

# Mechanisms of Lung Injury and Bronchopulmonary Dysplasia

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## Abstract

Although bronchopulmonary dysplasia (BPD) is the most frequent adverse outcome for infants born at < 30 weeks gestational age, there remain major gaps in understanding the pathophysiology, and thus there are few effective targeted therapies to prevent and treat BPD. This review will focus on the substantial problems and knowledge gaps for the clinician and investigator when considering lung injury and BPD. The epidemiology of BPD is clear: BPD is a lung injury syndrome predominantly in extremely low-birth-weight infants with an incidence that increases as gestation/birth weight decrease, with growth restriction, in males and with fetal exposures and with injury from postdelivery respiratory care. However, we do not have a good definition of BPD that identifies the infants that die of respiratory disease before 36 weeks or that predicts long-term outcomes as well. The injury resulting in BPD likely begins as altered lung development before delivery in many infants (small for gestational age, chorioamnionitis, tobacco exposure), can be initiated by resuscitating at birth, and then amplified by postnatal exposures (oxygen, mechanical ventilation, infection). Conceptually the events leading to BPD are the continued interplay of lung development that is altered progressively by injury and repair to result in poorly defined phenotypes of BPD. The injury pathways prominently cause inflammation, and as a proof of principle, corticosteroids can decrease the incidence and severity of BPD, as demonstrated by three recent trials of the early use of steroids. There are likely “adaptation” and “tolerance” responses that modulate the injury and repair to increase or decrease the damage, interactions that are not understood. BPD is a more complex disease.

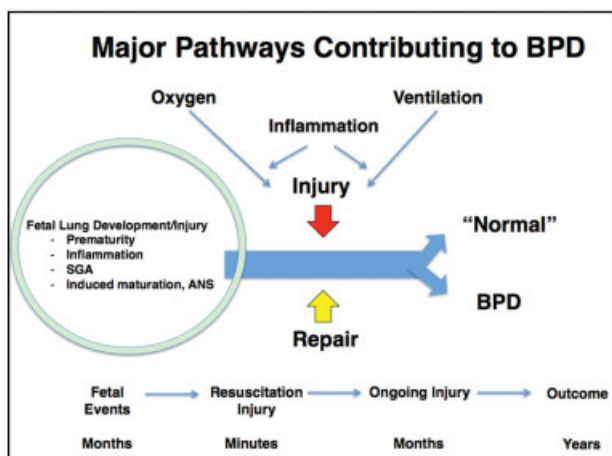
## Keywords

- ▶ lung injury
- ▶ injury repair
- ▶ postnatal steroids
- ▶ injury tolerance

## Definition and Epidemiology of BPD

Although the definition of bronchopulmonary dysplasia (BPD) has evolved as the surviving preterm infants that develop BPD have become more immature, the definition provides minimal insight into the pulmonary abnormalities.<sup>1</sup> The incidence of BPD in surviving infants  $\leq$  28 weeks gestational age has been approximately 40% for over 20 years.<sup>2</sup> The lack of decrease of incidence in part results in survival of smaller or more compromised infants that are more likely to develop BPD. The incidence and severity of BPD increase based on variables available at or shortly after birth—birth weight, gestational age, sex, growth restriction, and lung function. These variables relate to the fetal state of lung

development/maturation at birth (▶ **Fig. 1**). However, the definitions of BPD depend only on lung-directed therapy with supplemental oxygen and/or ventilator support with positive pressure at 36-weeks gestational age. Thus, the disease is defined by its therapy and not by pathology, radiology, or injury markers. Based on the multiple variables that contribute to lung injury in the preterm, it is likely that there are multiple pathologies in the airways, of epithelial surfaces, mesenchyme, and the pulmonary vasculature that are variably contributing to an infant being classified as having BPD. For example, traditional BPD definitions that rely on supplemental oxygen are problematic for infants that require pressure (continuous positive airway pressure, high



**Fig. 1** A diagram of some of the factors that can contribute to bronchopulmonary dysplasia. The focus is on how long development is modulated by multiple injuries and repair over time.

flow nasal catheters) but no oxygen.<sup>3</sup> The lung functional abnormalities may include decreased saccular/alveolar septation, decreased microvascular cross-sectional area with or without pulmonary hypertension, airway injury with or without increased airway reactivity, and abnormalities of control of breathing in various combinations. This complexity is not captured by the clinical definitions of BPD, and different phenotypes of BPD have not been well characterized in individual infants.

### Injury Mechanisms in BPD

I find a helpful concept to be that BPD is an injury syndrome superimposed on the essential lung growth and maturation (development) required for survival (► Fig. 1).<sup>4</sup> Counteracting the injury is a poorly understood repair program that must support repair of injury and lung development for the infant to survive. What are the injuries and are their common elements that might identify treatment options? The substrate for BPD is the very preterm lung that is certainly structurally immature even if there is sufficient maturation (saccularization and surface area plus surfactant) to support gas exchange. Chorioamnionitis can cause lung inflammation before birth; growth restriction can interfere with lung structural development, and maternal vascular diseases such as preeclampsia can disrupt fetal lung vascular development to increase the risk of BPD.<sup>1</sup> The major injury drivers for the fetal lung are inflammation and developmental disruptions such as growth restriction and nicotine exposure.

The assisted ventilation required to initiate breathing at birth in the very preterm lung can injure the lung by exposure to high pressures, volumes, and oxygen. Both ventilation and oxygen-mediated injury initially activate inflammatory pathways that can amplify preexisting injury (chorioamnionitis) or be amplified by continued exposure to oxygen and ventilation-mediated injury.<sup>5</sup>

Subsequent oxygen exposure and mechanical ventilation will cause continuous injury to the very preterm lung,

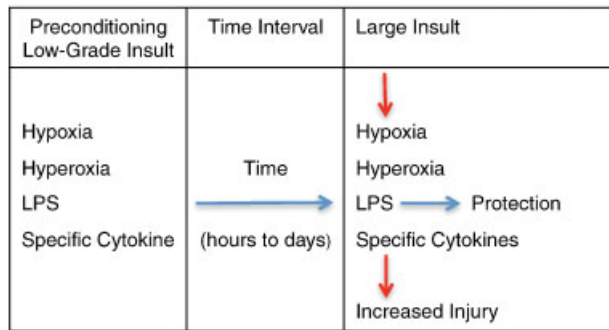
primarily mediated by inflammatory mechanisms. In term rodent models of BPD, blocking multiple inflammatory pathways (granulocyte recruitment, cytokines, prostanoids, oxidants) will prevent much of the inhibition of airway septation and microvascular injury. These experiments are proof of principle that multiple inflammatory pathways contribute to the pathology, although translation to clinical treatments has been disappointing.<sup>6</sup>

### Postnatal Corticosteroids: Revisited

Common threads through the mechanisms responsible for BPD are multiple inflammatory mediators and pathways. Corticosteroids are potent and pleiotropic anti-inflammatory drugs that are also developmental disruptors that interfere with airway septation and microvascular development. However, in numerous clinical trials corticosteroids decrease BPD when given either soon after birth to decrease BPD or later in the clinical course to decrease injury progression.<sup>7</sup> There has been a particular concern about using corticosteroids soon after birth because of gut and brain developmental complications. However, and consistent with the rodent models, three recent trials have demonstrated that corticosteroids can decrease BPD when given soon after birth, a proof of principle that inflammation initiated before or soon after birth is central to BPD progression. In large randomized controlled trials, Bassler et al<sup>8</sup> decreased BPD with a budesonide aerosol, Baud et al<sup>9</sup> decreased BPD using a 10-day low-dose hydrocortisone infusion beginning on the first day after birth, and Yeh et al<sup>10</sup> mixed surfactant with budesonide for the initial surfactant treatments of infants with respiratory distress syndrome and decreased BPD by 21%. The Yeh et al's trial is particularly intriguing as the corticosteroid is targeted to the lung soon after birth and results in minimal systemic exposure of the infant to the steroid. While anti-inflammatory therapies that are targeted to specific inflammatory mediators would be desirable, the clinicians should reconsider postnatal corticosteroid treatments along with continued efforts to minimize oxygen and ventilation injury in very preterm infants to decrease the incidence and severity of BPD.

### BPD Is Complex: Interactions

The simultaneous and continuous need to promote lung development, minimize injury, and optimize repair is a complex goal for which the field has insufficient information to optimize. Lessons from observations in other systems may provide some insight into the complexity of the pathophysiology that may be driving BPD. In immunology, a pathogen can directly damage tissue, induce host resistance (immunity) or induce a host inflammatory/immune response that may cause more injury than the initial pathogen exposure. The host also may have tolerance responses that can modulate the injury response.<sup>11</sup> Other variables are the effects of pre-exposures that can precondition or tolerize to a second more injurious stimulus (► Fig. 2).<sup>12</sup> Based primarily on studies of the fetal/newborn brain, a low-grade insult, such as hypoxia, hyperoxia, lipopolysaccharide or specific cytokines can greatly modulate the injury response to a second



**Fig. 2** Schematic of how exposure or increase to low grade injury mechanisms can modulate a secondary larger injury to decrease the injury by inducing protective mechanisms or by augmenting the injury.

insult, which can be the same or a different insult. That initial exposure can increase or decrease the response to the second exposure depending on the time interval between exposures. I suspect that the variability in injury and repair in infants at risk of BPD results from modulation of responses. These complex interactions remain to be explored.

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