar and vascular growth abnormalities induced by oxygen exposure of newborn rodents. iNO also will blunt the lung structural abnormalities and pulmonary hypertension caused by bleomycin in newborn rats (14). Vadivel and colleagues (15) mitigated the oxygen induced alveolar arrest in newborn rats with supplementation of L-citrulline, a precursor of NO. The animal data strongly support a protective role of iNO for injury of the saccular lung. The clinical challenge remains to develop treatment strategies that provide enough benefit to justify the cost of iNO or to identify other drugs to increase NO in the lung.

Oxygen Use and BPD

Chronic exposure of the developing rodent lung to high oxygen concentrations uniformly causes structural changes similar to the new BPD. Chronic exposure of infants who need oxygen after 32 weeks to a higher oxygen saturation range will increase the incidence of BPD (16). Depressed term infants can be resuscitated as effectively with room air as with supplemental oxygen, but preterm infants are different. Preterm infants born at 24–28 weeks gestation and in need of ventilatory support at delivery were initially resuscitated with 30% or 90% oxygen by Vento and colleagues (17). Oxygen exposures were adjusted to saturation targets of 75% at 5 min and 85% at 10 min. Heart rate responses were comparable and both groups received about 50% oxygen by 5 min and 30% oxygen by 10 min. The increased oxygen exposure for infants started at 90% oxygen from birth to 5 min of age correlated with more ventilatory support and a significant increase in BPD. Those infants with BPD had higher indicators of oxidant injury in blood and urine. This provocative report suggests that brief exposures of very preterm infants to high oxygen concentrations can initiate a lung injury resulting in BPD, despite comparable blood oxygen saturations over the period of resuscitation. The take home message for now is that resuscitation of very preterm infants should be initiated with 30–50% oxygen. These results need to be replicated.

A NICHD-Neonatal Research Network trial randomized infants of 24 to 27 weeks gestation from NICU admission to 36 weeks to oxygen saturation targets of 85–89% or 91% to 95% (18). The primary outcome for the trial was severe ROP or death, and the combined rates of severe ROP or death did not differ. However, in a classic demonstration of competing outcomes, the rate of death increased (relative risk 1.7, 95% CI, 1.01–1.60) and the rate of severe ROP decreased (relative risk 0.52, 95% CI, 0.37–0.73) with the lower saturation targets. BPD defined as oxygen use at 36 weeks also was decreased significantly for the population with the lower oxygen saturation target. These results, together with the Vento, et al. report (17) demonstrate how carefully oxygen exposures for very preterm infants may need to be regulated throughout the weeks of clinical management.

Ventilation and CPAP

As with oxygen exposure alone, mechanical ventilation alone can interfere with development of the saccular lung in animal models. Mokres, et al. (19) demonstrate that ventilation of newborn mice with room air for 24h induced apoptosis, disrupted alveolar septation, and inhibited angiogenesis. Recent clinical research has explored strategies to decrease ventilation-mediated injury or to avoid mechanical ventilation entirely. A meta-analysis of individual patient data from 10 randomized controlled trials demonstrates no benefit from high frequency ventilation relative to conventional ventilation for BPD or other adverse outcomes (20). Either approach to ventilatory support is effective but avoidance of mechanical ventilation is the best strategy in theory. A number of studies give the clinician guidance as to how that can be done in practice. The same 1316 infants that were randomized to oxygen saturation ranges in the NICHD trial (18) were also randomized prior to birth to intubation at delivery and surfactant treatment within 1 hour of birth or to CPAP

at delivery and surfactant as clinically indicated (21). The protocol specified early extubation when possible. Although there was no difference in the primary outcome of BPD or death, most of the respiratory indicators favored the CPAP group (Table 2). The large decrease in use of postnatal corticosteroids with CPAP is particularly interesting with respect to the new policy statement from the American Academy of Pediatrics that recommends caution for the use of postnatal corticosteroids for BPD (22). This trial randomized infants prior to birth such that it included both depressed and more healthy infants. The recent COIN trial randomized only infants requiring some ventilatory assistance at 5 min of age to CPAP or intubation, which excluded the depressed and "normal" infants (23). Most of the respiratory outcomes favored CPAP in the COIN trial.

A trial from the Vermont-Oxford Network randomized infants to 3 groups: 1) intubation, surfactant, and ventilation, 2) intubation, surfactant, and extubation to CPAP, or 3) CPAP with selective surfactant treatment (24). The outcomes of death or BPD were not different between groups, but qualitatively favored the CPAP groups. Only 46% of the CPAP and selective surfactant group were ventilated over the first 7 days vs. 99% of the ventilation group. Other groups evaluated other wrinkles to the general theme of how to avoid mechanical ventilation while using surfactant. Sandri, et al. (25) randomized 208 infants at birth with gestational ages of 25 to 28 weeks to either intubation within 30 min of birth, surfactant and extubation within 1h to CPAP, or CPAP with selective surfactant treatment. These infants did not require intubation following delivery and were initially stabilized with CPAP if needed. 51% of the selective surfactant group received surfactant. There were no differences in the need for mechanical ventilation within 5 days of age or in any other outcome. In contrast, Rojas, et al. (26) randomized infants of 27 to 31 weeks gestation who were receiving CPAP to surfactant treatment within 1h of birth and a return to CPAP or CPAP alone, with the primary outcome being need for mechanical ventilation. The subsequent need for mechanical ventilation was lower with surfactant treatment and CPAP (26%) than with CPAP alone (39%). Air leaks also were lower in the surfactant treatment groups, but other outcomes were not different. Another approach developed in Cologne, Germany is to support infants with CPAP and treat with surfactant via a fine feeding tube briefly placed into the trachea under direct vision, thus avoiding intubation (27, 28). In a randomized study, this gentle approach to surfactant treatment decreased the need for mechanical ventilation and decreased BPD (28).

Taken together, a strategy of early use of CPAP with surfactant treatment as clinically indicated is not worse than, and in most studies marginally better than, routine intubation and surfactant treatment for very preterm infants. Strategies for respiratory support of these tiny infants are not easily adapted to a practice guideline. In the delivery room, individual assessment (clinical judgment) will determine the intervention selected. Each infant should be continually assessed and given just the extra support needed, and CPAP may be sufficient for the majority of these infants for transition out of the delivery room. The decision about who to treat with surfactant, and how, remains to be refined, but the accumulating evidence supports surfactant treatment as soon as the infant has "significant RDS". For me, "significant" means a chest film consistent with RDS, an increased work of breathing as assessed clinically, and an oxygen requirement of about 35% and rising. Treatment of such infants early in their clinical course should decrease symptoms, decrease oxygen exposure, decrease air leaks, and shorten the clinical course.

The innovations to decrease BPD are new ways to give surfactant and more effective methods to deliver CPAP or noninvasive ventilation. Aerosolization of surfactant is an old idea that is again being evaluated (29). Synchronized nasal ventilation avoids the endotracheal tube and can support infants with apnea (30, 31). Neural adjusted ventilatory assist (NAVA) is a technique for timing and modulating mechanical ventilation cycles using

the electrical signal from the diaphragm detected with a fine catheter in the distal esophagus. NAVA is being evaluated for noninvasive ventilation of infants (32). Diblasi, et al. (33) recently reported that a change in configuration of the pressure controller for bubble CPAP can strikingly increase the ability of bubble CPAP to assist ventilation in animal models. A package of individualized interventions to support ventilation, minimize oxygen exposure, minimize apnea, and encourage growth should decrease both the frequency and severity of BPD, but this disease will not go away.

Stem Cells

The lung injury that is BPD is complex as it involves epithelial surfaces, the lung matrix, and the microvasculature. A dream for the future has been the concept of replacing injured cells with multipotent stem cells to "repopulate and re-grow" the BPD lung. There are a number of reports that demonstrate that stem cell treatments can mitigate oxidant injury in the developing rodent lung. van Haaften, et al. (34) gave bone marrow-derived mesenchymal stem cells by intratracheal injection to oxygen exposed newborn rats and found increased survival and improved exercise tolerance with less lung injury. However, few of the cells engrafted, and conditioned media from the cells blunted cell injury in vitro. Aslam, et al. (35) gave newborn mice intravascular injections with bone marrow-derived mesenchymal stem cells and found protection from oxygen, but with minimal engraftment of cells in the lungs. The conditioned median from the cells was as protective as the cells. Stem cell therapy in infants would be difficult, but the identification of products from stem cells that blunt the injury progression in BPD has real potential. The good news is that perhaps the stem cells are not required, just their secreted products.

There is also new information about stem cells from infants that will help frame questions about these therapeutic approaches. Baker, et al. (36) isolated endothelial colony-forming cells from cord blood of preterm infants and term infants. The cells from the preterm infants were recovered in higher numbers, but were more sensitive to oxygen in vitro than cells from term infants. Borghesi, et al (37) reported that these same endothelial progenitor cells were in lower numbers in cord blood of preterm infants who subsequently developed BPD. These observations in infants at risk of BPD are starting points for recovery of stem cells from infants for growth in vitro for treatment with those cells or media from those cells.

Lung Function in Childhood and Beyond

Major questions linger are how the BPD lung grows through childhood and ages. We do not have definitive answers, but several reports move these questions forward. Fakhourg, et al. (38) measured lung function sequentially at 6, 12, and 24 months after NICU discharge in children with moderate to severe BPD and found that the abnormalities persisted without improvement. Filippone, et al. (39) extended the observations to 9 and 15 years for infants with BPD who had lung functional abnormalities at 2 years of age. The 2-year-old children with significant airflow obstruction continued to have comparable findings in late childhood. Lung function also was assessed at 11 years for infants born at less than 26 weeks gestation using spirometry (40). This population of children had more chest deformities, more asthma, and more respiratory symptoms than did classmates born at term. Spirometry demonstrated airflow limitations that were most abnormal in the children with a history of BPD. A limitation of the traditional measurements of lung function in infants and children is that the measurements assess primarily small airway function. However, BPD causes decreased alveolar and vascular development – abnormalities of the distal lung parenchyma. Balinotti, et al. (41) combined physiological techniques to measure alveolar gas volume with measurements of carbon monoxide diffusion to evaluate lung parenchymal growth in normal children in the first 2 years of life. They found that gas diffusion increased proportionately to alveolar volume, suggesting that alveolar numbers were increasing. They then applied

these measurement techniques to children who had BPD and found decreased gas diffusion capacities, but normal alveolar gas volumes, suggesting a persistence of impaired alveolar development at 1 year of age (42). These measurements provide the first functional measurements of the distal lung in children with BPD.

Conclusions

This review is a selective sampling of progress in the understanding and treatment of BPD. The controversy of management of the PDA was not addressed (43). An area of intense interest in BPD is the development of biomarkers for disease progression (44, 45). Ultimately, a decrease in BPD will depend not only on new information, but on applications of packages of interventions that each may contribute to decreasing the severity and incidence of BPD (46, 47). My preferred practices are efforts to decrease the invasive nature of NICU care in general while empowering the very preterm infant to breathe spontaneously and grow. Such practices include transitioning infants from the delivery room with CPAP, early extubation for intubated infants, minimizing oxygen exposures and vascular catheters, and maximizing enteral nutrition.

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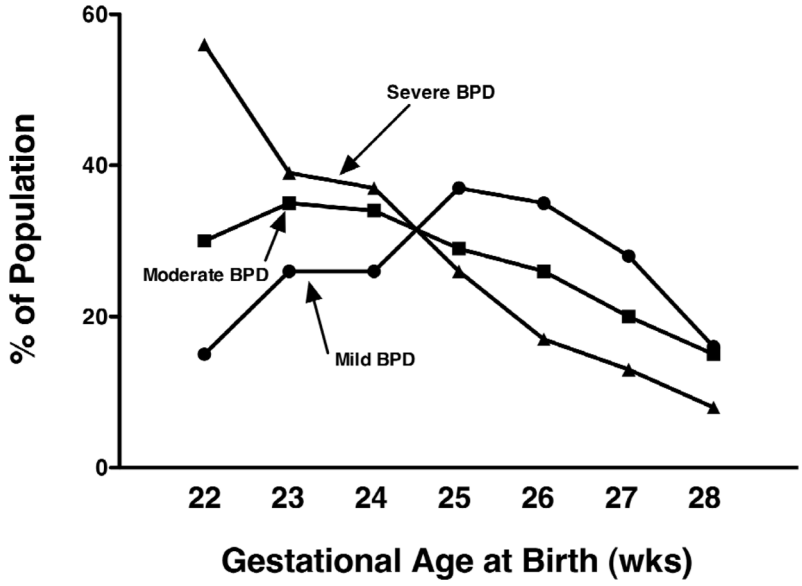

Figure 1.

Percent of population of 9575 infants categorized as to severity of BPD based on the 2000 NIH conference definition. 68% of these infants had BPD. Severity of BPD decreased as gestational age increased. Data abstracted from Stoll, et al., Pediatrics, 2010: 126, 443–456 (Reference #4).

Table 1

Clinical Characteristics of 1346 Infants Grouped by Patterns of Lung Disease to 14 Days of Age

	Consistently Low FiO_2	Pulmonary Deterioration	Persistent Lung Disease
N	249	484	576
Percent of Population	20%	38%	43%
Any Chorioamnionitis	55%	54%	53%
Initial FiO_2	0.25	029	0.38
FiO_2 – 7d	0.22	0.28	0.42
FiO_2 – 14d	0.21	0.40	0.49
Surfactant treatment	78%	89%	97%
CPAP – 7d	50%	30%	10%*
Mechanical Ventilation – 7d	21%	57%	84%*
No PDA	52%	36%	28%*
BPD	17%	51%	67%*

P<0.001 for trend across groups

Data abstracted from Laughon, et al., Pediatrics 2009, 123:1124–1131 (Reference #2)

Table 2

Outcomes for Early CPAP vs. Intubation and Surfactant

	Early CPAP	Intubation and Surfactant	P
N	663	653	
Gestational age (weeks)	26.2±1.1	26.2±1.1	
Death or BPD	47.8%	51.0%	0.30
Death	14.2%	17.5%	0.09
BPD – O_2 use at 36 weeks	48.7%	54.1%	0.07
Mechanical Ventilation (median)	10 days	13 days	0.03
Survival without mechanical ventilation	55.3%	48.8%	0.01
Any air leak	6.8%	7.4%	0.56
Postnatal steroids for BPD	7.2%	13.2%	<0.01

Data abstracted from Finer, et al., NEJM, 2010: 1970–1979 (Reference #2).