# Infection and Inflammation: Catalysts of Pulmonary Morbidity in Bronchopulmonary Dysplasia

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## Introduction

Despite improvements in the care of preterm infants with gentler ventilation techniques, antenatal glucocorticoid therapy, and surfactant treatment, bronchopulmonary dysplasia (BPD) remains a major public health problem worldwide. BPD, as defined by the need for supplemental oxygen at 36 weeks' postmenstrual age [1–3], is the most frequent pulmonary morbidity among survivors of prematurity—a chronic lung condition that affects more than 10,000 premature infants in the United States alone each year [4, 5]. Before the surfactant era, BPD was primarily a structural injury of the preterm lung characterized by decreased alveolarization and surface area, alternating atelectasis with hyperinflation, pulmonary lesions, and fibrosis

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[6]. Today, BPD represents a developmental arrest of the preterm lung with interruption of the pulmonary septation, alveolarization, and vascularization during the saccular and alveolar stages of lung development [7].The result is a lung with fewer, larger alveoli and a corresponding decrease in surface area available for gas exchange.

The 2014 National Institutes of Health Heart, Lung, and Blood Institute workshop on prevention of BPD identified six possible causative factors associated with BPD: structurally and biochemically immature lungs, hyperoxia and oxidant injury, mechanical injury associated with positive pressure respiratory support, poor respiratory drive and apnea, poor nutrition, and importantly, infection and inflammation [5]. Any or all of these factors, possibly in concert with genetic predisposition or epigenetic factors, could contribute to its occurrence, even though recent genome-wide association studies (GWAS) failed to identify any specific loci associated with moderate to severe BPD [8, 9]. Clearly, the pathophysiology of BPD is complex and likely multifactorial, but a central role for *pulmonary inflammation* seems critical to its development.

## Antenatal Infection and Inflammation

There is a substantial body of literature associating "chorioamnionitis" with the development of BPD, with recent meta-analyses demonstrating odds ratios of 3.0 and 2.2 for the occurrence of BPD at 28 days of age and 36 weeks postmenstrual age, respectively [10]. How chorioamnionitis contributes to the development of BPD, however, remains a topic of ongoing debate.

Chorioamnionitis is diagnosed often as symptomatic maternal disease with intrapartum fever in association with clinical and laboratory signs of infection or inflammation, but more appropriately, by histopathology [11]. The so-called histological chorioamnionitis can be acute or chronic based on neutrophilic or lymphocytic infiltration of the fetal membranes, respectively. Both neutrophils and lymphocytes may be of either maternal or fetal origins [12]. Unlike acute cases, chronic chorioamnionitis has both cellular (innate) and humoral (adaptive) immune responses, which could indicate maternal antibody-mediated antifetal rejection that has been associated with preterm birth [13]. The suggestion by Goldenberg et al. [14] that intrauterine infection and/or inflammation accounts for up to 90 % of preterm births before 28 weeks' gestation lends credence to the theory that predisposition of preterm infants to BPD may occur in utero.

*Ureaplasma parvum* and *Ureaplasma urealyticum*, both genital mycoplasmas, are the most common bacteria isolated from placentas with histological chorioamnionitis as well as from amniotic fluid [15, 16, 17]. These organisms are typically of low virulence, and thus capable of producing a chronic infection of the uterine cavity and fetal compartment [14, 18]. In fact, neonatal colonization with *Ureaplasma spp*. has been associated with chorioamnionitis [19].

Prospective cohort studies have associated *Ureaplasma* colonization with the development of BPD [20, 21]. Respiratory tract colonization with *Ureaplasma spp*. occurs in 28–33 % of infants with birth weight <1500 g, and among those < 26 weeks' gestation, as many as 65 % of infants are culture-positive or polymerase chain

reaction (PCR)-positive for *Ureaplasma spp*. at least once in the first month of age [22]. *Ureaplasma* colonization increases with decreasing gestational age, a finding that correlates with the risk of developing BPD [23].

Several mechanisms for the association of *Ureaplasma* colonization of preterm infants and BPD have been proposed. The ability of *Ureaplasma spp.* to hydrolyze urea as their sole source of energy results in the generation of ammonium ions that interact with lung water to form ammonium hydroxide and potentially result in mucosal/epithelial injury and inflammation [24]. However, the major virulence factor that has been identified experimentally is the *Ureaplasma* multiple banded antigen (MBA), a surface-exposed lipoprotein [22]. *Ureaplasma spp.* have been shown to evade the host immune response by varying the size of MBA and *mba* gene [22, 24]. Both MBA and *mba* gene size variants have been detected in infected sheep amniotic fluid and fetal lung, and the size variation also has correlated with the severity of chorioamnion inflammation.

Clearance of *Ureaplasma* species from the lung also appears to be dependent on local host immune response mediators, such as surfactant protein-A (SPA) [15]. Okugbule-Wonodi et al. [25] demonstrated that SPA increased phagocytosis and killing of *Ureaplasma spp*. by macrophages. In a mouse model, SPA-deficient mice showed delayed clearance of *Ureaplasma* from the lungs, increased inflammatory cells, and increased proinflammatory cytokine expression [26]. These findings are particularly relevant for preterm infants who lack robust immune responses and endogenous SPA production in the first 48 h of age.

## *Does Chorioamnionitis Cause BPD?*

Intra-amniotic inflammation (IAI) secondary to histological chorioamnionitis can result in premature maturation of the fetal lung that is mediated by such proinflammatory cytokines as interleukin (IL)-1α, IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α. These can act directly on fetal lung cells, including the Type II alveolar cells that produce surfactant [27, 28]. In rabbits, Bry et al. [29] demonstrated that IL-1α enhanced messenger RNA transcription of both surfactant proteins and lipids resulted in improved lung compliance [12, 29]. Although the proinflammatory cytokines protected against the development of respiratory distress syndrome (RDS), the fetal inflammation has been associated subsequently with increased incidence of BPD [12, 27, 30, 31].

While the signaling pathways responsible for lung development have been well characterized, the effects of chorioamnionitis and/or antenatal inflammation on those pathways have not [32, 33]. Bacterial antigens such as lipopolysaccharide can cause altered distribution of elastin, the mesenchymal structural protein responsible for proper septation of the lung [12, 34, 35]. Intra-amniotic inflammation also can cause dysregulation of critical growth factors necessary for lung development. Fibroblast growth factor (FGF)-10 expression is inhibited by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the major proinflammatory signaling pathway stimulated by IL-1 and TNF-α [36, 37]. FGF-10 plays a key

role in lung branching morphogenesis, remodeling, repair, and regeneration [12, 38]. Inhibition or dysregulation of these key functions as a consequence of histological chorioamnionitis or inflammation has resulted in a lung condition in animals that is similar to BPD in humans [35].

The effects of antenatal inflammation are not limited to the developing airway. The developing pulmonary vasculature also is susceptible to adverse remodeling due to antenatal inflammation, limiting the capacity for gas exchange in the preterm lung. Antenatal inflammation can inhibit vascular endothelial growth factor (VEGF), angiopoietin-1, transforming growth factor-β (TGF-β), endoglin, connective tissue growth factor (CTGF), endothelial nitric oxide synthase (eNOS), platelet endothelial cell adhesion molecule-1 (PECAM-1), and VEGF-receptor 2 (VEGF-R2) [12, 39, 40]. In addition, antenatal inflammation can cause smooth muscle hypertrophy in the pulmonary vasculature, predisposing to pulmonary hypertension that is a major complication of BPD [12, 39]. VEGF is responsible for the regulation of eNOS, which plays a crucial role in the regulation of pulmonary vascular tone and modulation of pulmonary vascular development. PECAM-1 and VEGF-R2 are essential for proper development of pulmonary endothelial cells [39].

It seems clear that antenatal inflammation alone has the potential to cause both impaired alveolarization and reduced development of the pulmonary vasculature leading to the development of BPD in some at-risk preterm infants, even in the absence of mechanical ventilation [39, 41]. However, other indirect mechanisms linking chorioamnionitis and/or inflammation to BPD may be involved.

## *Does Chorioamnionitis Make the Lung Susceptible to BPD?*

Exposure of the preterm fetus to chorioamnionitis may result in a systemic fetal inflammatory response syndrome (FIRS) with activation of the innate immune system [42, 43] and manifested by histological chorioamnionitis with funisitis and increased umbilical cord blood concentrations of proinflammatory cytokines [42]. Such infants have a decreased clinical response to exogenous surfactant, more frequent use of exogenous surfactant, increased need for mechanical ventilation, longer time to extubation, longer supplemental oxygen use, and more frequently develop BPD [43, 44, 45].

Mechanical factors also contribute to the development of BPD. Hillman et al. [46] showed that as few as six breaths at high tidal volumes were sufficient to eliminate the surfactant response in fetal sheep. Furthermore, 15 min of ventilation at escalating tidal volumes has been associated with a substantial inflammatory response in the preterm lung that is characterized by production of multiple classes of cytokines and other proinflammatory markers, increased mRNA for IL-1β and IL-6, increased inflammatory cell infiltrates, increased alveolar wall thickening, and decreased alveolar expansion, with a concomitant delayed or deficient release of the anti-inflammatory cytokine, IL-10 [47, 48]. Of note, stretch injury overlapped consistently with the maturational effects induced by chorioamnionitis and prolonged LPS exposure in utero [46].

Supplemental oxygen supplied to the preterm infant, whether by mechanical ventilation or other support measures, such as continuous positive airway pressure (CPAP) or nasal cannula, also has injurious effects on the preterm lung by inducing an inflammatory response [45]. This inflammation stimulates the activity of VEGF and causes breakdown of the alveolar–capillary barrier, vascular leakage, introduction of proinflammatory mediators, pulmonary edema, and, ultimately, endothelial apoptosis [45, 49]. An animal study of hyperoxia-induced BPD in preterm rabbits identified 2217 dysregulated pathophysiological pathways affecting inflammation, vascular development, and reactive oxygen species (ROS) metabolism [50]. Because antioxidant defense do not develop until much later in gestation, preterm infants receiving high concentrations of oxygen are particularly susceptible to ROS-mediated injury [51, 52].

Antenatal inflammation due to chorioamnionitis also has been linked to the development of BPD through immune tolerance due to the preterm lung's structural immaturity and the preterm infant's immature immune system [12, 53]. Several in vitro and animal studies have indicated that intrauterine endotoxin/LPS exposure can downregulate immune responses akin to tolerance [54–57]. LPS-induced immune paralysis may be caused by reduced expression of major histocompatibility complex II (MHC) antigen on fetal blood monocytes and increased expression of the immunosuppressive cytokines, IL-10 and TGF-β [12, 57].

Repeated exposure to LPS in *Ureaplasma*-infected fetal sheep induces both endotoxin tolerance and tolerance of other toll-like receptor (TLR) agonists [55]. Since TLRs are major activators of the immune system, cross-tolerance of toll-like agonists may enhance immune suppression in the preterm infant and increase the vulnerability to a "second hit"—sepsis, ventilator-mediated injury, or hyperoxia [12, 55]. On the other hand, Kramer and Jobe [56] hypothesized that this immunosuppressive fetal response may be an advantageous adaptation to chronic exposure to chorioamnionitis that prevents more serious inflammation-mediated lung injury. Indeed, Kallapur et al. [58] lent weight to this theory when they showed that chronic exposure to intra-amniotic endotoxin did not lead to progressive lung injury and extensive structural abnormalities in fetal sheep, but only to mild, persistent inflammation. However, chorioamnionitis leading to prolonged immune dysfunction may subsequently increase susceptibility to postnatal infections.

## Bacterial Sepsis and BPD

Early-onset sepsis (≤72 h after birth) has been shown to initiate an inflammatory cascade in preterm infants similar to that seen with exposure to histological chorioamnionitis. Similarly, late-onset sepsis (LOS; >72 h of age) causes both proinflammatory and profibrotic responses in the preterm lung, increasing its susceptibility to BPD [45, 59, 60].

In a retrospective study of 7509 infants born at <32 weeks' gestation in 29 neonatal intensive care units (NICUs) of the Canadian Neonatal Network from 2010 to 2011, Shah et al. [59] identified 1104 (15 %) infants with LOS, defined as a positive

blood and/or cerebrospinal fluid bacterial culture. Of these 1104 infected infants, 909 (82 %) had Gram-positive and 195 (18 %) had Gram-negative infections. As compared with no infection, the odds ratio (OR) of mortality/BPD was higher in infants who had Gram-negative (OR, 2.79; 95 % confidence interval [CI], 1.96–3.97) and Gram-positive (OR, 1.44; 95 % CI, 1.21–1.71) sepsis. Infants with Gram-negative sepsis were significantly more likely to have been born to mothers with chorioamnionitis than uninfected infants ($p = 0.004$) or those with Gram-positive infections ($p = 0.04$). This study supports the contention that the proinflammatory cascade that occurs with LOS can exacerbate preexisting inflammatory conditions associated with chorioamnionitis exposure or initiate an inflammatory and fibrotic response that results in BPD [45, 59, 61, 62]. Prevention of postnatal sepsis must remain a high priority for prevention of BPD.

## Cytomegalovirus Infection and BPD

Congenital cytomegalovirus (CMV) infection is the most common congenital viral infection in developed nations, occurring in approximately 0.1–2.0 % of all live births [63, 64]. CMV is a *Betaherpesvirinae* virus that infects human leukocytes, and transmission to the infant occurs transplacentally following primary maternal infection, reactivation of latent maternal infection, or maternal reinfection with a different viral strain [64]. In addition, infants can acquire the virus during birth from exposure to infected vaginal and cervical secretions, or postnatally by either blood transfusion or, more commonly, ingestion of human milk from a CMV-seropositive mother [65, 66]. Intrapartum and postnatal acquisition of CMV, defined as detection of CMV in body fluids at ≥21 days of age, and to a lesser extent congenital infection, can result in pneumonitis and increased likelihood for development of BPD in preterm infants [64, 67].

In 1976, Whitley et al. [68] first noted the association of perinatally acquired CMV infection with protracted pneumonitis in two infants with lower respiratory tract obstruction at 1 month of age [68]. Virological, serological, immunological, and electron microscopic studies indicated that CMV was a major causative factor. Subsequently, case reports associated multicystic lung disease, fibrosis, and pulmonary hypertension with postnatal CMV infection [1, 69–71].

Two recent studies provide new evidence for an association between postnatal acquisition of CMV and BPD. Mukhopadhyay et al. [72] conducted a retrospective review of 145 very low birth weight (VLBW, ≤1500 g) infants who were tested for CMV infection while in the NICU at Brigham and Women's Hospital, Boston from 1999 to 2013. Of the 145 infants, 27 (19 %) had postnatal detection of CMV defined as diagnosis at ≥21 days of age; all had birth weight <1250 g and were born at <32 weeks' gestation. Sixteen (59 %) infants presented with acute respiratory decompensation, and importantly, CMV-infected infants had significantly more exposure to mechanical ventilation ($p = 0.03$) and a higher incidence of BPD (OR 4.0; 95 % CI, 1.3–12.4; $p = 0.02$). The authors suggested that postnatal symptomatic

CMV infection, like late-onset bacterial sepsis, may predispose to development of BPD by a combination of direct pathogen effects on the lung, inflammation, and/or increased exposure to mechanical ventilation and supplemental oxygen.

Similarly, in a propensity-matched retrospective cohort study of 101,111 VLBW infants at 348 NICUs managed by the Pediatrix Medical Group from 1997 to 2012, 328 (0.3 %) infants had a diagnosis or detection of CMV at ≥21 days of age [73]. Postnatal CMV infection was associated with an increased risk for death or BPD at 36 weeks' postmenstrual age (risk ratio, 1.21; 95 % CI, 1.10–1.32) and BPD (risk ratio, 1.33; 95 % CI, 1.19–1.50). Changes in cardiorespiratory status associated with postnatal CMV infection included a new requirement for vasopressor medications (9 %; $n = 29$), intubation for mechanical ventilation (15 %; $n = 49$), a new oxygen requirement (28 %; $n = 91$), and death (1.2 %; $n = 4$).

Given the association of postnatal acquisition of CMV with BPD, the key challenge remains development of preventative measures against CMV acquisition in extremely low gestational age infants. Transmission of CMV by blood transfusion to preterm infants has been virtually eliminated by the use of CMV antibody-negative donors, freezing red blood cells in glycerol before administration, or leukoreduction. Ingestion of human milk now is the primary means by which preterm infants acquire CMV postnatally [74]. While pasteurization of human milk inactivates CMV, it also may reduce its known cognitive, immunological, and nutritional benefits. Freezing milk at −20 °C decreases CMV viral titers, but does prevent transmission [75, 76].

## Respiratory Viral Infection and BPD

The occurrence of respiratory viral infections in preterm infants in the NICU has been documented in a prospective surveillance study performed in two NICUs in Syracuse, NY during a 1-year period [77]. Fifty preterm infants <33 weeks' gestation who were in the NICU since birth underwent nasopharyngeal swab testing for detection of respiratory viruses (influenza A/B; respiratory syncytial virus [RSV] A/B; parainfluenza [PIV] 1–4; coronavirus, human rhinovirus/enterovirus [hRV]; adenovirus; human metapneumovirus [HMPV]) by multiplex PCR testing twice weekly within 3 days of birth and up to the time of discharge. Fifty two percent (26/50) of infants tested positive for a respiratory virus at least once during the NICU stay. Of 708 specimens obtained, the following viruses were detected: PIV-3, 13; hMPV, 9; RSV-B, 8; RSV-A, 7; PIV-2, 7; hRV, 7; and influenza B, 4. Of note, 18 samples (28 % of the positive swabs) included more than one virus, similar to studies performed in older infants with bronchiolitis where viral codetection is relatively common. Fourteen infants had sequentially positive specimens for the same virus over 3 to 13 days, suggesting that these were true positive results. Compared to infants who did not have a respiratory viral pathogen detected, virus-positive infants had significantly longer length of stay (70 d vs. 35 d, $p = 0.002$), need for intubation (65 % vs. 29 %, $p = 0.01$), duration of intubation (19 vs. 5 d, $p = 0.03$), duration of

oxygen requirement (51 vs. 13 d, $p = 0.002$), more episodes of desaturation ($p < 0.0001$), and clinical deterioration episodes ($p = 0.0001$), and importantly, BPD (46 % vs. 21 %, $p = 0.05$).

In a single-site prospective study performed in a German NICU from 8/2010–3/2014, Kidszun et al. [78] performed respiratory viral multiplex PCR testing on 88 infants (median gestational age, 27 weeks; median birth weight, 852 g) who underwent 137 evaluations for late-onset sepsis. A respiratory virus was detected in the nasopharynx of six (7 %) infants (2, RSV; 4, picornavirus). Similarly, Ronchi et al. [79] conducted a 1-year study (1/15/12–1/31/13) for the detection of respiratory viruses by multiplex PCR testing in infants evaluated for possible sepsis and in whom intravenous antibiotic therapy was initiated. During the 13-month study, 100 infants (mean gestational age, 31 weeks; mean birth weight, 1698 g) had 135 sepsis evaluations, and 8 infants (8 %), or 6 % ($n = 8$) of sepsis evaluations, had a respiratory virus detected from nasopharyngeal swabs. These included hRV($n = 4$), coronaviruses (1, HKU-1; 1, OC43), and PIV-3 ($n = 2$). These studies suggest that respiratory viral infections are under-recognized in premature infants in the NICU; yet, they are associated with acute morbidity. Their contribution to long-term respiratory and neurodevelopmental outcomes, however, remains unknown.

It is likely that respiratory viral infections can exacerbate the underlying lung abnormalities of infants with BPD and result in impairment of lung function through early childhood and possibly adolescence. Longitudinal studies of mice who received supplemental oxygen have found a lifelong increased susceptibility to infection with respiratory viruses, and in particular, influenza A virus, compared to preterm controls exposed only to room air [80–82]. Higher oxygen concentrations led to a dose-dependent inflammatory response to influenza A exposure [45, 52, 83], with enhanced recruitment of macrophages, neutrophils, and lymphocytes, as well as increased alveolar fibrosis, increased monocyte chemoattractant protein (MCP-1), and greater mortality [80]. O'Reilly et al. [80] demonstrated that alveolar type II cells that are responsible for surfactant production can express viral receptors on their surface, with surfactant protein-deficient mice having decreased viral clearance. Pulmonary outcomes of preterm infants infected with a respiratory virus early in life—and especially with RSV, hRV, PIV, and hMPV—bear striking resemblance to outcomes of very premature infants with BPD [84, 85]. Both BPD and early respiratory infection with RSV have been associated with recurrent wheeze and lung function abnormalities that persist to school age [64, 86]. In addition, viral lower respiratory tract infections (LRTIs) may be a marker for preexisting abnormal lung function in neonates [64, 87]. Infants with BPD have substantially more rehospitalizations due to RSV and hRV infection than age-matched controls without BPD [88, 89].

Similar to BPD, RSV also has been shown to cause persistently diminished lung function among preterm infants and increased wheezing throughout childhood [90, 91–94]. Preterm infants hospitalized with RSV infection are significantly more likely to require supplemental oxygen and mechanical ventilation, exposing them to additional pulmonary injury [88]. In 2015, the SPRING study demonstrated that among children born at 32–35 weeks' gestation, RSV hospitalization was associ-

ated with increased wheezing through 6 years of age, as well as increased utilization of health care resources and decreased self-reported quality of life [95].

The humanized monoclonal antibody, palivizumab, has been shown to significantly reduce RSV hospitalizations in infants and children at high risk for severe RSV infection [96]. Simoes et al. [97] conducted a cohort study of 421 preterm infants who had received palivizumab and were not hospitalized for RSV ($n = 191$) or who never received palivizumab ($n = 230$; 76 hospitalized for RSV). Infants who received palivizumab had significantly less parent-documented and physician-diagnosed recurrent wheezing. Similarly, the Dutch RSV Neonatal Network conducted a multicenter, double-blind, placebo-controlled trial of palivizumab prophylaxis in 429 otherwise healthy preterm infants of 33 to 35 weeks' gestation and demonstrated that palivizumab prophylaxis significantly reduced wheezing days during the first year of age [98]. These studies continue to implicate RSV infection as an important mechanism of recurrent wheeze during the first year of life in preterm infants.

## Future Directions

As the direction of causality between infection, inflammation, and BPD remains unanswered, research is needed to better elucidate their interaction and contribution to long-term pulmonary morbidity in preterm infants, with the ultimate goal of developing and implementing novel therapies and interventions. Nonetheless, a central role for pulmonary inflammation seems key, and the factors that contribute to its evolution need to be explored.

Early and prolonged antibiotic therapy in preterm infants has been associated with BPD [99], suggesting an important role of the airway microbiome as a mediator of the inflammatory process [100]. Recently, Lal et al. [101] reported temporal dysbiotic changes in the airway microbiome from birth to the development of BPD in preterm infants. They noted decreased *Lactobacillus spp.* in endotracheal aspirates of preterm infants who developed BPD and infants born to mothers with chorioamnionitis. How the airway microbiome is established, and the possible factors such as chorioamnionitis, antibiotic use, and postnatal infection that potentially contribute to its dysregulation need further exploration [102].

The human virome, or the viral component of the human microbiome, represents the collection of all viruses that are found in or on humans, including viruses that cause acute, persistent, or latent infection, and viruses that integrate into the human genome, such as endogenous retroviruses [103]. The human virome includes both eukaryotic and prokaryotic viruses (bacteriophages), the latter of which can infect the broad array of bacteria that inhabit the body and influence bacterial population structure or virulence. Its impact on human health has received less attention than that of the bacterial microbiome, even though it is likely to be equally important in homeostasis and disease. The potential importance of the human virome in the

development of BPD is not known, and our current lack of understanding of its ontogeny in preterm infants constitutes a major knowledge gap in our continuing efforts to decrease the incidence of BPD and its consequences.

Finally, genome-wide transcriptional profiles of the infant's inflammatory response to conditions associated with prematurity could provide new key evidence about the pathogenesis of BPD [104]. Analysis of the infant's transcriptome also could be used to support the clinical significance of detecting bacterial or viral sequences in clinical specimens by detecting expression of immune/inflammatory genes that may contribute to the development of BPD [105]. Importantly, such technology could aid in the identification and subsequent validation of candidate biosignatures and biomarkers for BPD in preterm infants with bacterial and respiratory viral infections.

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