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Recent Advances in Bronchopulmonary Dysplasia: Pathophysiology, Prevention, and Treatment

Jung S. Hwang and Virender K. Rehan

Department of Pediatrics, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, David Geffen School of Medicine, Torrance, CA, USA

Abstract

Bronchopulmonary dysplasia (BPD) is potentially one of the most devastating conditions in premature infants with longstanding consequences involving multiple organ systems including adverse effects on pulmonary function and neurodevelopmental outcome. Here we review recent studies in the field to summarize the progress made in understanding in the pathophysiology, prognosis, prevention, and treatment of BPD in the last decade. The work reviewed includes the progress in understanding its pathobiology, genomic studies, ventilatory strategies, outcomes, and therapeutic interventions. We expect that this review will help guide clinicians to treat premature infants at risk for BPD better and lead researchers to initiate further studies in the field.

Introduction

In 1967, Northway first described Bronchopulmonary Dysplasia (BPD) as a lung disease in premature infants, who required prolonged mechanical ventilation [1]. Since then, there has been an unrelenting effort to understand its pathophysiology and develop effective methods to prevent and treat BPD. Since its first description, the definition of BPD has evolved; currently, the National Institute of Child Health and Human Development (NICHD) severity and postmenstrual age (PMA)-based definition is used most widely. However, there are attempts to further refine this definition, e.g., recently, it has been suggested that oxygen/respiratory support at 40 weeks PMA might be a better predictor of chronic respiratory insufficiency and neurosensory morbidity than the traditional use of 36 week PMA [2]. The “Old BPD” was characterized by cystic changes and heterogeneous aeration in the involved lungs, whereas the “New BPD” in the antenatal steroid, post-surfactant, and gentler modes of ventilatory support era is characterized by more uniform inflation, less fibrosis, and the absence of airway epithelial metaplasia, and smooth muscle hypertrophy. The “New BPD”

Address for Reprint Requests and Correspondence: Virender K. Rehan, Department of Pediatrics, Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center, David Geffen School of Medicine at UCLA, 1124 West Carson Street, Torrance, CA 90502, vrehan@labiomed.org.

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includes pathological evidence of larger simplified alveoli and dysmorphic pulmonary vasculature [3].

Epidemiology

BPD affects premature low birth weight infants (LBWI), occurring slightly more frequently in Caucasian males, and genetic heritability plays an important role in its pathogenesis [4]. Although advances in perinatal care continue to improve the survival rates of premature infants, this has not consistently resulted in decreased BPD. However, health care practices clearly influence its incidence. For example, in 501–1500 gram birth weight (BW) infants, the incidence of BPD decreased from 47% to 21% by avoiding intubation, adopting new pulse oximeter limits, and transitioning to Continuous Positive Airway Pressure (CPAP) early [5]. There was a wide variability in the incidence of BPD in ten regions of Europe, suggesting that different care practices affect the incidence of BPD [6]. In the U.S., the incidence of BPD decreased between 1993 to 2006, likely related to the increased use of non-invasive ventilator support [7].

Pathobiology (See Figure)

Bronchopulmonary dysplasia primarily occurs in infants born at a stage when their lungs are still transitioning from canalicular to saccular stage. Premature delivery truncates lung development in these stages and is frequently compounded by prenatal events such as intrauterine growth restriction (IUGR) and exposure to inflammation and postnatal events related to initial resuscitation, oxygen administration, mechanical ventilation, and pulmonary and systemic infections, which can all lead to arrested pulmonary vascular and alveolar development. It remains unclear if prematurity itself causes BPD or factors that contribute to prematurity are its direct cause, or if there are other yet unrecognized factors that lead to BPD. For example, the role of lung microbiome in lung and host-immune development is an emerging field of interest. It has become clear that decreased diversity of lung microbiome, in particular, decreased lactobacilli abundance, at the time of birth in preterm infants is strongly correlated with the development of BPD [8] [9]. Understanding how an imbalanced microbiome (~ dysbiosis) affects pulmonary macrophage activation and the expression of genes critical for normal lung development is key to exploit lung microbiome modulation in BPD prevention and treatment. Since in BPD pathogenesis, multiple events affect the complex well-orchestrated molecular processes involved in the developing lung, it is unlikely that there is a single pathophysiological basis for BPD. Nevertheless, in a variety of cellular and animal models, a breakdown in alveolar epithelial-mesenchymal signaling, leading to the transdifferentiation of pulmonary alveolar lipofibroblasts to myofibroblasts has been demonstrated on exposure to hyperoxia, infection, volutrauma, and other insults that lead to BPD [10]. Transdifferentiated lipofibroblasts are unable to maintain pulmonary epithelial cell growth and differentiation, resulting in failed alveolarization, seen characteristically in BPD. This serves the basis of some the experimental interventions (reviewed below) that aim to maintain lipofibroblast phenotype in an attempt to prevent/treat BPD.

Risk Factors

Apart from premature delivery, amongst the many prenatal factors, smoking, preeclampsia, lower socioeconomic status, and birth weight z- score, used as a marker for fetal growth restriction are most related to BPD development after adjustment for a variety of other perinatal characteristics [11]. However, apart from birth weight, prematurity, and IUGR, other risk factors must be studied further to determine their definitive significance.

Genetic Susceptibility

Much work has been done to identify heritable factors linking certain genes, pathways, and molecules to the development of BPD. For example, over-transmission of the A allele of rs4351 in the angiotensin-converting enzyme gene from parents was observed in infants with BPD. Moreover, a marker downstream of surfactant protein D gene, rs1923537, was found to be overtransmitted from parents to preterm infants who had a diagnosis of respiratory distress syndrome, which increases the risk of developing BPD [12]. In a genome-wide association study, SPOCK2 gene was associated with BPD [13]. Molecular pathways such as miR-219, a pathway involved in acute inflammation resolution, and CD44, a hyaluronic acid cell surface receptor involved in leukocyte trafficking and alveolar septation, were associated with BPD [14]. In additions, heritability for BPD is suggested by several studies on twins [15]. However, at present, the clinical application of genetic susceptibility findings is difficult to ascertain with certainty.

Inflammation

Although a role of inflammation in BPD has been validated in numerous studies, in preterm infants born in the setting of maternal inflammation (chorioamnionitis) and/or fetal inflammation (umbilical vasculitis), both increased and reduced odds of developing BPD have been reported [16]. In contrast, neonatal sepsis is consistently associated with BPD, but the type of infection is important [17]. It is also clear that both early- and late-onset sepsis increase the risk of BPD [18]. Overall, irrespective of the timing, the inflammatory exposure from sepsis plays an important role in BPD development. A significant association between *Ureaplasma* and BPD, likely via the suppression of the innate immune system and/or by increasing the ventilator-induced lung injury, has also been reported [19].

Transfusion

Multiple studies have linked blood transfusion to the development or worsening of BPD [20]. Possible mechanisms include increased oxidative injury, increased non-transferrin bound iron, and inflammatory mediators present in stored blood products. In a retrospective review of infants who received blood transfusions, an association between the number or volume of transfusions and BPD was seen at 28 days of age, but not at 36 weeks corrected gestational age (GA) [21]. However, no study clearly distinguishes an association of blood transfusions with BPD from its causation.

Prognosis

Pulmonary outcome

Children with a history of BPD continue to have significant abnormalities with airflow limitation on lung function tests [22]. In an 11-year-follow-up study, preterm infants continued to have impaired lung function and increased respiratory morbidity, especially among those with BPD [23]. Overall, multiple studies show that BPD not only decreases pulmonary function during infancy but also has a considerable impact on pulmonary function later in childhood in addition to increasing the chance of developing asthma [24].

Neurodevelopmental outcomes with BPD

Given the hostile extrauterine environment for brain development, compared to the natural in-utero setting, preterm infants in general are predisposed to poor neurodevelopment outcomes. In addition to other predetermined factors, BPD adversely affects preterm infants' neurologic outcomes including a lower head circumference, cerebral palsy, and lower cognitive and language skills. Prolonged positive pressure ventilatory support, grade III–IV intraventricular hemorrhage, and discharge at > 43 weeks PMA have been found to be predictors of impaired neurodevelopment [25].

Cardiac outcome

Infants with BPD are at a higher risk for developing pulmonary hypertension (PH) and cardiac dysfunction. Patients with BPD and PH have substantially higher morbidity and mortality compared to patients with BPD without PH; for example, BPD with PH entails a mortality of up to 50% [26]. Although infants with BPD and BPD with PH share common risk factors, such as low GA at birth, IUGR, maternal preeclampsia, perinatal maternal inflammation, and prolonged durations of mechanical ventilation and oxygen supplementation, these risk factors are not unique only to BPD and BPD with PH. Only a few studies have evaluated the long-term cardiac function in infants in BPD, which suggest that almost 50% of infants with moderate/severe BPD at 36 weeks PMA have a lower right ventricular function on echocardiography compared to infants with no/mild BPD. Abnormal left ventricular myocardial performance also correlates with the severity of BPD [27]. Therefore, a high index of suspicion, active screening, and effective management of cardiac dysfunction are recommended in infants with moderate/severe BPD [28].

Prevention/Treatment

Anti-inflammatory therapy

Rationalizing inflammation as the final common pathway in the evolution of BPD, many studies have been conducted to decrease inflammation to prevent and/or treat BPD. Macrolide antibiotics have been tried for both antimicrobial and anti-inflammatory effects, i.e., via an inhibition of IL-6 expression and NF- κ B activation. Though earlier studies demonstrated that LBWI treated with azithromycin required a shorter duration of mechanical ventilation [29], other studies have found no demonstrable difference between the azithromycin and placebo groups in the incidence of BPD/death; however, the Ureaplasma positive subgroup that received azithromycin had a lower incidence of BPD

[30]. Nonetheless, the conclusive evidence from larger prospective antibiotic trials aimed to eradicate *Ureaplasma* respiratory colonization in preventing BPD is still awaited.

Hypothesizing vitamin D (VD)'s anti-inflammatory effects, a recent study demonstrated improvement in oxygenation and survival in a rat model following antenatal VD treatment [31]. In another study, rats exposed to inflammation/hyperoxia were treated with an IL-1 receptor antagonist, which decreased the incidence of severe BPD-like lung disease in the 65% O₂ exposed group, but not in the 85% O₂ exposed group [32]. Currently, more studies are in progress to test other anti-inflammatory approaches to treat and/or prevent BPD.

Postnatal Steroid Therapy

Postnatal steroid therapy, mainly dexamethasone therapy, during the first week of life has been tried as a preventive strategy against BPD. Although lower rates of failure to extubate and BPD are reported, adverse effects such as hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure preclude the routine use of this strategy to prevent BPD [33]. Similarly, reduction in BPD and facilitation of extubation have been observed with late postnatal (after 1st week) corticosteroid treatment. However, in view of the increased risk for infection and gastrointestinal bleeding with this approach, again, benefits do not outweigh the adverse effects [34]. Interestingly, as dexamethasone use has decreased over time, BPD rates have increased. Different dexamethasone doses are used at different institutions, which in fact also vary between clinicians at the same institution. Based on sixteen randomized controlled trials (RCTs), dexamethasone effect is most significant with a cumulative dose of 4 mg/kg, and when infants are treated moderately early, defined as 7–14 day of life [35]. However, multiple studies also show that postnatal steroids can result in a smaller brain volume and neurodevelopmental delays [36]. To avoid the systemic side effects, both inhaled and intratracheally administered steroids have been tried to prevent BPD. In a recent study, early intratracheal instillation of budesonide along with surfactant facilitated early extubation and improved pulmonary outcomes without significant adverse effects [37]. Though intratracheal administration of budesonide-surfactant combination appears to be a promising intervention to prevent BPD, there is a need for larger trials before this modality can be recommended as standard of care [38]. In addition, a recent RCT in extremely low birth weight infants (ELBWI) showed that prophylactic low-dose hydrocortisone during the first 10 days of life significantly decreased the incidence of BPD [39]. This effect was most pronounced in females and in infants exposed to chorioamnionitis before birth. Moreover, in contrast to studies suggesting adverse neurodevelopmental outcome with postnatal dexamethasone administration for preventing BPD, early low-dose hydrocortisone was not associated with a significant difference in neurodevelopment outcome at 2 years of age [40]. However, the long-term risk/benefit ratio for treatment with postnatal steroids still needs to be clearly defined, and there is no consensus on the type, dose, or the administration route of postnatal corticosteroids for preventing BPD.

Ventilatory Strategies

Multiple studies comparing high frequency ventilation with conventional mechanical ventilation have not demonstrated a clear benefit of one approach over the other. On the other hand, several studies reveal a significant reduction in the incidence of death or BPD

with gentler ventilation strategies, which include avoiding endotracheal intubation altogether, whenever possible, routinely using CPAP or non-invasive intermittent positive pressure ventilation (IPPV) starting in the delivery room, and timely surfactant administration, using less invasive modes of administration. If endotracheal ventilation is required, it is prudent to use the lowest required ventilator settings, accept permissive hypercapnia, and aggressively wean ventilator support to extubate as soon as possible [41]. Although recent data suggest decreased intubation rates following nasal IPPV institution in the delivery room [42], in a previous study, comparing nasal IPPV to nasal CPAP, no difference was observed in BPD incidence [43]. A large meta-analysis (nine trials) comparing volume-targeted ventilation to pressure-limited ventilation in preterm infants demonstrated a shorter duration of mechanical ventilation and a lower incidence of BPD with volume ventilation strategy [44]. More recently, the use of neurally adjusted ventilator assist (NAVA) to deliver synchronized breaths suggested improved pulmonary outcomes [45]. Clearly, more studies are needed to support the benefits of volume ventilation and NAVA.

Target Oxygen Saturations

In a multicenter, randomized trial, lower target oxygen saturation parameters (85–89% vs. 91–95%) showed a trend towards decreased BPD or death at 36 weeks PMA [46]. Another study implied that targeting the functional oxygen saturation in 95–98% range rather than in 91–94% range improved growth and neurodevelopment in preterm infants, but this was at the expense of an increased risk of BPD and a higher mortality from pulmonary causes [47]. Though unresolved issues remain, in infants with GA<28 weeks until 36 weeks' PMA, it is reasonable to aim for a SaO₂ in the 90–95% range [48].

Surfactant Therapy

Surfactant therapy and timing of its administration have been debatable and have varied widely. In a RCT, early surfactant therapy in the delivery room without mandatory ventilation decreased the need for mechanical ventilation [49]. Another RCT demonstrated lower oxygen requirements at 24 hours after surfactant therapy, but there was no evidence of decreased incidence of BPD in the surfactant treated group [50]. Surfactant therapy may decrease the need for mandatory ventilation; however, it does not decrease the rate of BPD. Cumulative data from studies using prophylactic surfactant followed by rapid extubation (INSURE or INTubate, SURfactant, Extubate) versus those randomized to routine intubation point to a decreased risk of BPD with the INSURE approach [51]. However, routine institution of CPAP in the delivery room reduces the risk of neonatal death and BPD, and in these infants selective administration of surfactant when significant respiratory distress manifests, is more beneficial [52]. Moreover, it is important to point out that now endotracheal intubation is no longer the preferred method for surfactant administration, since alternative modes of administration such as the aerosolized delivery and the less invasive surfactant administration (LISA) modes are used frequently in unstable preterm newborns, in whom the endotracheal intubation procedure still poses technical and ethical challenges [53]. It is also likely that newer and innovative synthetic surfactants, some of which are more resistant to inactivation and even have anti-inflammatory properties, might prove to be more effective in preventing BPD than what has been achieved so far [54].

Inhaled Nitric Oxide (iNO)

By decreasing pulmonary artery pressure and improving lung compliance, iNO was postulated to prevent BPD; however, in a multicenter RCT, no benefit in BPD reduction was noted [55]. Similarly, in iNO for Preventing Chronic Lung Disease trial, no benefit for the routine early use of iNO in preterm infants was observed. In 2010, the National Institutes of Health (NIH) Consensus Development Conference Statement concluded that the routine use of iNO was not recommended [56]. On the other hand, ELBWI who receive mechanical ventilation and iNO tend to receive less outpatient respiratory treatment including bronchodilators, inhaled or systemic corticosteroids, diuretics, and supplemental oxygen, but without any significant differences in re-hospitalizations or wheezing episodes, as reported by parents [57]. There are also data to suggest that some subpopulations of preterm infants might be more responsive and appropriate to consider for iNO treatment, e.g., infants with preterm premature rupture of membranes [58].

PDA ligation

Persistent patent ductus arteriosus (PDA) has been historically implicated in the development of BPD, with medical or surgical closure being the standard of care. However, recently, this approach has been questioned. Clyman et al. demonstrate that prophylactic surgical ligation of PDA significantly increased the incidence of BPD compared to the control group even though the control group had a higher incidence of necrotizing enterocolitis [59]. Surgical ligation of the PDA led to longer durations of mechanical ventilation and oxygen requirement compared to the pharmacologic closure group, indicating that there may be possible beneficial effects of medical closure [60]. In multiple studies, prophylactic surgical ligation of PDA has failed to show a consistent decrease in the incidence of BPD [61]. In a recent study comparing mandatory closure vs. a noninterventional approach to manage hemodynamically significant PDA in ELBWI, despite longer PDA exposure, the noninterventional approach was associated with significantly less BPD [62]. Additional studies are warranted to determine the benefits and risks of nonintervention for the hemodynamically significant PDA in ELBWI.

Vitamin A

Vitamin A is stored in the septal cells of the alveoli, and its deficiency can result in disruption of epithelial cell integrity and diminished alveolar septation. A NICHD Neonatal Network study indicated that supplementation with vitamin A decreases BPD or death at 36 weeks [63]. A meta-analysis on vitamin A use for BPD prevention also showed a borderline reduction in BPD [64]. However, possibly, due to the required invasive intramuscular dosing in ELBWI, who have limited muscle mass, fragile skin, and pain associated with injections, only about 20–30% centers routinely administer vitamin A supplementation. It is important to note that no significant differences were reported between the vitamin A-supplemented and control groups at 18–22 months of age [65]. A recent study also indicated that routine intramuscular injections of vitamin A were associated with an increased risk of sepsis in patients weighing > 1 kg [66]. Lastly, a retrospective study comparing vitamin A administration alone to vitamin A+iNO administration in extremely preterm infants revealed

a lower incidence of BPD and improved neurocognitive outcomes at 1 year in infants who had received combined therapy [67].

Caffeine

In a relatively large study, early caffeine therapy (before 3 days of life) was associated with a lower incidence of BPD (23% vs. 30%), a shorter duration of mechanical ventilation, and less need for PDA treatment; however, this was associated with a slightly higher mortality (4.5% vs. 3.7%) [68]. Institution of caffeine administration immediately after birth, i.e., starting in the delivery room has shown to decrease the need for invasive ventilation in ELBWI [69]. On the other hand, a small observational study on infants with GA < 30 weeks showed that 24 hours after the caffeine load, IL-10 levels decreased significantly, and at one week from the initial load, caffeine levels directly correlated with TNF, IL-1 β , and IL -6 levels, but inversely correlated with IL-10 when caffeine levels were > 20 mg/L. This implies caffeine's pro-inflammatory effect when its levels are out of the therapeutic range [70]. Therefore, though multiple studies suggest beneficial effects of caffeine on BPD, caution is warranted since outside of the therapeutic range caffeine might be associated with a pro-inflammatory pulmonary profile.

Diuretics

Diuretics are widely used "off-label" in many units to prevent or treat BPD, and their frequency and specific regimens vary greatly. A meta-analysis of treatment effects of loop diuretics on infants with BPD demonstrated short-term benefits by improving pulmonary mechanics and oxygenation; however, long-term sequelae need to be studied further to determine benefit vs. harm of diuretics in the prevention and treatment of BPD [71].

Stem Cell Therapy

Based on novel understanding of the role of both resident lung and circulating stem cells in alveolar microvasculature formation, injury repair, and tissue homeostasis, there is an enormous interest in exploiting this knowledge and study stem cells to prevent BPD. Multiple promising preclinical studies convincingly show the reparative potential of stem/progenitor cells for lung growth and in preventing lung injury [72]. In animal models, using a variety of progenitor cells, protection against lipopolysaccharide and hyperoxia-induced neonatal lung injuries has been demonstrated [73]. Cell-based therapies primarily function by their paracrine effect rather than by stem cells directly constituting the repaired tissue [74]. More likely, stem cells can modulate innate and adaptive immune responses, decrease inflammation, enhance injury repair, and cause anti-apoptotic effects by producing paracrine factors [75]. In 2014, a phase I dose-escalation study examined the safety and feasibility of a single intratracheal transplantation of allogeneic human umbilical cord blood (hUCB)-derived mesenchymal stem cells (MSCs) in nine ELBWI at high risk for BPD. There was decreased severity of BPD in the transplanted group vs. the control group without any adverse outcomes [76]. Although this study suggested hUCB-MSC to be safe and a feasible therapy in preterm infants, further work is required before stem cells themselves or their conditioned medium can be safely used in clinical settings.

Vitamin D (VD)

VD, in addition to its anti-inflammatory role, as alluded to above, also mediates key alveolar signaling pathways, promoting perinatal lung maturation [77]. In animal models, VD administration protects against hyperoxia-induced neonatal lung injury as well as the development of a lung asthma phenotype associated with perinatal VD deficiency [78]. These experimental data provide an exciting opportunity to test VD's role in preventing BPD in premature infants.

Peroxisome Proliferator-Activated Receptor (PPAR) γ Agonists

The nuclear transcription factor PPAR γ plays an important role in mediating alveolar homeostasis and injury repair [79]. Multiple PPAR γ agonists have been shown to promote alveolar maturation, and effectively block myofibroblast differentiation, a key event in BPD pathogenesis. In a neonatal rat model, both systemically and locally administered PPAR γ agonists including curcumin have been shown to enhance neonatal lung maturation and block hyperoxia- and lipopolysaccharide-induced neonatal lung injuries, protecting both lung structure and function [80]. Therefore, PPAR γ agonists offer a compelling rational approach to prevent/treat BPD; however, detailed pharmacodynamics, pharmacokinetics, and safety studies are needed before translating this approach to humans.

Phosphodiesterase Inhibitors (PIs)

Sildenafil, a selective cGMP-specific PI, has been extensively studied in the management of persistent PH in term neonates; however, there are only few studies examining its role in preventing BPD-induced PH. In experimental models, it preserves lung angiogenesis and alveolar growth, decreases pulmonary vascular resistance, right ventricular hypertrophy (RVH), decreases pulmonary inflammatory response, and improves survival [81], but in small retrospective clinical studies, the benefits have been only modest [82]. To assess sildenafil as a standard clinical therapy in BPD, larger prospective RCTs are needed.

Recombinant Human Clara Cell 10 Protein (rhCC10)

Clara Cell 10 Protein (CC10) inhibits phospholipase A2 and possesses potent anti-inflammatory and immunomodulatory properties. It is normally abundant in the respiratory tract but is deficient in premature infants [83]. In some animal models, CC10 has been shown to reduce lung inflammation and injury, improve pulmonary function, and up-regulate surfactant protein and vascular endothelial growth factor (VEGF) expression, rendering intratracheally administered CC10 protein a promising agent for preventing BPD [83] [84]. Currently, a RCT assessing its efficacy in preventing respiratory morbidity in infants 24–29 weeks GA is under way [85].

In addition to the above reviewed anti-inflammatory agents, many other agents have been tested for treating or preventing BPD [86]; despite this, there are only a few agents, e.g., vitamin A [64], caffeine [68], and postnatal steroids [33] [34], that have demonstrated a reduction in BPD. It appears that despite much promising experimental data, we still are not close to finding an effective pharmacologic intervention to prevent or treat BPD in the clinical setting any time soon.

Conclusion

As BPD has evolved since its first description by Northway five decades back, its definition, epidemiology, pathophysiology, prevention, and management have continued to evolve. This review summarizes the current information on pathophysiology, prevention, and treatment based on studies published mostly in the last decade. The knowledge on its pathophysiology is now poised to move forward rapidly, which is likely to open further avenues for effective BPD prevention and management. The majority of the interventions tried so far have not proven to be beneficial in rigorous meta-analyses of eligible studies. Currently, it is important that we focus on strategies that have been shown to help, namely, ensuring mothers at risk of preterm delivery get antenatal steroids; to avoid endotracheal intubation altogether, whenever possible; routinely initiate CPAP or IPPV in the delivery room; and when surfactant administration is required, to administer it early, using less invasive modes for its administration. If endotracheal ventilation is required, it is prudent to use the lowest required ventilator settings, accept permissive hypercapnia, and aggressively wean ventilator support to extubation at the earliest. Moreover, patients with moderately severe BPD need to be actively screened for PH and cardiac dysfunction. It is likely that these measures along with novel, innovative and targeted molecular interventions, and stem cell-based approaches will significantly lessen the burden of BPD within the next decade.

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Figure 1.
Bronchopulmonary Dysplasia: Pathogenesis