



Neonatal Review

In this issue...Volume 2, Number 12

As we approach the 40 year anniversary of Dr. Northway's seminal 1967 report (1), bronchopulmonary dysplasia (BPD) remains a constant concern in the Neonatal Intensive Care Unit (NICU). Despite an evolution in describing the pathologic appearance of BPD, the long-reported abnormalities remain: influx of alveolar macrophages and neutrophils, and later lymphocytes; cellular injury in particular to type I cells and endothelial cells; type II cell hyperplasia; alveolar fibrosis; impaired alveolar development; and impaired vascular development. Also, over the past decades, there has been a change in the patient population most likely to be affected by this disease: it is now more commonly seen in very premature, extremely low birth weight infants (<1000 grams) and rarely seen in infants born at term. Despite both the marked increase in survival of extremely premature infants and ongoing advances in neonatal technology and management, BPD is still common and takes a toll in both mortality and morbidity.

With BPD affecting as many as 25,000 U.S. infants each year — and with estimated overall costs second only to those for treating asthma and far exceeding the costs of treating cystic fibrosis (Division of Lung Diseases and Office of Prevention, Education, and Control, November 1998) — it has become clear that BPD is itself an independent risk factor for poor neurodevelopmental outcome. The concept that the exposure of the lung at such an early stage of development to becoming the organ of gas exchange is fundamental to the pathogenesis of BPD and has long been a focus of study, including, in recent years, a strong concentration on understanding the arrest of alveolar development and abnormal vasculature. The molecular basis of lung development itself has been the subject of extensive research to define and comprehend the mechanisms of changes in the alveolarization and vascularization seen in BPD.

In this issue we focus on the contributions of *inflammation*, the *development of the vasculature and alveolarization*, and *genetic predispositions* to the pathogenesis of BPD.

Course Directors

Edward E, Lawson, M.D.

Professor
Department of Pediatrics — Neonatology
The Johns Hopkins University School of Medicine

Lawrence M. Noguee, M.D.

Associate Professor
Department of Pediatrics — Neonatology
The Johns Hopkins University School of Medicine

Christoph U. Lehmann, M.D.

Assistant Professor
Department of Pediatrics, Health Information
Science and Dermatology
The Johns Hopkins University School of Medicine

Lorraine A. Harbold, R.N., M.S.

The Johns Hopkins Hospital
NICU Education Coordinator

Recommend to a Colleague

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Learning Objectives

The Johns Hopkins University School of Medicine and The Institute for Johns Hopkins Nursing take responsibility for the content, quality, and scientific integrity of this CE activity.

At the conclusion of this activity, participants should be able to:

- Discuss the recent contributions of inflammation to the pathogenesis of bronchopulmonary dysplasia
- Describe the fundamental connection between lung development and bronchopulmonary dysplasia
- Identify the exciting developments in the area of genetic associations and bronchopulmonary dysplasia

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LENGTH OF ACTIVITY

0.5 hours

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NEXT ISSUE

September 15, 2005

Guest Editors of the Month



Commentary, Figure and Reviews:

Rita M. Ryan, MD

Chief, Division of
Neonatology
State University of
New York at Buffalo,
Women and Children's
Hospital of Buffalo,
Buffalo, New York



Reviews:

Ibrahim S. I. Mohamed, MD

Fellow, Division of
Neonatology
State University of
New York at Buffalo,
Women and Children's
Hospital of Buffalo,
Buffalo, New York

Guest Faculty Disclosure

Rita M. Ryan, MD

Faculty Disclosure: No relationship with commercial supporters.

Ibrahim S. I. Mohamed, MD

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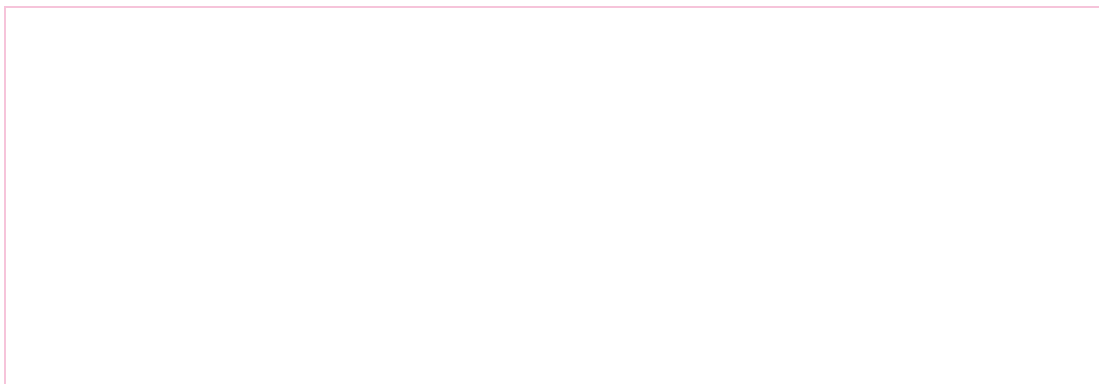
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COMMENTARY

Over the years several animal models were developed to study the pathophysiology of BPD. Early models focused on hyperoxia in neonatal animals, as the high levels of supplemental oxygen used to treat babies with respiratory distress syndrome (RDS) were believed to be important in the pathophysiology of BPD. Fundamental contributions originated from the laboratories of Drs. Frank, Massaro, and colleagues. Today, although lower FiO₂ levels may be used clinically, the concept that even room air represents "hyperoxia" to the very immature lung is consistent with oxidant injury being an important pathophysiologic factor in BPD (2). Two large animal models of BPD were developed, in the baboon (Drs. Coalson, DeLemos, Yoder, Seidner and colleagues (3)), and in the sheep (Drs. Bland, Albertine, Carlton, and colleagues (4)).

Our first focus is on inflammation, including antenatal inflammation (e.g., chorioamnionitis), and ongoing postnatal inflammation, and inflammation related to infection. Drs. Jobe, Ikegami, Kallapur, Kramer and colleagues have made significant contributions with their studies of inflammation and its effects on the preterm lung. Human clinical studies, such as that by Viscardi and colleagues (5), have also corroborated the concept that early inflammation is an independent risk factor for BPD. Multiple previous studies found an association of proinflammatory cytokines in tracheal aspirates with the subsequent development of BPD; herein we discuss a recent one by Baier and colleagues. As we develop better tools for use in human infant samples (for



solidly designed, randomized controlled trials focusing on the everyday questions we face in the NICU: appropriate targets for pO₂ / oxygen saturation and carbon dioxide levels; methods of supporting respiration; optimal nutrition; favorable environmental influences; ways to decrease infection and to control inflammation; etc. As we are all aware, there is still much work to be done to prevent and ameliorate this important disease.

1. Northway, W.H., Jr., R.C. Rosan, and D.Y. Porter. [Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia.](#) New England Journal of Medicine 1967;276(7): p. 357-68.
2. Dennery, P.A. [Role of redox in fetal development and neonatal diseases.](#) Antioxidants & Redox Signaling 2004;6(1): p. 147-53.
3. Coalson, J.J., V. Winter, and R.A. deLemos. [Decreased alveolarization in baboon survivors with bronchopulmonary dysplasia.](#) American Journal of Respiratory & Critical Care Medicine 1995;152(2): p. 640-6.
4. Albertine, K.H., G.P. Jones, B.C. Starcher, J.F. Bohnsack, P.L. Davis, S.C. Cho, D.P. Carlton, and R.D. Bland. [Chronic lung injury in preterm lambs. Disordered respiratory tract development.](#) American Journal of Respiratory & Critical Care Medicine 1999;159(3): p. 945-58.
5. Viscardi, R.M., C.K. Muhumuza, A. Rodriguez, K.D. Fairchild, C.C. Sun, G.W. Gross, A.B. Campbell, P.D. Wilson, L. Hester, and J.D. Hasday. [Inflammatory markers in intrauterine and fetal blood and cerebrospinal fluid compartments are associated with adverse pulmonary and neurologic outcomes in preterm infants.](#) Pediatric Research 2004;55(6): p. 1009-17.
6. Warner, B.B., L.A. Stuart, R.A. Papes, and J.R. Wispe. [Functional and pathological effects of prolonged hyperoxia in neonatal mice.](#) American Journal of Physiology 1998;275(1 Pt 1): p. L110-7.
7. Veness-Meehan, K.A., D.N. Rhodes, and A.D. Stiles. [Temporal and spatial expression of biglycan in chronic oxygen-induced lung injury.](#) American Journal of Respiratory Cell & Molecular Biology 1994;11(5): p. 509-16.
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INFLAMMATIONA MAJOR PLAYER IN BPD PATHOGENESIS

Baier RJ, Abdul Majid, Parupia H, Loggins J, and Kruger TE.
CC chemokine concentrations increase in respiratory distress syndrome and correlate with development of bronchopulmonary dysplasia.

Pediatr Pulmonol.2004; 37:137-148.

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Young KC, Del Moral T, Claire N, Vanbuskirk S, Bancalari E.
The association between early tracheal colonization and

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bronchopulmonary dysplasia.

J Perinatol. 2005 Jun;25(6):403-7.

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Kallpur SG, Bachurski CJ, Le Cras TD, Joshi SN, Ikegami Machiko, and Jobe AH.

Vascular changes after intra-amniotic endotoxin in preterm lamb lungs.

Am J Physiol Cell Mol Physiol, 2004; 287:1178-1185.

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Examining the role early inflammation may play in the pathophysiology of the disease

Premature infants are exposed to systemic and lung inflammation *in utero* (e.g., chorioamnionitis, ureaplasma), and postnatally during times of infection and systemic illness. A number of studies have examined the role of early inflammation by measuring proinflammatory cytokines in tracheal aspirates and there is evidence that inflammation and tracheal elevations in proinflammatory cytokines are associated with future and concurrent BPD. Earlier studies of the role of cytokines in BPD focused on the role of proinflammatory cytokines including interleukin-1 β (IL-1 β), tumor necrosis factor α (TNF- α) and IL-6, and the neutrophil chemotactic chemokine, IL-8. Neutrophil influx into the lung occurs early in respiratory distress syndrome (RDS). However the alveolar macrophage plays a central role shortly thereafter in RDS, as well as in animal models of lung fibrosis.

Migration to the lung and activation of macrophages is mediated largely through the action of proinflammatory cytokines called CC chemokines (chemotactic cytokines). Chemokines are classified into 4 families (C, CC, CXC, and CX3C) according to the number and spacing of cysteine residues. Baier *et al.* studied whether CC chemokine family members increase in the tracheal aspirates obtained from mechanically ventilated preterm infants during the first 3 weeks of life.

The study population consisted of 56 preterm babies with birth weight <1500 g, who were mechanically ventilated, had a radiologic diagnosis of RDS, and survived to 28 days. Serial tracheal aspirates (TA) were obtained daily for the first 21 days of life for as long as the infant remained on mechanical ventilation. The concentrations of different CC chemokines were measured using ELISA assays, and normalized to the secretory component of IgA. Routine bacterial cultures were performed on tracheal aspirates collected in the first 24h. Cultures for both mycoplasma huminis (Mh) and ureaplasma urealyticum (Uu) were performed on admission and repeated two times during the first week of life if the infant remained intubated. Placental inflammation was considered present if the pathologist's report indicated the presence of histologic inflammation of fetal membranes.

The mean gestational age and birth weight of the study population were 26.8 weeks and 917g. TA cultures obtained during the first few days of life grew Uu on at least one occasion from 23 (41%) and Mh from 3 (5%) infants. Thirty of 56 (54%) infants studied were oxygen dependent at 28 days ("BPD28"), and 14 (25%) were oxygen dependent at 36 weeks corrected gestational age ("BPD36"). Oxygen dependent infants were smaller and of lower gestational age, were more often treated with postnatal steroids, and were more likely to have pulmonary hemorrhage. BPD28 infants were more likely to have a TA culture positive for Uu (but not BPD36 infants). TA concentrations of most CC chemokines increased significantly over time during the course of RDS, although the pattern varied for different chemokines. Early on, CC chemokine concentrations were similar in BPD and non-BPD infants, but there was a greater subsequent rise in levels in BPD28 infants. The maximum TA CC chemokine level for each chemokine studied was associated with BPD28, and maximal TA concentrations of all chemokines studied were also higher in BPD36 infants although only two were statistically significant. This study demonstrates that increased production of CC chemokines is associated with later BPD suggesting that this family of chemokines, in addition to previously described inflammatory mediators, may play an important role in the development of BPD in premature newborns.

Young and colleagues studied 308 infants with birth weight 500 to 1000 grams who were intubated by day 1 to examine the correlations among chorioamnionitis, initial tracheal aspirate culture results and BPD (oxygen requirement at 28 days, "BPD28," and at 36 weeks gestation, "BPD36"). They found that there was an association between chorioamnionitis and both BPD28 ($p=0.05$) and BPD36 ($p=0.008$). The infants who had chorioamnionitis were significantly more likely to have a positive initial tracheal culture, although the association between a positive initial tracheal culture and BPD did not reach statistical significance. However, this association was highly significant in the subgroup of infants born at 700-1000g, with 61% of initial tracheal culture positive infants going on to develop BPD28 compared to 39% of non-colonized infants. Again, this study adds credence to the concept of early inflammation being a "setup" for BPD.

Kallapur et al addressed this important question: does exposure to antenatal inflammation alone, without exposure to mechanical ventilation or oxygen toxicity, cause pulmonary vascular changes and remodeling similar to that seen in BPD? This would add another mechanism by which inflammation contributes to the development of BPD. The authors hypothesized that intraamniotic (IA) endotoxin would inhibit expression of proteins critical for endothelial function followed by vascular remodeling in preterm lung.

Pregnant ewes at 118 days gestation (term 150 days) were given IA injections of saline (control) or endotoxin, and preterm lambs delivered at 119-125 days gestation. mRNA and / or protein levels for molecules important in vascular development, including VEGF, PECAM-1 (platelet endothelial cell adhesion molecule-1) and endothelial NOS (nitric oxide synthase) were determined. Vascular morphology, including measurements of arteriolar wall thickness, thickness of muscularis media, area of smooth muscle, and adventitial fibrosis with quantitative scoring were performed.

The cord blood hematocrit, pO_2 , pCO_2 , and pH were similar between control and endotoxin-exposed preterm lambs. Whole lung e-NOS protein was decreased after intra-amniotic endotoxin with a maximum decrease at day 4 and e-NOS expression appeared to be selectively reduced in the small pulmonary arteries compared with large conducting vessels. IA endotoxin also decreased VEGF mRNA and protein, as well as PECAM-1 and receptors for VEGF and other angiogenic factors. Increased arteriolar smooth muscle thickness, along with increased adventitial layer fibrosis and cellularity, were also observed after endotoxin injection. These data support the hypothesis that antenatal inflammation alone decreases vascular-related proteins. The vascular changes induced by fetal lung inflammation may contribute to decreased alveolarization. This study offers one possible mechanism to explain the association between antenatal inflammation (chorioamnionitis) and BPD observed in clinical studies.

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THE ALVEOLAR-CAPILLARY UNIT ... WHAT HAPPENS IN BPD?

Bhatt AJ, Pryhuber GS, Huyck H, Watkins RH, Metlay LA, and Maniscalco WM

Disrupted pulmonary vasculature and decreased vascular endothelial growth factor, Flt-1, and TIE-2 in human infants dying with bronchopulmonary dysplasia.

Am J Respir Crit Care Med 2001, 164:1971-1980.

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Van Tuyl M, Liu J, wang J, Kuliszewski M, Tibboel D, and Post M.

Role of oxygen and vascular development in epithelial branching morphogenesis of the developing mouse lung.

Am J Physiol Cell Mol Physiol 2005, 288:L167-L178.

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Kunig AM, Balasubramaniam V, Markham NE, Morgan D, Montgomery C, Craver TB, Akbar SH

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Montgomery G, Grover TK, Adman SM.

Recombinant human VEGF treatment enhances alveolarization after hyperoxic lung injury in neonatal rats.

Am J Physiol Lung Cell Molec Biol, in press.

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Thebaud B, Ladha F, Michelakis E, Moudgil R, Dyck J, Eaton F, Hashimoto K, Harry G, Archer SL.

VEGF gene therapy increases survival, promotes lung angiogenesis and prevents alveolar damage in hyperoxia-induced lung injury: Evidence that angiogenesis participates in alveolarization.

Circulation, in press.

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Studying the associated vascular abnormalities seen in impaired alveolarization

Impaired alveolarization and capillary development are hallmarks of BPD. Although there have been many significant studies with a focus on impaired alveolarization, more attention has recently been paid to the associated abnormalities seen in the vasculature. *Bhatt et al* studied autopsied human infant lung for a marker of endothelial cells (platelet endothelial cell adhesion molecule-1, PECAM-1), and for VEGF and its receptors. The objective was to demonstrate the relationship between abnormal vascularization and possible abnormal expression of angiogenic growth factors or their receptors in the setting of chronic lung disease in premature infants. Lung samples were obtained at autopsy from infants with BPD (n = 5) and from "control" term or near term patients dying without lung disease (n = 5).

The patients with no lung disease (NLD group) were significantly more mature at birth than the BPD group. While the chronologic age at death was significantly greater in the BPD group, there was no difference in the post conceptional age at death, suggesting that the potential lung developmental stages at death were similar. Compared with infants in the NLD group, babies with BPD had decreased PECAM-1 immunostaining and the alveolar capillaries were frequently noted in thickened alveolar septa. PECAM-1 protein and mRNA in whole lung were significantly decreased in the BPD group compared to NLD group, suggesting a possible decrease in the relative number of endothelial cells in the patients with BPD. Furthermore, the mRNAs for the angiogenic growth factor VEGF and its receptor were also decreased in BPD patients. This study suggests that infants dying with BPD may have disrupted alveolar vascular development, and that these abnormalities may result from impaired expression of VEGF and angiogenic endothelial receptors.

The work of *Van Tuyl et al* adds additional insight to the understanding of the epithelial-vascular interaction and the importance of the fetal hypoxic state for lung development. In their elegant experiments, they used genetically engineered mice that expressed a "reporter" gene exclusively in either endothelial or epithelial cells, such that cells expressing the reporter gene could be analyzed by specific staining. Explants of embryonic lungs were maintained in an atmosphere of either 3% O₂ or 20% O₂ and the production of hypoxia-inducible factor (HIF-1 α), an important regulator of VEGF, and VEGF itself were also able to be blocked.

In this lung explant model, exposure to low oxygen (3% O₂) enhanced both epithelial branching morphogenesis and vascular development compared to 20% O₂, with more complex epithelial and vascular branching. Explants cultured in 3% O₂ also had increased expression of a specific marker for alveolar type II cells, suggesting maintenance of appropriate epithelial differentiation. The increase in vascularization in explants cultured at 3% was associated with greater PECAM-1 expression, again confirming that low oxygen stimulates vascular development in embryonic lung explants. VEGF mRNA was also dramatically increased in explants exposed to 3% O₂. Critical to the discussion of impaired alveolarization being associated with impaired vascularization, blockage of HIF-1 α as well as VEGF production resulted in a marked decrease in vascular development in the explants with large areas devoid of vessels and this was accompanied by decreased branching morphogenesis. This effect was significantly ameliorated by addition of

recombinant VEGF to lung explant cultures. Finally, blockage of VEGF production was associated with complete abrogation of epithelial branching morphogenesis in explants exposed to 20% O₂, although the effect was less in explants exposed to 3% O₂. This study lends credence to the current concept that even room air (21% O₂) is likely toxic to the developing lung and that this "relative hyperoxia" inhibits both pulmonary vascular development and epithelial branching morphogenesis, suggesting caution should be used in determining appropriate saturation targets for premature infants.

Two exciting studies specifically examining the effect of VEGF on alveolarization are "in press." *Kunig et al* exposed two day old rat pups to 75% O₂ or room air for 12 days. Both groups were then exposed to room air, and treated with a form of VEGF or normal saline from days 14 to 22. Careful morphometric analysis demonstrated that hyperoxia resulted in findings of decreased alveolarization and vessel density, despite an 8 day recovery period in room air. VEGF treatment after hyperoxia ameliorated these findings. The results caused the authors to speculate that "persistent abnormalities of lung structure after hyperoxia may be partly due to impaired VEGF signaling."

Thebaud et al exposed neonatal rats to 95% O₂ from birth (PAS meeting 2004). The VEGF receptor was blocked by subcutaneous injection of a VEGF trap at day 4, 7 and 10. At 15 days, morphometric studies demonstrated that VEGF-trap decreased lung VEGF and VEGF receptor 2 and led to enlargement of the air spaces and loss of lung capillaries, mimicking BPD. In hyperoxia-exposed rats there was air space enlargement and loss of lung capillaries, associated with decreased lung VEGF and VEGFR-2. *In vivo* intratracheal gene transfer of a form of VEGF at day 4 using a viral vector increased lung capillary growth and improved alveolarization. Again, these authors suggest that "VEGF-driven angiogenesis promotes alveolar development." These elegant studies are generating ideas for the next generation of treatment and prevention of BPD.

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"HIGH RISK TO DEVELOP SEVERE BPD" -- CAN WE TELL FROM THE GENETIC MAP?

Kazzi SN, Kim UO, Queasney MW, and Buhimschi I.
Polymorphism of tumor necrosis factor and risk and severity of bronchopulmonary dysplasia among very low birth weight infants.

Pediatrics. 2004; 114(2).

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Rova M, Haataja R, Marttila R, Ollikainen V, Tammela O, and Hallman M.

Data mining and multiparameter analysis of lung surfactant protein genes in bronchopulmonary dysplasia.

Hum Mol Genet.2004;13: 1095-1104.

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Haataja R, Rova M, Marttila R, Hallman M, Oulu, Seinajoki.
TDT analysis of surfactant protein B gene intron 4 deletion variants in Finnish infants with Bronchopulmonary dysplasia.

Proc Am Thoracic Soc 2005; 2: A24.

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Reporting on new developments on the role of genetic factors in the pathophysiology of BPD

Certain infants develop severe BPD despite exposure to the same clinical risk factors and treatments as infants who do not develop BPD. The role of genetic factors in the development of this disease is emerging. Inflammation plays an important role in the

pathogenesis of BPD, and one of the earliest proinflammatory cytokines produced during an inflammatory response is tumor necrosis factor- α (TNF- α). TNF- α triggers the release of secondary mediators of inflammation, such as interleukin-1 and interleukin-6, as well as of itself. Frequently occurring DNA sequence variants (polymorphisms) within the TNF- α gene have been identified, and several have been associated with increased levels of TNF- α . The objective of the study by *Kazzi et al* was to examine the effect of three such polymorphisms involving the presence of either adenine (A) or guanine (G) in the TNF- α (TNF- α -238, TNF- α -308) or TNF- β (LT- α +250, also known as lymphotoxin, LT) genes on the development and severity of BPD among very low birth weight (VLBW) infants.

Preterm infants with a birth weight of ≤ 1250 g were genotyped for the TNF polymorphisms. Other variables examined included gestational age, severity of respiratory illness at the time of entry into the study, diagnosis of patent ductus arteriosus, pneumonia, late onset sepsis, and necrotizing enterocolitis. The definition and severity of BPD among surviving infants were as described by Jobe and Bancalari: oxygen therapy used for at least 28 days and severity based on status at 36 weeks or at discharge, whichever came first: 1) mild BPD: infant breathing room air at 36 weeks; 2) moderate BPD: infant requiring $< 30\%$ oxygen at 36 weeks; 3) severe BPD: infant required $> 30\%$ supplemental oxygen and/or positive pressure therapy at 36 weeks.

A total of 154 infants were enrolled; 120 infants survived to 36 weeks gestational age. Infants who developed BPD had a lower birth weight and younger gestational age, were likely to have been exposed to prenatal corticosteroids, to have prolonged rupture of fetal membranes (>18 h), and to have an Apgar score at 5 minutes of ≤ 5 . In this population, there were no associations between BPD and the alleles LT- α +250 or TNF- α -308. However, infants with BPD were significantly less likely to carry the TNF- α -238 AA or GA genotype, compared with infants without BPD. None of the infants with BPD carried the TNF- α -238 AA genotype, compared with 3% of infants without BPD, and only 2% of infants with BPD carried the GA TNF- α -238 genotype, compared with 14% of infants without BPD. Examining the severity of BPD, none of the infants

American Thoracic Society meeting in May 2005 utilizing the Transmission disequilibrium test (TDT) to evaluate the familial segregation of SP-B intron 4 alleles from parents to affected offspring. Eighty-seven Finnish father-mother-offspring trios with an affected baby of <32 weeks of gestation were included in the analysis. BPD was defined as the need for supplemental oxygen at least 28 days after birth. The SP-B intron 4 deletion variant allele frequency was significantly higher in the affected infants compared to the frequency of parental non-transmitted alleles ($P = 0.025$). The deletion variant allele showed significantly increased transmission to affected offspring, compared to the other SP-B intron 4 alleles. There was no paternal or maternal preference in transmission of the risk allele. These results support the previous finding of this SP-B intron 4 deletion variant as a risk factor predisposing to BPD. Genotypic analysis of VLBW infants at risk of developing BPD may provide clinicians with a useful tool of targeting preventative therapies in the future.

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Learning Objectives · [back to top](#)

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- Discuss the recent contributions of inflammation to the pathogenesis of bronchopulmonary dysplasia
- Describe the fundamental connection between lung development and bronchopulmonary dysplasia
- Identify the exciting developments in the area of genetic associations and bronchopulmonary dysplasia

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Hopkins Nursing to require the disclosure of the existence of any significant financial interest or any other relationship a faculty member or a provider has with the manufacturer(s) of any commercial product(s) discussed in an education presentation. The presenting faculty reported the following:

- Dr. Noguee has indicated a financial relationship of grant/research support with Forest Laboratories and has received an honorarium from Forest Laboratories.
- Dr. Lawson has indicated a financial relationship of grant/research support from the NIH. He also receives financial/material support from Nature Publishing Group as the Editor of the Journal of Perinatology.

All other faculty have indicated that they have not received financial support for consultation, research, or evaluation, nor have financial interests relevant to this e-Newsletter.

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