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Can We Prevent Bronchopulmonary Dysplasia?

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Northway et al first described Bronchopulmonary dysplasia (BPD), a chronic condition resulting from injury to the developing lung and pulmonary vasculature, in larger preterm infants with severe respiratory failure after exposure to high oxygen and ventilator pressures exposure.¹ Today, BPD most commonly occurs in extremely preterm infants and is characterized by a milder but protracted course and a different pathobiology than the BPD described 50 years ago.²

An evolving demographic, clinical and pathogenic picture has challenged the long-sought goal of BPD prevention. Many antenatal factors, such as maternal hypertension, smoking and infections that trigger preterm delivery also adversely affect *in utero* lung development. After birth, preterm infants are exposed to multiple injurious factors that can disrupt development and alter repair mechanisms of the lung and pulmonary vasculature.³ BPD prevention will require a multi-pronged approach that combines strategies to limit lung and vascular injury while promoting normal lung development. Over the past 50 years, multiple preventative/therapeutic strategies have had variable success. We highlight some of these strategies and outline opportunities for primary prevention of BPD (Figure).²

PRENATAL INTERVENTIONS

There is evidence that individuals follow a pulmonary function trajectory established very early in gestation and that this trajectory can be influenced by prenatal and preconception exposures.³ BPD likely begins in-utero and may be impacted by preconception and obstetric

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risk factors including intrauterine toxins, gene mutations, epigenetics, and gene-environment interactions (Figure). The current operational term “BPD” represents a combination of several chronic lung diseases, and improved endotyping to identify patient-specific pathophysiologic mechanisms of altered lung development will allow personalized prevention approaches, potentially prenatally. This will require precise definitions of obstetrical conditions (such as preeclampsia and chorioamnionitis); non-invasive study of the human fetal lung; development of surrogate markers of fetal lung injury from amniotic fluid or maternal blood; and elucidation of the role of the placenta in fetal lung development. Several potential causal pathways and preconception/prenatal windows for primary prevention identified from clinical research are highlighted below.

Obstetric Practices/Prevention of Prematurity

The most effective intervention to decrease BPD is to prevent or decrease premature deliveries. Progesterone, smoking cessation, cervical cerclage, and changes in fertility practice to transfer fewer embryos are effective in select patient populations.⁴ Studies designed to decrease preterm births have not rigorously examined the impact on BPD.

Genetics of BPD

Twin studies demonstrate that moderate to severe BPD has a heritability of 50–80%. Several candidate genes have been associated with high risk for BPD, including surfactant proteins, SPOCK2, TNF, IL-18, superoxide dismutase, and VEGF, and others,⁵ but validation studies are lacking. A recent genome-wide association and gene set analysis for BPD suggest that phenotypic differences in the severity of BPD are also manifest at the genomic level, with distinct biologic pathways associated with these phenotypes.⁶ Progress in BPD prevention and its genetic underpinnings will likely require further studies with adequate validation cohorts in order to specifically target specific pathways for intervention as identified by “personalized genomics.”

The Barker Hypothesis, Fetal Programming, and Maternal Nutrition

Fetal undernutrition leads to uneven fetal growth and may program persistent changes in postnatal growth and development.⁷ Fetal growth restriction in extremely low gestational age newborns is independently associated with the risk of BPD,⁸ which is likely due to decreased lung growth. Protein deprivation impairs alveolarization in animal models and maternal high fat diet during pregnancy is associated with wheeze and asthma in the offspring.⁹ Although few studies have examined the effects of maternal diet on BPD risk, past studies suggest the need for further research on the impact of maternal diet on the premature lung, including the role of maternal vitamin deficiency in disease pathogenesis. Prevention of BPD will require further delineation of the role of abnormal placental pathology such as maternal vascular under-perfusion, such as occurs with preeclampsia and fetal growth restriction, both of which are associated with increased risk of BPD.¹⁰

Environmental Exposures

Multiple environmental exposures can directly or indirectly affect lung development at any gestational age, but preterm infants may be particularly vulnerable. Epigenetic changes

consisting of DNA methylation, histone modifications, and microRNA changes in response to a variety of environmental stimuli such as toxins, oxidative stress, and infection may increase BPD susceptibility by altering the expression of genes involved in prenatal and postnatal lung development.² For instance, a recent study identified multiple genes potentially regulated by DNA methylation during normal alveolar septation in the mouse and human lung, and in BPD.¹¹ In utero smoke exposure modifies the methylation of specific genes, has been associated with changes in indices of global DNA methylation, and biologic pathways impacted through epigenetic changes by in utero smoke are being identified.¹² Maternal prenatal stress, cortisol, in-utero smoke, particulate exposure, and obesity have been shown to be independently associated with child wheeze, likely through programming mechanisms. Longitudinal samples from patients at risk for BPD are needed to examine longitudinal methylome and transcriptome changes.

Inflammation and Host Immune Responses

Prenatal inflammation is strongly associated with an increased risk for BPD.¹³ Better understanding of the role of lung inflammation and host immune responses in BPD pathobiology should facilitate development of inflammatory biomarker panels for BPD prediction and intervention targets. Selective anti-inflammatory therapies and modulators of innate immunity at the maternal-fetal interface and its impact on the subsequent lung microbiome of the preterm infants at risk for BPD need to be further defined.

POSTNATAL INTERVENTIONS

Respiratory support at birth and strategies to reduce ventilator associated injury

Most extremely low birth weight (ELBW) infants require respiratory support at birth. Animal studies have demonstrated that even a brief exposure to large tidal volumes at birth may cause significant lung injury predisposing to BPD.⁹ Because invasive respiratory support is a major contributor to the development of BPD, application of non-invasive respiratory support has become a popular strategy in its prevention. A recent meta-analysis showed a significant decrease in the incidence of BPD or death (OR 0.83; CI: 0.71–0.96) with early NCPAP versus mechanical ventilation.¹⁴ Studies have evaluated nasal ventilation (NIPPV) as an alternative to NCPAP or intubation, but a large RCT did not show superiority of this approach in reducing death or BPD compared with NCPAP (OR 1.09; CI: 0.83–1.43, P 0.56).¹⁵

RCTs of approaches to minimize ventilator associated lung injury, including high frequency oscillatory ventilation and volume-targeted ventilation have shown inconsistent effects on the incidence of BPD. Although none of these trials showed clear differences in long-term outcomes, a meta-analysis showed a reduction in BPD or death with the use of volume targeting modes (RR 0.73; CI: 0.57–0.93, NNT8).¹⁶

Surfactant treatment

Exogenous surfactant replacement decreases mortality and respiratory distress syndrome severity, but does not reduce the incidence of BPD, which may be due to enhanced survival, as surfactant reduces the combined outcome of BPD or death at 28 days of age (RR 0.83, CI

0.77–0.90).¹⁷ Minimally invasive modes of surfactant delivery, such as through the use of a strategy known as Less Invasive Surfactant Administration (LISA), may reduce the incidence of death or BPD.¹⁸ A large RCT of the use of late surfactant therapy in premature intubated infants did not show reduced BPD.¹⁹

Oxygen therapy and BPD

The use of 100% oxygen during resuscitation has been associated with increased mortality and possible lung injury, but data on the effects of low versus high oxygen for resuscitation of the premature infant are inconsistent. A recent meta-analysis failed to show a reduction in BPD with use of low (FiO₂ 0.3) versus high oxygen (FiO₂ 0.6)²⁰ and recent trials have shown higher mortality in infants receiving room air when compared with higher oxygen.²¹ After resuscitation, the inspired oxygen is titrated according to the targeted oxygen saturation (SpO₂). Three large RCTs of more than 5000 premature infants compared the effects of low (85–89%) and high (91–95%) targeted SpO₂ on neonatal morbidities and mortality. Two of these trials showed that low SpO₂ targets reduced the incidence of BPD but was associated with an increase in mortality.²²

Nutrition and fluid management

Postnatal growth failure is common in infants with BPD, a consequence of insufficient nutrition, increased energy use and adverse effects of drug therapies.²³ Animal models suggest that undernutrition is associated with impaired lung growth and may increase the risk of BPD independent of the severity of early respiratory failure.²³ Use of maternal milk has been associated with a reduction in BPD, possibly due to its antioxidant properties.²⁴ Although large RCTs of different nutritional approaches for BPD prevention are lacking, a nutritional strategy of adequate macro- and micro-nutrients to prevent postnatal growth failure has sound physiological rationale.

Pharmacologic interventions

Methylxanthines—Caffeine reduced BPD in an RCT of caffeine versus placebo, from 47% to 36%; $P < .01$).²⁶ Possible mechanisms are the shorter duration of mechanical ventilation use, or anti-inflammatory or diuretic effects. These results have led to early use of caffeine, but further safety evidence on this early indication is needed.

Postnatal Steroids—Corticosteroids have been used in infants with evolving BPD to improve lung function and facilitate extubation. Multiple reports of adverse neurodevelopmental outcomes after prolonged courses of high dose dexamethasone²⁷ have led to renewed effort to find an optimum regimen of corticosteroid therapy, particularly dexamethasone in high risk patients.^{28;29} Hydrocortisone may provide an alternative prevention strategy for BPD with less potential for neurotoxic effects.³⁰ A recent RCT using low dose hydrocortisone in ELBW infants showed increased survival without BPD³¹ and without significant neurodevelopmental effects at 2 years of age.³² Early inhaled budesonide versus placebo in ELBW infants reduced BPD but there was a concerning trend toward increased mortality.³³ A meta-analysis of 10 trials of early inhaled steroids in infants <1500 grams showed decreased BPD among survivors (RR 0.76, 95% CI 0.63 to 0.93; NNTB 14).³⁴ Yeh et al studied surfactant mixed with budesonide and surfactant alone for preterm

infants with severe RDS. Infants receiving surfactant with budesonide had a lower incidence of BPD (42% vs 66%; RR, 0.58; CI: 0.44–0.77; $P < .001$) without evidence of neurological side effects.³⁵

Vitamin A—Vitamin A and its metabolites play an important role in lung development and repair of respiratory epithelium. A recent meta-analysis showed a small reduction in incidence of BPD with Vitamin A supplementation as compared with placebo (RR 0.87 CI 0.77–0.99 NNTB 11 CI 6–100).³⁶ However, vitamin A is not universally used due to high cost, limited availability, and need for frequent intramuscular injections..

Inhaled Nitric Oxide—Endogenous nitric oxide is required for alveolar and vascular development and decreased production may contribute to the pathogenesis of BPD. Trials evaluating inhaled nitric oxide (iNO) for prevention of BPD have produced inconsistent results and a systematic review showed no beneficial effect on incidence of BPD.³⁷

Emerging Therapies—Better understanding of molecular pathways involved in alveolar and vascular development, and mechanisms of lung injury and repair has opened multiple potential targets for innovative BPD prevention strategies. Clara Cell Protein (CC10) has strong anti-inflammatory and immunomodulatory properties. Administration of recombinant human CC10 (rhCC10) upregulates surfactant protein and vascular endothelial growth factor expression, improves lung mechanics and decreases lung injury in animal models. A pilot study of rhCC10 in preterm infants showed significant anti-inflammatory effects in the lung and was well tolerated.³⁸

Stem cell therapy is a promising intervention for BPD prevention. In animal models of hyperoxia-induced lung injury, mesenchymal stem cells have been shown to be effective preventative and treatment strategies of lung injury.³⁹ Preliminary results from a small phase I study also showed promising results in infants with RDS but larger RCTs are needed.³⁹

Conclusion

BPD remains the most common chronic sequelae affecting preterm infants. To prevent BPD, improved understanding of factors contributing to both lung health and disease in the fetus and premature infant is required. Innovative techniques for noninvasive, longitudinal measurements of airway anatomy and lung mechanics in infants and young children must be developed as current testing is limited by the need for sedation, use of ionizing radiation, and lack of regional specificity of lung function. Given the complex antenatal and postnatal factors affecting alveolar and vascular development, no single therapy will eradicate BPD. Rather, a combination of multiple strategies acting on the various causal pathways is more likely to be effective in the future prevention of BPD.

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List of abbreviations

BPD	bronchopulmonary dysplasia
ELBW	extremely low birth weight
RCT	randomized controlled trials
NCPAP	nasal continuous positive airway pressure
NIPPV	nasal intermittent positive pressure ventilation
iNO	inhaled nitric oxide

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Figure.

Windows of opportunities for Prevention of BPD.

Antenatal and postnatal factors can predispose the structurally and biochemically immature lung to the development of BPD. BPD most commonly occurs in ELGAN born during the canalicular or early saccular phases of lung development. However not all extremely premature infants develop BPD, suggesting BPD can be prevented. Figure 1 identifies potential windows of opportunity for primary prevention of BPD. IUGR= Intrauterine growth retardation

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