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Pathogenesis and Treatment of Bronchopulmonary Dysplasia

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Abstract

Purpose of review—Bronchopulmonary dysplasia (BPD) is a chronic lung disease of infancy affecting mostly premature infants with significant morbidity and mortality. Improved survival of very immature infants has led to increased numbers of infants with this disorder. Acute and chronic lung injury and impaired postnatal lung growth are thought to be responsible for the development of BPD. While changes in clinical practice have improved the clinical course and outcomes for infants with BPD, over the last decade, the overall incidence of BPD has not changed. This review will describe the pre and postnatal factors that contribute to the pathogenesis of BPD as well as current and experimental therapies for treatment of BPD.

Recent findings—The factors that contribute to the pathogenesis of BPD are well described, however recent studies have better defined how these factors modulate lung growth. Inflammation, proinflammatory cytokines and altered angiogenic gene signaling contribute to lung injury and impair pre and postnatal lung growth resulting in BPD, however to date no therapy has been identified that potently and consistently prevents or reverses their effects on lung growth. We will discuss the cell signaling pathways affected in BPD and current therapies available for modulating these pathways.

Summary—Despite current advances in neonatal care, BPD remains a heavy burden on health care resources. New treatments directed either at reducing lung injury or improving lung growth are under study.

Keywords

Bronchopulmonary Dysplasia; Pre-eclampsia; Chorioamnionitis; mechanical ventilation; inhaled nitric oxide

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that most commonly occurs in premature infants who have needed mechanical ventilation and oxygen therapy for acute respiratory distress (1-3), but can also occur in immature infants who have had few signs of initial lung disease (4). Although the disorder is most often associated with premature birth, it can also occur in infants born at term who need aggressive ventilator therapy for severe, acute lung disease. The introduction of prenatal steroid use, surfactant treatment, new ventilator strategies, improved nutrition, and other treatments have resulted in major improvements in the clinical course and outcomes of premature newborns with respiratory distress syndrome over the past 40 years. (5,6), however despite these treatments the overall incidence of BPD, has not changed over the past decade (7).

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First characterized by Northway and colleagues in 1967, BPD has traditionally been defined as the presence of persistent respiratory signs and symptoms, the need for supplemental oxygen to treat hypoxemia, and an abnormal chest radiograph at 36 weeks post menstrual age (gestational age plus chronological age (8) (Table 1 (9). There is now growing recognition that infants with chronic lung disease after premature birth have a different clinical course and pathology than had been recorded before surfactants were used. (5,6,10,11). The classic progressive stages with prominent fibroproliferation that first characterized BPD are generally less striking now, and the disease is now predominantly defined by a disruption of distal lung growth, and has been termed the “new bronchopulmonary dysplasia”(4) (Table 2, (10) figure 1). Unlike the original form of the disease, this “new” form often develops in preterm newborns who may have needed little or no ventilatory support, and have had low inspired oxygen concentrations during the early postnatal days (5,6). At autopsy, the lung histology of these infants with the new form has regions of more uniform and milder injury, but impaired alveolar and vascular growth remain prominent (table 1). Here we review the pathogenesis and of BPD, and provide an overview of existing and potential preventive treatments.

Pathogenesis

Although BPD has a multifactorial etiology (figure 2), the pre and postnatal factors responsible for disrupted alveolar growth remain fairly well defined. While the strongest association is with preterm birth, other factors such as prenatal infection and inflammation, mechanical ventilation, oxygen toxicity with decreased host antioxidant defenses, patent ductus arteriosus and postnatal infection all contribute to the pathogenesis of BPD. Recently preeclampsia alone has been defined as a risk factor for the subsequent development of BPD (12). While antiangiogenesis is known to contribute significantly to disruption of lung development in animal models (13,14), recent studies have implicated impaired angiogenesis in the development of preeclampsia (15,16,17). Preeclampsia is associated with increased membrane-bound fms-like tyrosine kinase 1 (sFlt-1) which is a receptor for VEGF and placental growth factor (PlGF), a related pro-angiogenic protein with antagonist activity of both VEGF and PlGF. It is produced in excessive amounts by the villous trophoblast in preeclampsia and neutralizes VEGF and PlGF [15,16,17]. Infants with maternal preeclampsia have demonstrated higher cord blood sFlt-1 but lower PlGF and VEGF levels corresponding with the subsequent development of BPD (18).

Altered vascular endothelial growth factor (VEGF) signaling contributes to hyperoxia-induced vascular disease in both BPD and retinopathy of prematurity (ROP) (19,20,21). In human studies of BPD, VEGF was decreased in tracheal fluid samples from at risk premature neonates who subsequently developed BPD, and lung VEGF and VEGF receptor-1 (VEGFR-1) expression was decreased in infants who died with BPD (22,23). In animal studies, hyperoxia decreases alveolar VEGF expression (24), and selective VEGF receptor inhibition reduces lung vascular growth and alveolarization (14,25). These results suggest that endothelial-epithelial cross-talk, especially via VEGF signaling, is critical for normal lung growth following birth and that disruption of VEGF signaling impairs lung vascular growth and alveolarization.

Chorioamnionitis and prenatal inflammation are well known contributors to the development of BPD (26-29). Changes in both pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF), Interleukin-1beta (IL-1), Interleukin-6 (IL-6), Interleukin-8 (IL-8), cytokine modifiers (p55, p75, and IL-1 receptor antagonist (IL-1RA)), and C-reactive protein have been found in umbilical serum of infants born to mothers with severe chorioamnionitis. (30) Elevated cytokine levels in the setting of chorioamnionitis are correlated with the subsequent development of BPD (31,32). More recent studies have

expanded on these findings demonstrating that this inflammatory milieu can alter cell signaling pathways important in lung branching morphogenesis. Fibroblast growth factor 10 (FGF-10) is among the key mesenchymal growth factors for lung development, promoting airway extension and branching (33). Nuclear factor kappa B (NF- κ B), promotes the expression of many genes, including proinflammatory cytokines associated with the development of BPD. It is activated by a variety of factors, including infectious stimuli, inflammatory cytokines, deformation, oxidants, and other causes of cell stress (34). IL-1 and TNF- α activation of NF- κ B disrupts the normal expression of FGF-10 in fetal lung mesenchyme and inhibits lung morphogenesis (35).

Even in the absence of chorioamnionitis cytokines mediate acute lung injury, (36) exacerbate ventilator-associated lung injury (37) and modulate host defenses (38). Elevated cytokine concentrations have been observed in tracheal aspirates (39,40) and serum (41,42) of infants with respiratory distress syndrome and predict the subsequent development of BPD. More specifically, elevated concentrations of IL-1, IL-6, IL-8, IL-10 and INF gamma and lower concentrations of interleukin 17 are predictive of BPD

Alterations in TGF- β 1 signaling have been shown to be important in the pathogenesis of BPD. In bronchoalveolar lavage fluid, increased TGF- β 1 has been reported to predict the progression to BPD, or the need for oxygen supplementation [43] and in newborn rat lungs the transfer of the active form of the TGF- β 1 gene induces histological changes consistent with BPD [44]. A more recent study demonstrated a relationship between amniotic fluid TGF- β 1 levels, chorioamnionitis and fetal lung injury (45), linking prenatal infection and inflammation to BPD.

Postnatal hyperoxia exposure increases the production of cytotoxic oxygen free radicals, which can overwhelm the host antioxidant defense mechanisms, and cause lung injury (46,47). Premature infants are deficient in antioxidant enzyme systems at birth, and have low levels of antioxidants such as vitamins C and E, increasing their vulnerability to oxygen toxicity. Hyperoxia also decreases VEGF expression (24), and increases TGF- β 1 expression (48) as well as levels of proinflammatory cytokines (49). The need for mechanical ventilation after birth strongly correlates with the development of BPD. Mechanical ventilation increases production of TNF- α , IL-1 β , IL-6, IL-8 and IL-1 α (50) and markedly alters angiogenic gene profiling in the lung. Antiangiogenic genes up-regulated in ventilated lungs include thrombospondin-1, collagen XVIII alpha-1, and tissue inhibitor of metalloproteinase-1 (TIMP1), as well as endoglin, transforming growth factor- α , and monocyte chemoattractant protein-1 (CCL2). Proangiogenic down-regulated genes included angiogenin and midkine, as well as vascular endothelial growth factor (VEGF)-B, VEGF receptor-2, and the angiopoietin receptor TEK/Tie-2 (19). Increases in proinflammatory cytokines and alterations in angiogenic genes from ventilator-associated lung injury may in part be due to volutrauma. The development of BPD secondary to volutrauma is suggested in part by an inverse relation between low PaCO₂ levels and the risk of development of BPD (51). As a consequence, high tidal volumes should be avoided during early mechanical ventilation, and even during resuscitation in the labor suite. In an experimental study of the link between the size of manual inflations and lung damage in lambs, adverse effects were recorded even with inflations of 8 mL/kg (52).

Mechanical ventilation is an essential treatment for extremely preterm infants at the border of viability. Recent studies comparing volume-targeted ventilation to pressure ventilation have shown some promise. The use of volume ventilation resulted in a reduction in the combined outcome of death or bronchopulmonary dysplasia, pneumothorax, days of ventilation and hypocarbia (53). These findings were supported by decreased IL-6 and IL-8 levels from tracheal aspirates of patients treated with volume targeted ventilation when

compared with pressure targeted ventilation (54). Alternative ventilatory strategies might also play a role in the reduction of BPD. Although the early, routine use of HFOV has not been demonstrated to improve pulmonary outcomes in premature newborns, Courtney et al showed that the use of HFOV as a rescue strategy (in infants with high conventional mechanical ventilation requirements despite treatment with surfactant), decreased the incidence of BPD (55).

There may also be an association between patent ductus arteriosus (PDA) and bronchopulmonary dysplasia. Long-term exposure to a symptomatic PDA, worsens pulmonary morbidity (56). A PDA with left to right shunting increases fluid and protein efflux from the pulmonary vasculature into the lung parenchyma. The increased fluid and protein in the lung interstitium increases pulmonary microvascular filtration pressure and increased lung lymph flow eliminates excess fluid and protein from the lung. This compensatory increase in lung lymph inhibits fluid accumulation in the lung (57). With persistent ductal patency, this compensatory mechanism is overloaded and pulmonary edema develops. In the presence of sepsis and RDS this mechanism is more easily overwhelmed (5). Despite the relationship between PDA and BPD, aggressive treatment of the PDA using either medical or surgical approaches has not been shown to reduce the incidence of BPD. In fact, in one study, surgical ligation of the PDA increased the incidence of BPD (58).

Animal models of hyperoxia induced lung injury have demonstrated a role for progenitor cells (endothelial and mesenchymal) in the pathogenesis of BPD and implicate these cells as contributing to repair after injury (59,60). Endothelial progenitor (EPCs) and mesenchymal stem cells (MSCs) are easily isolated from cord blood with 24-28 week gestation cord blood yielding predominantly MSCs and 32-36 week gestation cord blood yielding EPCs (61) (Figure 3(62)). In neonatal mice pups, after hyperoxia exposure bone marrow, circulating and lung EPCs are markedly reduced (59) and in extremely preterm human infants, decreased numbers of cord blood endothelial progenitor cells following extremely preterm birth may be associated with the risk for developing lung vascular immaturity characteristic of new BPD (63). The presence of decreased circulating progenitor cells and its association with BPD may have enormous therapeutic potential for these cord blood derived cells. Animal studies to date have shown stem cell-based therapies may offer new therapeutic avenues for lung diseases that currently lack efficient treatments.

Genetic factors may also contribute to the development of BPD, Genetic polymorphisms in TNF , Toll like receptor 10 and VEGF have been suspected as playing a role in the development of BPD (20). Surfactant proteins are important for regulating surfactant activity and innate host defense and genetic variants in surfactant proteins may increase risk for BPD. In a recent study ten susceptibility haplotypes for SP-B (allele B-18_C, microsatellite marker AAGG_6 and SP-B-linked microsatellite markers)(64) were predictive for the development of BPD. Other SP-A SP-B and-SP-D protective haplotypes have also been identified (64).

Treatment of Bronchopulmonary Dysplasia

Factors that contribute to the pathogenesis of BPD are myriad and to date treatment strategies for BPD have failed to demonstrate a reduction in the rates of BPD. For this reason, strategies aimed at preventing the development of BPD are key. The use of antenatal steroids in mothers at high risk of delivering a premature infant reduces the incidence of neonatal death and respiratory distress syndrome by 50%, but even in combination with postnatal surfactant, fails to reduce the incidence of BPD. Exogenous surfactant therapy reduces the rate of death from BPD, but does not prevent the disease; arguably, this could be

due to the increased survival of very immature infants at high risk of BPD. The association of barotrauma or volutrauma with BPD has led to the use of strategies such as permissive hypercapnia (65) to keep lung injury to a minimum. Recent evidence suggests some benefit to volume guarantee as a ventilator mode for preventing BPD and decreasing inflammation associated with mechanical ventilation (54,55). Further large randomized trials will be needed to confirm this finding. Although no ideal ventilation mode has so far emerged, it is clear from physiological studies that tidal volumes and inspired oxygen concentrations should be kept as low as possible to avoid hypocarbia, volutrauma, and oxygen toxicity, and lung recruitment strategies should be used.

An alternative approach to reduce BPD has been to avoid intubation and mechanical ventilation by using early nasal continuous positive pressure (CPAP). A study comparing the outcomes of premature infants weighing 500–1500 g at birth who were treated in either Boston or New York, USA, reported that the incidence of BPD was much higher in Boston (22%) than in New York (4%), and the increased risk of the disease was associated with early endotracheal intubation and mechanical ventilation (66). Many centers now minimize their use of mechanical ventilation, preferring nasal continuous positive pressure with or without exogenous surfactant, and report low incidences of BPD in high-risk infants. Large controlled clinical trials, however, have not yet been able to duplicate the single center experience. The COIN trial randomized 610 infants who were born at 25-to-28-weeks' gestation to CPAP or intubation and ventilation at 5 minutes after birth and found early nasal CPAP did not significantly reduce the rate of death or bronchopulmonary dysplasia, as compared with intubation (67). This study again demonstrated the efficacy of surfactant in reducing airleak, as CPAP was associated with significantly increased risk of pneumothorax. Another recent study randomized 1316 infants to intubation and surfactant treatment (within 1 hour after birth) or to CPAP treatment initiated in the delivery room, with subsequent use of a protocol-driven limited ventilation strategy and also found no difference in the primary outcome of death or bronchopulmonary dysplasia as defined by the requirement for supplemental oxygen at 36 weeks (68). Based on these findings caution should be taken in selecting a population that might benefit from this approach and adverse events, such as hemodynamic instability and necrotizing enterocolitis, should be carefully monitored.

A meta-analysis of seven randomized trials shows that systemic supplementation with vitamin A in sufficient quantities to establish normal serum retinol concentrations reduces oxygen dependence at 36 weeks' post-menstrual age (69), but does not change long term outcomes. Vitamin A levels, however, must be carefully monitored and while beneficial in the short term, the lack of proven beneficial long-term effects on pulmonary and neurological outcome has limited use of this therapy.

Corticosteroid therapy, although directed at reducing the lung inflammation seen in infants with evolving or established BPD, is perhaps the most controversial area of care. Clinical studies have consistently shown that steroids acutely improve lung mechanics and gas exchange, and reduce inflammatory cells and their products in tracheal samples of patients with BPD (70,71). A meta-analysis of randomized trials shows that corticosteroids reduce chronic oxygen dependency at 28 days, and 36 weeks post-menstrual age, if given systemically in the first 96 h, (72) but there are important concerns regarding increased mortality and adverse effects on head growth, neurodevelopmental outcomes, and lung structure (72-74). The routine early use of high-dose steroids in premature newborns is strongly discouraged, as reflected in editorials from the American Academy of Pediatrics and others (75,76). The adverse findings, however, are generally based on data from studies that have used high doses of dexamethasone started in the first few days of life and administered for long periods. Many questions persist regarding the risk-benefit relation in the use of other steroids for shorter study periods. As a result, some centers recommend use

of steroids outside the first week of life at lower doses and for shorter durations (5–7 days) in ventilator-dependent infants with severe, persistent lung disease. Due to the observed side effects of dexamethasone, postnatal steroid administration using hydrocortisone has been studied for the prevention of BPD. While no study has shown clear benefit with hydrocortisone administration, the direction of effect favors hydrocortisone in all studies and in the largest study to date, for infants exposed prenatally to chorioamnionitis, hydrocortisone significantly decreased mortality and increased survival without BPD (77). No adverse short or long term effects have been demonstrated with hydrocortisone use in any studies. For infants with established BPD and ventilator dependent chronic lung disease, hydrocortisone administered at a dose of 5 mg/kg per day, tapered over 3 weeks was as effective as dexamethasone for weaning infants from the ventilator and decreasing supplemental oxygen therapy, with fewer short and no long term adverse effects (78). The possible beneficial effects of hydrocortisone therapy need to be weighed against the increased incidence of gastrointestinal perforation, especially with concomitant use of indomethacin (77). To avoid the adverse effects associated with systemic administration, steroids have also been given by inhalation, but no important benefits have been noted with this method. The major effect of inhaled betamethasone in a multicentre randomised trial was to decrease the perceived need for the use of systemic steroids (79-81). A more recent analysis demonstrated an increased rate of successful extubation with 1-4 weeks of inhaled steroid use, without a reduction in the incidence of BPD (82).

Inhaled nitric oxide (NO) has been shown to be effective in improving lung structure in many experimental models of BPD. These studies include neonatal mice and rat pups after hyperoxia exposure (83,84), bleomycin induced BPD in neonatal rat pups (85) and premature lambs with RDS (86). 3 large randomized control studies of inhaled NO for prevention as well as treatment of established BPD have been published (47,48,49). The first study randomized 793 newborns less than 34 weeks gestation requiring mechanical ventilation within the first 48 hours of life to receive either NO (5ppm) or placebo gas for 21 days or until extubation. In this trial, iNO reduced the incidence of BPD by 50% for infants with a birth weight greater than 1000g. Inhaled NO also decreased the incidence of brain injury in premature newborns. (87). However, a subsequent study found that the early initiation of low dose NO does not prevent the subsequent development of BPD (88). Another study randomized 582 infants with a birth weight less than 1250 g requiring ventilatory support between 7 and 21 days of age. Treated infants received decreasing concentrations of nitric oxide, beginning at 20ppm for 48 to 96 hours, and the doses were subsequently decreased to doses of 10, 5, and 2 ppm at weekly intervals, for a minimum of 24 days. NO increased the rate of survival without BPD by 7% and also improved short and long term pulmonary function (89). Although the current evidence does not support the routine use of iNO for prevention of BPD in preterm infants (90), a clinical trial of non-invasive iNO therapy in premature infants at risk for BPD and a trial designed to study the effects of iNO in infants with evolving BPD (after the first week) are ongoing. These studies will further inform the debate.

It is also important to recognize that for infants less than 34 weeks in the setting of pulmonary hypoplasia and pulmonary hypertension (e.g. infants born after premature and prolonged rupture of membranes), inhaled NO is an important therapeutic option. Of the available strategies to treat pulmonary hypertension, iNO is the safest and most effective treatment. Some premature newborns have critical hypoxemia associated with pulmonary hypertension, and iNO is the optimal treatment. It is possible that high doses of NO in preterm infants with birthweights < 750g in the first days of life may be associated with increased risk of intracranial hemorrhage (91). However, the safety of 5ppm in the first week of life has been established.

Emerging Preventive Treatments

A promising method for preventing the development of BPD is prophylactic supplementation of human recombinant antioxidant enzymes (92). In preliminary studies in premature infants, the prophylactic use of both single and multiple intratracheal doses of recombinant human CuZn superoxide dismutase (rh superoxide dismutase) seemed to mitigate inflammatory changes and severe lung injury from oxygen and mechanical ventilation with no associated toxicity. In a randomized, placebo-controlled trial, prophylactic, intratracheal rhSOD at birth to premature infants (birthweight 600–1200 g) at high-risk for developing BPD was associated with much fewer episodes of respiratory illness (wheezing, asthma, pulmonary infections) severe enough to require treatment with bronchodilators or corticosteroids at 1 year corrected age (93). This suggests that rhSOD could prevent long-term pulmonary injury from reactive oxygen species in high-risk premature infants.

While the therapeutic potential of progenitor cells (both MSCs and angiogenic progenitor cells) have been demonstrated in animal models of BPD, especially after hyperoxia exposure, to date no human trials has been performed. Intratracheal administration of MSCs and injection of bone marrow derived angiogenic cells prevent the development of BPD after hyperoxia exposure in neonatal mice (60,94). There remain concerns as to the long-term effects of progenitor cells despite their therapeutic potential. Future studies will elucidate if safe therapeutic benefit exists with stem cell therapies.

Conclusion

Nearly 40 years after its original description, BPD remains a major complication of premature birth and a challenge for the future. BPD has evolved to be characterized largely by inhibition of lung development. Future strategies that improve long-term outcomes will depend on the successful integration of basic research on fundamental mechanisms of lung development and the response to injury, as well as studies that test novel interventions to lower the occurrence and severity of the cardiopulmonary sequelae of BPD. New ways of preventing or modulating BPD are on the horizon, and will hopefully lead to continued improvement of long-term outcome of prematurely born newborns.

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Keypoints

BPD is a major complication of preterm birth with multifactorial etiology.

Changes in sFlt-1, VEGF, TGF- β 1 and NF- κ B signaling as well as increases in proinflammatory cytokines contribute to the pathogenesis of BPD

Treatment strategies for BPD have failed to demonstrate a reduction in the rates of BPD.

Strategies that prevent the development of BPD are key.

Integration of basic and clinical research will lead to novel therapies effective in the prevention and treatment of BPD.

Figure 1.

Left: Chest x-ray showing early bronchopulmonary dysplasia with showing small hazy lung fields

Right: Chest x-ray showing established BPD with widespread interstitial shadows in both lung fields, consistent with fibrosis. The demineralization of the ribs is consistent with osteopenia of prematurity, a frequent association of bronchopulmonary dysplasia.

Figure 2. Etiology of bronchopulmonary dysplasia is multifactorial with pre and postnatal factors contributing to the pathogenesis of BPD.

Figure 3.

Differentiation of hemangioblasts into hematopoietic cells and endothelial cells. Bone marrow derived cells can differentiate down different cell lineages to give rise to endothelial cells that can partake in postnatal vasculogenesis or angiogenesis²¹. For this reason bone marrow derived cells have great therapeutic potential in bronchopulmonary dysplasia. Reproduced with permission from [62]

Table 1

NIH diagnostic criteria for bronchopulmonary dysplasia ⁹.

	Gestational age	
	<32 weeks	>32 weeks
Time point of assessment	36 weeks post-menstrual age or discharge [*]	>28 days but <56 days postnatal age or discharge [*]
Treatment with oxygen	>21% for at least 28 days	>21% for at least 28 days
Bronchopulmonary dysplasia		
Mild	Breathing room air at 36 weeks post-menstrual age, or discharge [*]	Breathing room air by 56 days postnatal age, or discharge [*]
Moderate	Need for <30% O ₂ at 36 weeks post-menstrual age, or discharge [*]	Need for <30% O ₂ to 56 days postnatal age, or discharge [*]
Severe	Need for >30% O ₂ , with or without positive pressure ventilation or continuous positive pressure at 36 weeks post-menstrual age, or discharge [*]	Need for >30% O ₂ , with or without positive pressure ventilation or continuous positive pressure at 56 days postnatal age, or discharge [*]

^{*} Whichever comes first.

Table 2

Difference in pathological features of the “old” and “new” bronchopulmonary dysplasia ¹⁰

Pre-surfactant (“old”)	Post-surfactant (“new”)
Alternating atelectasis with hyperinflation	Less regional heterogeneity of lung disease
Severe airway epithelial lesions (eg, hyperplasia, squamous metaplasia)	Rare airway epithelial lesions
Marked airway smooth muscle hyperplasia	Mild airway smooth muscle thickening
Extensive, diffuse fibroproliferation	Rare fibroproliferation changes
Hypertensive remodelling of pulmonary arteries	Fewer arteries but “dysmorphic”
Decreased alveolarisation and surface area	Fewer, larger and simplified alveoli