Bronchopulmonary Dysplasia: NHLBI Workshop on the Primary Prevention of Chronic Lung Diseases

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Abstract

Bronchopulmonary dysplasia (BPD) is the most common complication of extreme preterm birth. Infants who develop BPD manifest aberrant or arrested pulmonary development and can experience lifelong alterations in cardiopulmonary function. Despite decades of promising research, primary prevention of BPD has proven elusive. This workshop report identifies current barriers to the conduct of primary prevention studies for BPD and causal pathways implicated in BPD pathogenesis. Throughout, we highlight promising areas for research to improve understanding of normal and aberrant lung development, distinguish BPD endotypes, and ascertain biomarkers for more targeted therapeutic approaches to prevention. We conclude with research recommendations and priorities to accelerate discovery and promote lung health in infants born preterm.

Keywords: very preterm infants; mechanical ventilation; normal preterm lung; lung injury; lung repair

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Bronchopulmonary dysplasia (BPD), defined as a need for supplemental oxygen at 36 weeks' postmenstrual age, impacts the pulmonary and overall health of 10,000 premature infants in the United States annually. Infants with BPD have prolonged and recurrent hospitalizations, higher rates of other serious complications of prematurity, and may experience lifelong alterations in lung function. Importantly, not all infants born extremely preterm develop BPD; thus we propose that BPD can be prevented, not just ameliorated, in most patients.

Preterm birth can interrupt the rapid increase in airway septation and vessel growth that takes place during the saccular and alveolar stages of normal lung development. Factors implicated in the aberrant pulmonary development associated with BPD include a structurally and biochemically immature lung, infection and inflammation, hyperoxia and oxidant injury, mechanical injury associated with positive pressure respiratory support, poor respiratory drive and apnea, and poor nutrition (Figure 1). It is likely that the responses of individual patients to these insults are modulated by genetic, epigenetic, and antenatal factors, and that distinct causal factors dominate in different patients. Whereas multiple risk factors have been described, resilience or protective factors have received little experimental attention.

BPD Primary Prevention Research

Prior Primary Prevention Studies for BPD: Few Successes, Many Failures

Despite numerous randomized controlled trials (RCTs) of pharmacologic treatments, respiratory care practices, and nutritional therapies, few have demonstrated efficacy. Two medications have been shown convincingly and safely to prevent BPD:

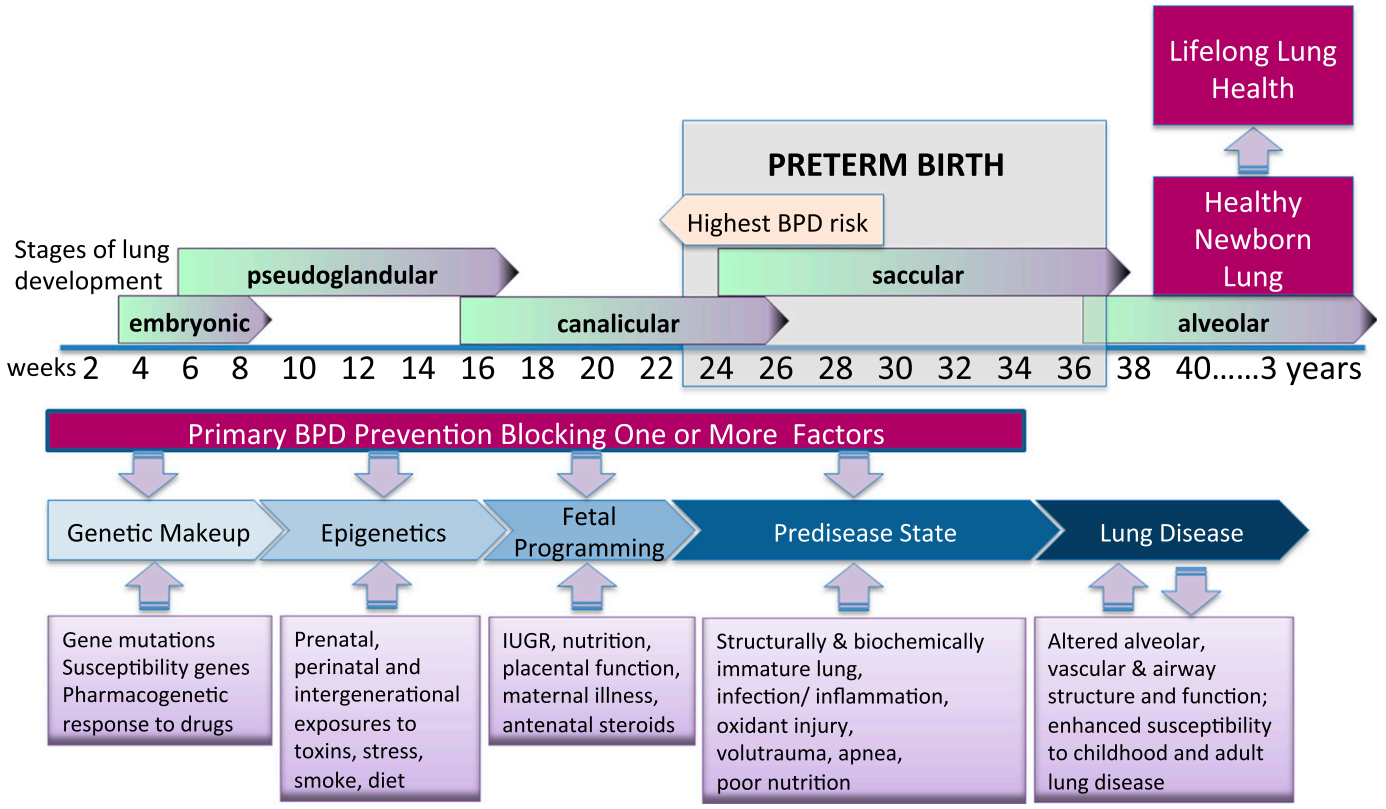

Figure 1. Primary prevention for bronchopulmonary dysplasia (BPD): Windows of opportunity. A host of antenatal and postnatal factors can predispose the structurally and biochemically immature lung to the development of BPD. BPD most commonly occurs in extremely premature infants born during the canalicular or early saccular phases of lung development. However, not all extremely premature infants develop BPD, suggesting BPD can be prevented. Shown here are potential windows of opportunity for the primary prevention of BPD. IUGR = intrauterine growth retardation.

caffeine and vitamin A (1, 2). Antenatal steroids (3, 4) and postnatal surfactant (5, 6) decrease respiratory distress syndrome and death, but have not been proven to decrease BPD in survivors (7–9). Ineffective pharmacologic interventions include early administration of inhaled nitric oxide (iNO) (10, 11), superoxide dismutase (12), glutathione precursors (13), and cimetidine (14). RCTs of various respiratory support approaches (15–17), including permissive hypercapnia (18), failed to significantly decrease BPD.

Lessons Learned from Prior BPD Primary Prevention Studies

Despite many negative studies, important lessons learned can inform future studies. Future prevention studies should target a select population of preterm infants at high risk for development of BPD. Large numbers of preterm infants with variable risk of developing BPD were enrolled in early prevention trials of high-dose dexamethasone, which was later shown to be associated with excess cerebral palsy (19) and intestinal perforation (20). Refinement of BPD risk by endotypes, inclusion of BPD severity classifications in outcome measures, and definition standardization with a room air oxygen saturation test may improve the sensitivity and accuracy of BPD as a modifiable outcome in future trials of primary prevention.

Challenges of Primary Prevention Research for BPD

The optimal timing for primary prevention interventions is unclear. Does BPD start *in utero*, at the time of delivery, or in the early postnatal period? How do interactions between antenatal exposures and postnatal events modulate the risk or severity of BPD? How do various BPD phenotypes evolve over time? There is a need for validated biomarkers that predict later disease and serve as surrogates for long-term respiratory outcomes. Improved understanding of the pathophysiological mechanisms of BPD will facilitate the development of tailored, personalized therapeutic approaches, while reducing health care costs and the risks of broadly applying those therapies. However, it must be acknowledged that improving patient endotyping before randomization, while potentially enhancing the safety and efficacy of RCTs of novel therapies, may increase screening costs and result in fewer eligible babies requiring larger multicenter collaborative efforts.

The inherent challenges of research in premature infants represent a barrier to the conduct of appropriately powered intervention studies to prevent BPD. BPD is a rare disease with different phenotypes, necessitating multiinstitutional collaborations. Ethical challenges include balancing risks and benefits of preventive strategies, knowing that some premature infants not destined to develop BPD will be exposed to experimental therapies with potential adverse effects. There are unique challenges related to institutional review board consent for preterm infants and other

vulnerable populations, particularly when the therapeutic margin is narrow and various organ systems are in different stages of development and vulnerability to toxic effects (21–23). A special concern for extremely preterm infants is the possibility of harm with no guarantee of benefit that is superimposed on a significant baseline risk of mortality or serious morbidity. The need for sedation to perform lung imaging or pulmonary function testing in infants and children is yet another barrier to advances in the field of primary prevention research for BPD. Unfortunately, pharmaceutical companies are reluctant to study a critically ill pediatric population with high mortality and long statute of limitations (24).

Scientific knowledge gaps must be overcome for a successful primary prevention agenda. These gaps include incomplete understanding of normal lung growth and repair mechanisms; poor understanding of the timing, trajectory, and mechanisms of disease; and few human repositories of normal and diseased lungs at various gestational and postnatal ages. Research progress is also hindered by imperfect and costly animal model systems. This is further complicated by the inherent heterogeneity of the disease in humans. The preterm lamb is a useful model but differs from humans in the mechanisms of parturition and placental structure as well as the trajectory of fetal lung development. The nonhuman primate closely models human BPD and allows for translatable *in utero* studies, but is considerably more expensive; a long-standing primate center resource focused specifically on BPD and sequelae of prematurity is no longer funded. Preclinical studies in rodents have identified multiple promising therapies, but limited funding and lack of pharmaceutical industry support have delayed translation into early-phase clinical trials.

Last, strategies for primary prevention are stymied by methodologic obstacles, not the least of which is the inherent shortcoming of defining a disease by its treatment and the use of a definition that provides no information about pathophysiology, disease progression, or phenotype variability. There is relatively poor correlation between a diagnosis of BPD, as currently defined, and later childhood respiratory morbidity (25, 26). Failure to identify subpopulations with distinct mechanisms of disease (endotypes) contributes to exposures to therapies unlikely to benefit individual patients and skepticism about biologically plausible therapies that may benefit a subset of at-risk infants. There is a need for development of advanced lung structure/function imaging techniques and noninvasive pulmonary baseline and provocative functional tests that are applicable to infants and children.

Defining a "Healthy Lung" in the Premature Infant

The abnormal trajectory of a premature lung evolving to BPD must be understood in the developmental context of normal lung growth and function in fetuses and preterm infants who do not progress to BPD. Exposure of the rapidly developing premature lung to nonphysiological tidal breathing and oxygen (even room air) may contribute to lung injury or arrest of lung growth. A new research paradigm with a focus on the evolution of lung health in infancy through adulthood is needed.

BPD likely begins *in utero* and may be impacted by epigenetic and gene–environment interactions. Perinatal interventions represent a unique opportunity in BPD prevention research as longitudinal studies have shown that individuals track along their predefined pulmonary function percentile throughout their life (27), with small improvements in neonatal lung function translating into significant improvements in childhood and adulthood respiratory health.

Causal Pathways Implicated in BPD Pathogenesis

Understanding the molecular pathways that underlie the pathogenesis of BPD is key to its prevention. The following sections outline several causal pathways identified from basic and clinical research; Table 1 identifies corresponding promising areas for future research.

Endothelial Injury and Dysfunction

Normal lung growth and function require coordinated and intimate development of the pulmonary airways and vasculature. Injury or maldevelopment of the pulmonary vascular bed may drive subsequent or synchronized arrest of alveolar development, the so-called vascular hypothesis of BPD (28). Identification of early markers of endothelial or vascular injury may lead to mechanistic and time-sensitive interventions to support normal vascular and alveolar growth and prevent BPD.

Preclinical studies strongly support NO insufficiency as a contributing factor to impaired alveolar and vascular growth (29). Long-term treatment with iNO improves lung structure in multiple experimental models of BPD (30, 31). Negative results from most, but not all, RCTs of iNO to prevent BPD suggest that its effects depend on timing, dose, duration of therapy, and the underlying pathobiology of lung disease in individual patients (10, 32–34).

Vascular endothelial growth factor (VEGF), an endothelial cell–specific survival factor upstream of NO, stimulates angiogenesis and protects against endothelial injury. Pharmacological and genetic VEGF inhibition during perinatal development decreases alveolarization and pulmonary arterial density (35, 36), features encountered in clinical BPD. Reduced VEGF and VEGF receptor (VEGFR) have been reported in lungs of infants with fatal BPD (37, 38). Chronic treatment of newborn rats with a VEGFR inhibitor causes enlargement of distal air spaces, decreased vascular growth, and pulmonary hypertension (PH), which persist into adulthood (39). Pulmonary vascular disease after premature birth broadly contributes to the pathogenesis of BPD and BPD mortality. Other angiogenesis-promoting factors may play a role in normal lung development. Expressions of endoglin (CD105), a hypoxia-inducible transforming growth factor-β coreceptor, and angiopoietin-1, a vascular endothelial growth factor, are altered in the lungs of preterm infants exposed to short- and long-term ventilation (40).

Redox Status and Oxidative Stress

Oxidative stress has been implicated in the development of BPD. Factors that augment oxidative stress in the preterm newborn include exposure to supplemental oxygen and hyperoxia, immature antioxidant defenses, increased susceptibility to infection and inflammation, and free iron (41).

Progenitor and Stem Cells

Advances in stem cell biology have sparked interest in the reparative potential of

Table 1. Targeting causal pathways implicated in bronchopulmonary dysplasia pathogenesis

Section	Promising Areas for Research
Endothelial injury and dysfunction	Measurement of endothelial injury markers (number of endothelial microparticles or circulating endothelial cells) and their associations with BPD and long-term measures of lung function Biomarker discovery that identifies patients with NO deficiency/insufficiency and RCTs targeting a select, high-risk population likely to respond to iNO therapy Define how altered angiogenesis contributes to BPD pathogenesis and whether pharmacologic restoration of related signaling pathways can enhance lung structure/function Biomarker and autopsy studies of lung angiogenic factors Elucidate how the pulmonary vasculature promotes alveolar growth during development and contributes to maintenance of alveolar structures throughout postnatal life and how these processes are disrupted by preterm birth and BPD Define mechanisms through which early changes in the developing endothelium and epithelium cause long-lived alterations of lung development
Redox status and oxidative stress	Therapies that stimulate coupled eNOS activity and NO production, such as bioavailable substrate or cofactors Biomarker studies of redox status, antioxidant capacity, and oxidative stress as predictors for BPD, followed by interventions to supply needed substrate to improve antioxidant capacity
Progenitor and stem cells	Elucidate the roles, predictive value, and therapeutic potential of EPCs in the developing lung Determine the mechanisms underlying the protective effects of cell-based therapies, including EPCs, MSCs, and progenitor cell–derived products during lung development and with injury
Inflammation and host immune responses	Develop panels of inflammatory biomarkers and key effector cells that predict BPD risk and can serve as targets for interventions Relationships between the gastrointestinal, maternal vaginal, and neonatal lung microbiome and whether changes in the microbiome impact lung inflammation or increase BPD risk Studies of selective antiinflammatory therapies, and novel modulators of innate immunity to attenuate the inflammatory response in the developing lung
Genetic underpinnings of BPD	Prospective multicenter genetic cohort studies with robust sample sizes or extreme healthy and diseased phenotypes
Epigenetic and environmental factors	Effect of environmental factors (*in utero* smoke, second-hand smoke, air pollution, stress, maternal obesity) on the epigenome in the context of BPD prevention Longitudinal specimen collection from patients at risk for BPD to examine the methylome and transcriptome and their changes over time

(Continued)

endothelial progenitor cells (EPCs). Preclinical studies suggest that lung and circulating EPCs are decreased in experimental BPD (42). Clinical studies suggest that reduced EPCs in cord blood are strongly associated with risk for the development of moderate to severe BPD (43). Mesenchymal stem cells (MSCs) preserve lung development in rodent models of BPD. These effects do not require MSC engraftment and are mediated through release of MSC-derived products (44, 45), which may lead to the potential for novel interventions for BPD prevention.

Inflammation and Host Immune Responses

Preclinical and clinical studies have implicated a critical role for lung inflammation and host immune responses in the pathobiology of BPD. Prenatal inflammation caused by chorioamnionitis is strongly linked to increased risk for BPD in human infants (46) and causes BPD-like changes in lung histology in animal models, even in the absence of postnatal injury (47). Genetic polymorphism studies have linked diverse cytokine genes and related signaling pathways with increased BPD susceptibility (48).

Genetic Underpinnings of BPD

A number of familial aggregation, twins, candidate genes, and genome-wide association studies have examined genetic factors influencing the development of BPD. Several twin studies have estimated that the heritability for moderate–severe BPD is 50–80% (49, 50). Candidate genes identified include those encoding surfactant proteins, SPOCK2, TNF, IL-18, superoxide dismutase, Toll-like receptors, TLR4, MIF, human leukocyte antigens, and VEGF among many, but few studies have been replicated (51).

Epigenetic and Environmental Factors

The developmental origins of infant and adult lung diseases are understudied. The epigenome responds dynamically to the environment. Data on the importance of maternal phenotypes in shaping the methylome and transcriptome of the offspring and epigenetic studies of BPD pathogenesis are limited. *In utero* smoke, second-hand smoke, particulate exposure, and prenatal and postnatal stress (52)

Table 1. (CONTINUED)

Section	Promising Areas for Research
Maternal and infant nutrition	Studies of the relationship between parenteral amino acid and lipid composition/quantities and risk of BPD Development of alternative forms for administration of vitamin A, by nonintramuscular route Relationship between BPD and ratios of vitamin E isoforms in serum or in the diet of preterm infants
Obstetrical and postnatal practices	Prenatal studies powered to examine longer term infant outcomes including BPD Development of better tools to predict successful extubation in order to limit the duration of mechanical ventilation RCTs of minimally invasive administration of aerosolized surfactant Confirm or refute the association between excessive inspired oxygen concentrations during the first minutes after birth and worse long-term respiratory outcomes Evaluate whether use of automated systems for oxygen saturation targeting can reduce oxygen exposure and improve short- and long-term respiratory outcomes

Definition of abbreviations: BPD = bronchopulmonary dysplasia; eNOS = endothelial nitric oxide synthase; EPCs = endothelial progenitor cells; iNO = inhaled nitric oxide; MSCs = mesenchymal stem cells; NO = nitric oxide; RCTs = randomized controlled trials.

increase the incidence of infant wheeze, likely through fetal programming.

Maternal and Infant Nutrition

Few RCTs of maternal nutritional interventions have demonstrated an impact on subsequent development of BPD in their offspring. A meta-analysis of marine n-3 fatty acids versus placebo in pregnancies with spontaneous preterm labor and preterm birth demonstrated a significant decrease in preterm deliveries (53) but no decrease in BPD. A large trial of pregnant women randomized to vitamins C and E versus placebo for the prevention of preeclampsia demonstrated no difference in preeclampsia or perinatal outcomes (54).

Poor nutrition is common in preterm infants because of increased work of breathing, immature gastrointestinal function, and oral feeding difficulties. Optimal and early nutrition is critical to normal lung development and function, lung repair, and defense against infection. Studies of early lipid administration or long-chain polyunsaturated fatty acid–supplemented formula have yielded inconsistent results (55). Intramuscular vitamin A decreases BPD (2), but its use has not been widely adopted in clinical practice. Trials of glutamine (13), inositol (56), and selenium (57) supplementation have not shown a decrease in BPD.

Obstetrical and Postnatal Practices

Prevention of prematurity is the most effective measure to decrease its morbidities, including BPD. A few interventions, such as progesterone (58) and smoking cessation (59), have shown efficacy in select patient populations, but study designs have failed to rigorously examine longer term infant outcomes, including BPD.

Clinical practices vary widely among neonatal intensive care units, as do rates of BPD. Less invasive respiratory support modalities and avoidance of excessive pressure/volume can prevent pulmonary damage and preserve lung structure and function. Maintenance of higher arterial oxygen saturations in preterm infants has been associated with worse respiratory outcomes in some, but not all, studies (60, 61). Nutritional and infection prevention strategies, and pharmacological practices, including use of intramuscular vitamin A (2) and optimal use of caffeine therapy (1), may prevent BPD but are not consistently implemented and are insufficiently studied. A bundled approach to BPD-preventive strategies may prove more efficacious than a single intervention. However, implementation of "best practices" using a cluster, randomized, controlled design had inconsistent results (62).

Recommendations for Future BPD Primary Prevention Research

Research and development of novel methodologies are needed to define different BPD endotypes and lung growth trajectories, which will offer insights into windows for personalized interventions. Existing birth cohorts should be maintained and leveraged for longitudinal studies of lung health in infancy and early childhood.

Promising Near-Term Opportunities for Primary BPD Prevention Research

Basic and translational research priorities.

1. Basic laboratory and translational studies to improve understanding of normal lung growth, injury, and repair mechanisms, with particular emphasis on molecular mechanisms and causal pathways (i.e., mechanical and oxidant injury, inflammation, and immune responses) leading to BPD
2. Investigations of cell-based therapies (progenitor and stem cell research), endothelial–epithelial interactions, and the role of the vasculature in normal and aberrant lung growth and pulmonary function
3. Studies in animal models of BPD to evaluate modulators of molecules that mediate alveolar and pulmonary vascular development and lung injury and repair (e.g., VEGF and other growth factor pathways). Development of animal models that explore antenatal mechanisms of disease to provide insights into critical factors beyond hyperoxia, mechanical ventilation, and other adverse postnatal stimuli
4. Establishment of human lung tissue repositories for histopathological characterization of healthy and diseased lungs at various gestational and postnatal ages

Clinical research priorities and specific clinical trials for BPD prevention.

1. Early caffeine therapy in mechanically ventilated infants for BPD prevention

2. Inhaled nitric oxide or NO donors, substrate, or cofactors that modulate eNOS activity, or drugs that target downstream pathways involved with NO signaling in targeted high-risk populations with biomarker evidence of NO insufficiency
3. Antioxidant therapies and/or antiinflammatory agents (antagonists and inhibitors of inflammatory mediators) in high-risk populations with biomarker evidence of oxidative injury or exaggerated host responses to inflammation
4. Bundles of care, with special emphasis on combinations of interventions that interrupt different etiologic pathways

Strategies and Prerequisites for a Long-Term Research Blueprint to Prevent BPD and Its Enduring Pulmonary Sequelae

Effective primary prevention strategies for BPD will require the study of healthy term infants, longitudinal and cross-sectional studies, and multidisciplinary collaboration of specialists across the life span. Studies should be designed to determine the relative contributions of the *in utero* versus extrauterine environment, whether "catch-up" growth occurs and under what circumstances, and the impact of the normal aging process when lung function normally declines.

The following areas of research are essential to identify mechanisms of altered lung development and opportunities for interventions that will promote lung health and avoid long-term pulmonary morbidities associated with preterm birth and BPD.

1. Longitudinal and cross-sectional studies of healthy term and preterm infants across the gestational age spectrum to delineate trajectories associated with different phenotypes, from no overt pulmonary disease, to resolved early lung disease, to persistent pulmonary disease of prematurity (63, 64)
2. Development and adaptation of novel methodologies (advanced functional imaging techniques, noninvasive infant pulmonary function tests, biometric monitoring) for assessment of pulmonary function in neonatal and pediatric populations; incorporation of these validated tools into clinical trial designs to assess effectiveness of novel interventions and their value as surrogate end points and proxy measures of lung health
3. Validation of an array of sensitive and specific early "omic" signatures that can differentiate BPD endotypes on the basis of underlying mechanisms of disease, followed by study designs that incorporate "personalized medicine" using biomarkers and experimental therapies tailored to the underlying pathobiology
4. Evaluation of the role of the microbiome and the impact of maternal and infant nutrition on respiratory outcomes
5. Investigation of the role of epigenetics and environmental influences in the antenatal and early postnatal period on lung health, resiliency, and disease
6. Pharmacokinetic and RCTs to translate promising therapies identified in animal models to the bedside, including clinical trials of combination therapies.

Facilitators of this strategic priority include the following:

a. Partnerships between industry and government funders and incentives for pharmaceutical companies to study the neonatal population
b. Organization of academic "consortiums" with the capacity to enroll large numbers of premature patients in clinical studies, collect data and biological specimens, measure validated biomarkers, and carry out rapid cycles of interventions leveraging National Center for Advancing Translational Sciences resources

Conclusions

BPD remains the most important cause of adverse health outcome for infants born preterm. Moreover, it is increasingly apparent that lung injury sustained prenatally and early in life is a key determinant of later childhood and adult lung health and disease. The associated economic impact and quality-of-life implications of poor lifelong lung health resulting from BPD warrant a renewed research emphasis on the prevention of this important cause of pulmonary morbidity throughout the life course. With a shift in research priorities and focused bench-to-bedside research efforts, primary prevention of BPD and its long-term sequelae on pulmonary and overall health can be achieved. ■

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