NICHD/NHLBI/ORD Workshop Summary

Bronchopulmonary Dysplasia

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BACKGROUND AND REASON FOR WORKSHOP

Bronchopulmonary Dysplasia (BPD) was first described by Northway and colleagues in 1967 as a lung injury in preterm infants resulting from oxygen and mechanical ventilation (1). A National Heart, Lung and Blood Institute (NHLBI)-sponsored workshop further defined the disease and suggested research initiatives in 1978 (2). The pathophysiology of BPD was extensively reviewed by O'Brodovich and Mellins in 1985 (3). Subsequent research with animal models has shown that the very preterm lung can be acutely injured by either oxygen or mechanical ventilation, resulting in interference with or inhibition of lung alveolar and vascular development (4, 5). A change in the pathology of the lungs of infants who have died of BPD has also been found as smaller and more immature infants have come to constitute the majority of the infants who develop BPD (6, 7). A recently published book contains multiple reviews of all aspects of BPD (8). This workshop was organized by the National Institute of Child Health and Human Development (NICHD) and the NHLBI, together with the Office of Rare Diseases (ORD), to review the definition of BPD and lung injury in very preterm infants, to identify gaps in knowledge about lung development and the best indicators of outcome for infants with BPD, and to determine priorities for future research.

BPD is now infrequent in infants of more than 1,200 g birth weight or with gestations exceeding 30 wk (9). Gentler ventilation techniques, antenatal glucocorticoid therapy, and surfactant treatments have minimized severe lung injury in larger and more mature infants. However, some patients who develop BPD are more enigmatic. These consist of very low birth weight infants who initially have minimal or no lung disease but who develop increasing oxygen and ventilatory needs over the first several weeks of life (9, 10). Some of these infants with minimal lung disease that progresses to BPD may have been exposed to chronic chorioamnionitis (11). The incidence of BPD defined as an oxygen need at 36 wk postmenstrual age is about 30% for infants with birth weights $< 1{,}000$ g (6). Some of these infants have severe lung disease requiring ventilation and/or supplemental oxygen for months or years.

PATHOLOGY OF THE NEW BPD

Burri reviewed normal lung development and identified a number of questions and controversies surrounding it (12, 13). The concept that only conducting airways are formed during the pseudoglandular period of lung development may not be correct, because future gas-exchanging airways can already be identified at this point. Burri proposed that a mantle of mesenchyme over the saccular lung may be producing undifferentiated cells that become integrated in the differentiating lung. The alveolar stage of lung development in the human is from about 36 wk gestation to 18 mo postnatally, but the majority of alveolarization occurs within 5 to 6 mo of term birth. The current concept is that primary septation forms saccules and that secondary septal crests indicate alveolarization. Burri questions whether these are separable processes rather than a continuum of septation, with some potential for alveolar development even after most alveolarization has ceased. The arborization of the pulmonary microvasculature is intense as the lung grows, even after completion of the major phase of alveolarization (14). An in-depth understanding of the interdependence of alveolization and microvascular development is needed for a better understanding of the pathophysiology of BPD.

Hussain characterized the "new" BPD on the basis of pathology found in infants dying from BPD (15). Before the surfactant treatment era, airway injury, inflammation, and parenchymal fibrosis were the prominent findings in BPD. More recently, the lungs of infants dying from BPD have shown less fibrosis and more uniform inflation. The large and small airways are remarkably free of epithelial metaplasia, smooth-muscle hypertrophy, and fibrosis. However, there are fewer and larger alveoli, indicating an interference with septation despite an increase in elastic tissue that is proportionate to the severity and duration of the respiratory disease before death (16). Some specimens also have decreased pulmonary microvascular development. The few biopsy specimens available from surviving infants show a similar decrease in alveolarization (5). More information is needed about the progression of the lung injury in survivors of BPD.

Mechanical ventilation and oxygen can interfere with alveolar and vascular development in preterm baboons and sheep (5, 17). Coalson demonstrated that 7 d of mechanical ventilation of preterm baboons of 140 d gestation with 100% oxygen severely reduced the numbers of alveoli (4). The same interference with septation of the more preterm 125-d–gestation baboon lung occurs after surfactant treatment and ventilation but without exposure to large amounts of supplemental oxygen (5). The large decrease in surface area is associated with a decreased and dysmorphic pulmonary microvasculature. These anatomic changes are associated with persistent increases in white blood cells and cytokine levels in airway samples. Although ventilation of preterm baboons from birth with high-frequency oscillatory ventilation resulted in somewhat better gas exchange, better lung mechanics, and lower proinflammatory cytokine levels than did conventional ventilation, both ventilation techniques interfered with septation (18). The relationships between the lung injury and inflammatory responses and lung vascular and alveolar hypoplasia need to be better characterized.

Infants with severe BPD have pulmonary hypertension and abnormal vascular development. In model systems of pulmonary hypertension caused by chronic hypoxia in calves, Stenmark has identified vascular adventitial fibroblasts that proliferate and migrate into the media of resistance vessels in the

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presence of hypoxia (19). These hypoxia-sensitive cells express matrix metalloproteinase-2, and inhibitors of this metalloproteinase block migration of the cells into the vessels. These fibroblasts of adventitial origin may be sentinel cells that can transdifferentiate and contribute to pulmonary hypertension. The molecular signals causing hypoxic activation of adventitial fibroblasts are being identified (20). The relationship between the decrease in septation and vascular development in BPD is not understood, nor is the potential for recovery from either of these abnormalities.

Genetics may contribute to BPD at multiple levels. Genetic polymorphisms in the population may result in increased risks for developing BPD, as was recently shown for respiratory distress syndrome in the Finnish population (21). Through the use of gene ablation in animal models, factors such as fibroblast growth factor-10, Bmp-4, and NKx2.1 were shown to be essential for early lung development (22). This signaling circuitry of morphoregulators of early lung development is likely to be equally important and more complex in location and in developmental timing for alveolar and vascular development. Newly developed techniques to regulate genes at precise times during development will provide critical information about the effects of specific genes on lung developmental stages relevant to BPD. Minoo emphasized that there will undoubtedly be complex interactions between morphoregulators of lung development and the inflammatory mediators present in the injured lung (23). Factors such as transforming growth factor (TGF)-β exhibit sexual dimorphism and may predict the development of BPD of sufficient severity as to need home oxygen therapy (24). Advances in expression technology and proteinomics should be applied to lung injury in the preterm infant to begin to identify those genes that contribute to the injury sequence.

MECHANISMS OF LUNG INJURY

Multiple factors contribute to BPD, and probably act additively or synergistically to promote injury. The traditional view has been that BPD is caused primarily by oxidant- and ventilation-mediated injury. Oxygen alone can arrest septation of lungs that are in the saccular stage of development (4, 25). Infants with BPD who were exposed to higher levels of supplemental oxygen to achieve higher levels of oxygen saturation were found to have more persistent lung disease (26). Mechanical ventilation of preterm animals without simultaneous exposure to high levels of supplemental oxygen also results in the pathologic lesion of BPD (5, 17). The initiation of mechanical ventilation in surfactant-treated preterm animals causes a proinflammatory response, suggesting that any mechanical ventilation of the preterm lung may be injurious (27). The avoidance of intubation and mechanical ventilation with the use of continuous positive airway pressure (CPAP) in the delivery room was associated with a lower incidence of BPD, although this has not been validated by randomized trials (28). Therefore, the development of ventilation and oxygen-exposure strategies that minimize lung injury is a priority for improving outcomes.

Continuing the theme of the possible importance of early postnatal events as contributors to lung injury in the preterm fetus, D. Carlton noted that the preterm lung contains very few mature macrophages or granulocytes, and that granulocytes appear in the lung soon after the initiation of ventilation in animal models (29). The appearance of granulocytes in alveolar washes correlates with pulmonary edema and with the appearance of early indicators of injury, and occurs in parallel with a decrease in circulating granulocytes. Preterm infants who have a decrease in circulating granulocytes at about 1 h of age have an increased risk of developing BPD (30). Proteases produced by activated white blood cells in the lungs may contribute to the progression of lung injury, as suggested by initial evaluations of α_1-antitrypsin to decrease the risk of BPD (31). The recruitment of neutrophils to the lungs soon after birth indicates that the events surrounding birth have consequences that can increase the risk of BPD. More information is needed about what modulates neutrophil sequestration in the preterm lung, and about the downstream events that result in lung injury.

The theme that inflammation is central to the development of BPD was further developed by Speer. Multiple proinflammatory and chemotactic factors are present in the air spaces of ventilated preterm infants, and these factors are found in higher concentrations in the air spaces of infants who subsequently develop BPD (32). Factors such as macrophage inflammatory protein-1 and interleukin (IL)-8 persist in the air spaces, and counterregulatory cytokines such as IL-10 may be decreased, resulting in unregulated and persistent inflammation. Infants exposed to antenatal infection/inflammation or fetal colonization with *Ureaplasma urealyticum* have proinflammatory indicators in their air spaces at delivery (33). Inflammatory cells are prominent in the interstitium as well as in the air spaces, and lung epithelial cells also may synthesize inflammatory mediators. Free radical production, enhanced by free iron in the air spaces, can result in production of TGF-β production and fibrosis. The relative importance of the different factors discussed here to the pathophysiology of BPD remains to be defined, and multiple pathways to injury are plausible.

Sunday has evaluated bombesin-like peptides (BLP) produced by neuroendocrine cells as mediators in BPD (34). Infants and baboons with BPD have increased numbers of neuroendocrine cells, mast cells, and eosinophils in their lungs, and treatment of preterm baboons with an anti-BLP blocking antibody decreases the numbers of these "immunologic" cells and results in less lung injury. BLP and other factors may elicit or promote proinflammatory responses that progress to BPD. Urinary BLP levels correlate with the severity of BPD in preterm baboons, and infants destined to develop BPD have increased urinary levels of BLP. BLP may be a useful early indicator for the identification of infants at risk for BPD.

Because decreased numbers of alveoli are so striking in the lungs of very preterm infants who die of BPD, understanding the developmental regulation of septation and alveolarization is a high priority in understanding the pathology of BPD. In experimental models, hyperoxia, hypoxia, or poor nutrition can decrease septation, as can glucocorticoid treatment (35). In transgenic mice, overexpression of the cytokines tumor necrosis factor-α, TGF-β, IL-6, or IL-11 also can interfere with alveolarization, suggesting that the proinflammatory environment of the air space of the preterm infant may contribute to the altered septation (7). Massaro noted that all-*trans* retinoic acid can increase septation in newborn rodents, and promote septation in adult rats with elastase-induced emphysema (36). These findings have been extended to the observations that mice lacking the retinoic acid receptor (RAR)β have early-onset septation, and that treatment of rats with an RARβ agonist inhibits septation (37). There are several classes of RAR, and their signaling relative to septation will need to be understood. The inhibition of septation induced by glucocorticoids in neonatal rats also can be reversed with retinoic acid (38). These studies demonstrate that alveolarization can be regulated once the signaling pathways involved in it are understood.

INTERVENTIONS FOR BPD

Nutrition plays an important supportive role in the process of normal lung development and maturation. Sosenko noted that

general undernutrition, and specifically insufficient protein intake, may increase the vulnerability of the preterm infant to oxidant-induced lung injury. Decreased glutathione levels may impair the response to oxidant-induced lung injury, and protein undernutrition may interfere with lung growth and DNA synthesis. A protective effect of polyunsaturated fatty acids against lung injury was reported in experimental animals (39). However, several randomized, controlled clinical trials of polyunsaturated fatty acid administration soon after birth failed to show protection against BPD in preterm infants (40). The lack of effect may have been related to the presence of toxic lipid peroxidation products in the lipid preparations. The commercial lipid preparations now available have reduced hydroperoxide contents, and new trials may be justified. Vitamin A is a nutrient that is important to cell growth and differentiation and to airway epithelial cell integrity. In a recent randomized, controlled multicenter clinical trial, vitamin A supplementation caused a small but significant reduction in BPD (41). Additional nutrients, such as inositol, sulfur-containing amino acids, and selenium may provide the premature infant with additional protection against the development of BPD (42). Evaluations of nutritional interventions are warranted.

Many premature infants are exposed to increased oxygen concentrations, and endogenous antioxidant enzyme activity is relatively deficient at birth. Hyperoxic lung injury can be ameliorated both in cell culture and in animals by the administration of recombinant human superoxide dismutase (rhSOD) (43). Davis reviewed a placebo-controlled multicenter trial of the safety and efficacy of rhSOD in preventing BPD (44). Placebo or rhSOD was instilled into the trachea after the first dose of exogenous surfactant, and the treatment was continued for up to 28 d or for as long as infants were ventilated. Although there was no difference in the primary outcome of death and/or BPD, the administration of rhSOD was associated with less severe intraventricular hemorrhage and periventricular leukomalacia. At 6 mo and at 12 mo of corrected age, infants treated with rhSOD had a reduced need for respiratory medications as compared with infants receiving placebo (45). Antioxidant administration for the prevention and treatment of BPD will need to be further evaluated.

Ballard (46) noted that lung development results from the balance between stimulatory and inhibitory influences, and that two of the key regulators are glucocorticoids and TGF-β. Glucocorticoids accelerate the maturation of parenchymal structure, increase surfactant production and lung compliance, reduce vascular permeability, and increase lung water clearance. The net results are improved lung function, better responses to surfactant, and improved survival (46). Glucocorticoids modulate both the transcriptional and posttranscriptional regulation of surfactant components, and the effects are reversible after treatment (47). Maturation of the surfactant system is also induced by analogs of cyclic adenosine monophosphate. In contrast, TGF-β is an inhibitor of lung development (48). TGF-β isoforms and receptors are expressed by fibroblasts and epithelial cells in lung during early gestation. In cultured fetal lung, TGF-β inhibits branching and blocks differentiation of type II cells. TGF-β increases in tracheal aspirates on the first day of life in premature infants who subsequently develop BPD, suggesting that TGF-β is involved in initiation of the injury in BPD.

Watterberg discussed the role of postnatal glucocorticoid therapy for BPD. Many infants at risk for developing BPD are treated with high doses of glucocorticoids, a therapy associated with adverse effects, such as gastrointestinal perforation, cardiac hypertrophy, short- and long-term growth failure, and the possibility of neurodevelopmental compromise (49). Glucocorticoids impair alveolar septation in animal models. Watterberg questioned the rationale for the high doses of dexamethasone frequently used in BPD. Cortisol is a key factor in the response of the lung to injury, and cortisol synthesis is suppressed until relatively late in fetal life. Very preterm infants may lack the capacity to produce enough cortisol to respond to extrauterine stress, and infants who develop BPD have low cortisol levels and a decreased response to adrenocorticotropic hormone (50). In a pilot study, low-dose hydrocortisone, when begun shortly after birth and given for 12 d, increased survival without BPD at 36 wk postmenstrual age (51). Further studies are needed to evaluate low dose glucocorticoid therapy.

Pulmonary vascular resistance (Rpv) is often increased in infants with BPD, and decreased vascular development may be an important component of the pathophysiology of the disease (52). Abman reported that the administration of antiangiogenesis drugs such as fumagillin and thalidomide impaired pulmonary vascular and alveolar development in rats, demonstrating that angiogenesis can be a regulator of alveolar septation (53). Nitric oxide (NO) is an important regulator of pulmonary vascular tone, and NO synthase is expressed in the vascular endothelium and bronchiolar epithelium. NOS increases in the early canalicular stage of development, and inhaled NO increases pulmonary blood flow and decreases Rpv in fetal lambs. NO also decreases Rpv in infants with severe RDS and can improve oxygenation (54). Although possible side effects of NO in the preterm infant have not been adequately evaluated, NO may decrease the risk of BPD by decreasing intrapulmonary and extrapulmonary shunting and by decreasing inflammation in infants with severe hyaline membrane disease. Clinical trials are needed to evaluate NO therapy to prevent and treat BPD.

Mechanical ventilation alone can cause severe lung injury. Carlo noted that insufficient positive end-expiratory pressure (PEEP) and large tidal volumes are the main causes of acute lung damage with mechanical ventilation (55). In adults with acute respiratory distress syndrome, ventilation at low tidal volume (V_T) was associated with improved outcomes and decreased mortality (56). This ventilation strategy has not been evaluated in infants. No detrimental effects were observed in an initial randomized, controlled trial of permissive hypercapnia in preterm infants, although no benefit was demonstrated (57). Because arterial carbon droxide tension may not be a good substitute for V_T, a prospective study, assessing varying levels of V_T and PEEP, will be required.

EPIDEMIOLOGY AND EVALUATIONS OF BPD

Preterm births continue to be the major challenge in obstetrics and neonatology, accounting for most of the perinatal mortality and long-term neurologic morbidity among newborns (58). Andrews noted that approximately half of all preterm births result from the spontaneous onset of preterm labor, and that about a third result from preterm premature rupture of the amniotic membranes. The remaining 20% of preterm births are medically indicated for specific maternal or fetal conditions. The rate of clinically asymptomatic colonization of the chorioamnion and the amniotic fluid increases as the gestational age at delivery decreases. In one study, positive cultures of chorioamnion were reported in 73% of women with spontaneous preterm births occuring prior to 30 wk gestation, and in 83% who had newborns with birth weights under 1 kg. The colonizing bacteria initiate an inflammatory cascade and the release of numerous cytokines, chemokines, prostaglandins, and other bioactive substances that can induce cervical ripening, preterm labor, and membrane rupture (59). This inflammatory response may also cause adverse neonatal outcomes, such as neurologic damage and cerebral palsy, necrotizing enterocolitis, and BPD.

Palta presented the results at 8 yr of a six-center follow-up of infants with birth weights below 1.5 kg in an effort to identify predictive factors for early and late respiratory and functional outcomes (60, 61). Radiographic evidence of BPD at 36 wk was predictive for rehospitalization at ages 0 to 1 yr, of the need for asthma medications, and of wheezing at age 8 yr, but the predictive value of the radiographic changes diminished as the children became older. On the other hand, patent ductus arteriosus increased in predictive importance as the children aged. Oxygen use at 36 wk was not predictive of outcomes after 2 yr of age. A family history of asthma was predictive of most respiratory outcomes among children without BPD. Many infants with BPD seem to recover without long-term respiratory problems.

Tepper reviewed techniques to evaluate pulmonary outcomes. The main determinant of chronic morbidity in patients with BPD is the development of obstructive airway disease. This is demonstrated by a decreased forced expiratory flow (FEF), increased airway reactivity, and increased RV with a normal TLC (62–64). In addition, carbon monoxide diffusion capacity may be decreased. All abnormalities may normalize during the first 3 yr of life, except for that in FEF, which may remain decreased to adulthood (65). Patients with BPD have increased airway reactivity to bronchoconstricting agents, as well as persistent respiratory symptoms. Curves of FEF versus volume, generated with the squeeze or the forced suction method, are helpful in detecting airway abnormalities even in patients who are clinically asymptomatic. High-resolution computed tomographic scans may provide information on airway size, wall thickness, and hyperinflation caused by gas trapping, and on heterogeneity within the airways and lung parenchyma. Longitudinal studies of large cohorts of infants with BPD, from the neonatal period through infancy, childhood, and to adulthood, are needed. The development of new techniques to evaluate pulmonary structure and function in different age groups will be crucial to identifying the underlying mechanisms for persistent lung-functional abnormalities in survivors of BPD.

With the change in clinical presentation of BPD, the original description now applies only to a minority of patients (1). A variety of definitions of BPD have been used in the literature. The most widely used was that of the 1979 BPD workshop, which defined BPD as 28 d of oxygen therapy with radiographic changes (2). The oxygen requirement at 36 wk postmenstrual age was suggested as a better predictor of long-term respiratory outcomes (66). These definitions have the limitation that oxygen administration may vary according to clinical practice among different centers. In an attempt to find a better definition, Ehrenkranz analyzed the NICHD Neonatal Network data base for all infants with birth weights under 1 kg and gestational ages under 32 wk who were born between January 1995 and December 1997. Oxygen administration for the first 28 d resulted in the highest sensitivity, specificity, and positive and negative predictive values for oxygen administration at 36 wk. With respect to predicting oxygen use at discharge, oxygen administration at 36 wk postmenstrual age had the highest values for sensitivity, specificity, and the percent of infants correctly classified. Rehospitalization for respiratory causes, and the use of pulmonary medications after discharge, were predicted similarly by the 28-d and the 36 wk oxygen requirements. Given the importance of a consistent definition of BPD, a subcommittee was asked to develop a new definition.

GENERAL DISCUSSION, NEW DEFINITION OF BPD, AND RESEARCH PRIORITIES

All workshop participants contributed to a discussion of gaps in knowledge and research priorities relating to BPD. The best name of the disease referred to as BPD in the older literature, and more recently as chronic lung disease, was discussed. The consensus was to retain the name BPD because it is clearly distinct from the multiple chronic lung diseases of later life. A new definition, which categorizes the severity of BPD, is proposed (Table 1). The definition for infants with gestational ages < 32 wk was validated preliminarily with the NICHD Neonatal Network data base and Palta's data (61), but extensive validation will be needed to determine whether this definition is superior to previous definitions of BPD. Radiographic findings of BPD are inconsistently interpreted and not routinely available at precise ages, and did not contribute to the resolution of the new definition.

Research and training initiatives that are critical to better understanding of the pathophysiology of BPD, and for exploring therapies for it, are outlined in Table 2. The rapid progress in understanding the developmental biology of the lung will provide the essential information about the major signaling pathways for lung-structural development. The stages of particular interest for BPD will be saccular-to-alveolar development, with the associated extracellular matrix and vascular development. Once signaling pathways for alveolar and vascular development are identified, studies of how oxidants, mechanical stress, and inflammation may alter that signaling will be critical to understanding BPD. Expression arrays developed with preterm models of BPD and from human tissue should complement mouse models in which manipulation of specific genes is possible. Such studies will ultimately define what happens when lung injury is superimposed on a prealveolized and minimally vascularized developing lung.

TABLE 1. DEFINITION OF BRONCHOPULMONARY DYSPLASIA: DIAGNOSTIC CRITERIA

Gestational Age	< 32 wk	≥ 32 wk
Time point of assessment	36 wk PMA or discharge to home, whichever comes first	> 28 d but < 56 d postnatal age or discharge to home, whichever comes first
	Treatment with oxygen $> 21\%$ for at least 28 d **plus**	
Mild BPD	Breathing room air at 36 wk PMA or discharge, whichever comes first	Breathing room air by 56 d postnatal age or discharge, whichever comes first
Moderate BPD	Need* for $< 30\%$ oxygen at 36 wk PMA or discharge, whichever comes first	Need* for $< 30\%$ oxygen at 56 d postnatal age or discharge, whichever comes first
Severe BPD	Need* for $\geq 30\%$ oxygen and/or positive pressure, (PPV or NCPAP) at 36 wk PMA or discharge, whichever comes first	Need* for $\geq 30\%$ oxygen and/or positive pressure (PPV or NCPAP) at 56 d postnatal age or discharge, whichever comes first

Definition of abbreviations: BPD = bronchopulmonary dysplasia; NCPAP = nasal continuous positive airway pressure; PMA = postmenstrual age; PPV = positive-pressure ventilation.

* A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range.

BPD usually develops in neonates being treated with oxygen and positive pressure ventilation for respiratory failure, most commonly respiratory distress syndrome. Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) are considered common to the broad description of BPD and have not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen $> 21\%$ and/or positive pressure for nonrespiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen $> 21\%$ means that the infant received oxygen $> 21\%$ for more than 12 h on that day. Treatment with oxygen $> 21\%$ and/or positive pressure at 36 wk PMA, or at 56 d postnatal age or discharge, should not reflect an "acute" event, but should rather reflect the infant's usual daily therapy for several days preceding and following 36 wk PMA, 56 d postnatal age, or discharge.

TABLE 2. PRIORITIES FOR BETTER CHARACTERIZING THE PATHOPHYSIOLOGY OF AND DEVELOPING EFFECTIVE PREVENTIVE AND TREATMENT STRATEGIES FOR BRONCHOPULMONARY DYSPLASIA

Research Priorities
Understand the developmental processes of septation, alveolarization, and vascularization
Regulatory genes
Signaling pathways
Learn how inflammation and injury are expressed by the developing lung
Differential gene expression in uninjured and injured lungs
Identify modulators of inflammation and injury
Use animal models of BPD to test new treatments
Clinical research priorities
Characterization of BPD
Establish a resource for tissue from infants dying with BPD
Develop new clinical tests for lung function in infants and children
Study genetic contributors to BPD in human populations
Prevention of BPD
Develop standards of care as a basis for clinical trials
Evaluate delivery room procedures and ventilation techniques
Evaluate nutritional, antioxidant, and antiinflammatory interventions
Training priority
Train physicians and physiologists with expertise in evaluating lung function in infants and children

Definition of abbreviations: BPD = bronchopulmonary dysplasia.

New insights into how the lung develops may yield useful strategies for maturing the preterm lung that are more selective and have fewer adverse effects than glucocorticoids. Also, knowledge of the specific signaling pathways that interfere with normal alveolar and vascular development should yield treatment options to better promote lung development despite preterm birth and the inevitable oxygen and ventilation exposures necessary for clinical care. Optimizing this information will require research targeted toward the specific abnormalities of BPD, including unique characteristics of inflammation and tissue responses in the preterm infant. These studies will require animal models that are appropriate to the questions being asked. Ultimately, the biological question is whether normal lung development can be altered by injury or by treatment strategies without adversely affecting subsequent development. A risk is that interventions targeted at one component of the system (e.g., the type II cell) may have a dichotomous effect and adversely alter another component such as vascular development. Animal models of BPD will be critical for testing treatment strategies that affect lung-developmental sequences.

Clinical research is needed to better characterize the long-term outcomes of infants with BPD as newly defined. Airway disease and reactivity can be measured from early infancy. However, there are no tests with which to evaluate the abnormalities resulting from the arrested alveolar and vascular development in BPD, or for monitoring how these abnormalities change with time. Tests of gas diffusion with exercise may provide information about the function of the alveolar–capillary barrier. High-resolution imaging techniques may be useful. Poor neurodevelopmental outcomes are associated with BPD, and their possible pathophysiologic link to the disease via proinflammatory mediators needs to be explored (58). Surrogate indicators for the anatomic and functional consequences of early lung injury resulting in BPD need to be developed to facilitate treatment-directed clinical research.

Because BPD results from multiple insults to the preterm lung that probably cause additive or synergistic injurious responses, multiple aspects of care need careful assessment. Given the wide variation in incidence of BPD among neonatal care units (28), different elements of care in current use need to be identified and subsequently evaluated with intervention trials. Factors that are thought to contribute to BPD (delivery-room care, oxygen, ventilation, macro- and micronutrient deficiencies, antenatal and postnatal infection) will need to be evaluated with clinical trials.

The pathologic description of the new BPD is based on tissue from infants who have died. Much of this tissue is not optimally collected and prepared. Better pathologic information depends on the careful collection of tissue from infants who die of BPD and infants with BPD who die from other causes. The collection of tissue prepared according to protocol by a centralized tissue bank could provide tissue with which investigators could test for possible pathophysiologic factors as they are identified in experimental models. The clinical research and development of tests of pulmonary function for infants, and the wide application of such tests, require trained personnel. There is a severe lack of physicians with expertise in the evaluation of lung function of infants and children, and training programs in this area are needed.

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