



### March 2008: VOLUME 5, NUMBER 7

#### *BPD and Inflammation*

#### In this Issue...

Bronchopulmonary dysplasia (BPD) is a major cause of morbidity and mortality in preterm infants and results from a variety of insults.<sup>1</sup> While previous issues of *eNeonatal Review* have discussed antioxidants and other novel treatments for BPD (June 2007), and the etiology of BPD (August 2005), inflammation as an important contributor to BPD<sup>2,3</sup> has not been specifically addressed. The preterm infant at risk for BPD is exposed to inflammatory stimuli in the antenatal period (chorioamnionitis), at birth (resuscitation), and postnatally (mechanical ventilation, oxygen, infections). Thus, a concept of exposure to continuous inflammation of varying intensity and duration as one of the determinants of BPD has emerged.<sup>4</sup> An equally important but understudied aspect of inflammation is the host response. Although little is known of the fetus or preterm's innate or acquired immune responses, recent studies shed light on how their immune system is modulated in response to different inflammatory stimuli.

In this issue, we review clinical/epidemiological studies and animal experiments pertaining to *Ureaplasma* chorioamnionitis, compare mechanical ventilation versus CPAP during resuscitation, and discuss the modulation of the innate immune system, as well as the adaptive immunity, in preterm animal models of BPD.



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- 1.0 hours Physicians
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### ***Guest Faculty Disclosure***

**Dr. Kallapur** has disclosed that he has received grants or research support from Merck & Co.

**Dr. Hillman** has disclosed no relevant financial relationships.

### ***Unlabeled/Unapproved Uses***

The authors have indicated that there will be no reference to unlabeled/unapproved uses of drugs or products in the presentation.

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## LEARNING OBJECTIVES

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

- Describe to colleagues how the different modalities of respiratory support impact the incidence of BPD in preterm infants
- Discuss with colleagues the contribution of antenatal inflammation to BPD
- Explain to colleagues the changes in immune function in preterm animals exposed to an inflammatory stimulus

## MARCH PODCAST



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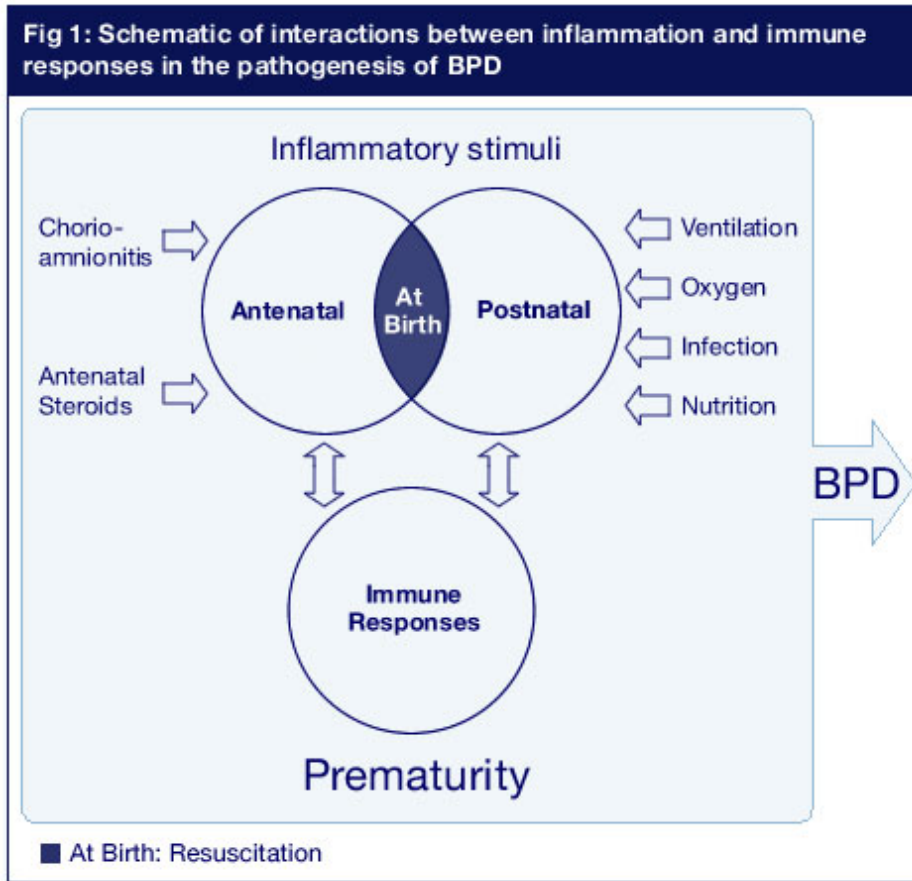
## COMMENTARY

Although inflammation is widely accepted as a major contributing factor in the development of BPD, the clinical studies are confusing. For example, earlier studies reported an increased association of BPD with chorioamnionitis,<sup>5,6</sup> but more recent articles do not show a clear association.<sup>7,8</sup> These discrepancies may partly be due to the different patient populations in the different studies. Previous studies had documented the presence of bacterial products in the chorioamnion of a majority of preterm infants,<sup>9,10,11</sup> but less than 2% of these infants had positive blood cultures soon after birth.<sup>12</sup> However, Goldenberg et al (reviewed in this issue) reported the astounding observation that nearly 25% of preterm infants, less than 32 weeks gestation, were cord blood culture-positive for *Ureaplasma* or *Mycoplasma* species.<sup>13</sup> Interestingly, in the same series of neonates from Alabama, while histologic chorioamnionitis did not correlate with BPD, infants with a positive cord blood culture for *Ureaplasma* or *Mycoplasma* had an increased incidence of BPD. Therefore, there may be subsets of patients exposed to chorioamnionitis at a greater risk for BPD than others.

Other variables in the development of injury responses in the preterm neonate are the differences in the immune responses to inflammatory stimuli. Using a preterm sheep model of lipopolysaccharide (LPS) induced chorioamnionitis, Kallapur et al (reviewed in this issue) report that: a) chorioamnionitis "matured" the normally immature fetal monocytes, making them responsive to LPS; and b) while a single exposure to LPS caused lung and systemic inflammation, repeated exposures to intra-amniotic LPS blunted inflammatory responses, consistent with tolerance to endotoxin (LPS). While endotoxin tolerance may blunt injury responses, it may also increase the risk for nosocomial sepsis and death, as has been reported in adult patients in an intensive care setting.<sup>14</sup> Therefore, both positive and negative



modulation of innate immunity can result from exposure to inflammatory stimuli, and immune responses can, in turn, influence inflammation and injury responses. This interaction is visualized below:



In an elegant study in preterm baboons developing BPD, Rosen et al (reviewed in this issue) documented precocious maturation of thymic cells and development of auto-reactive T-cells. Interestingly, treatment with an antibody against bombesin-like peptide reversed these T-cell changes and decreased BPD.<sup>15,16</sup> Clinical studies aimed at understanding the role of immune alterations in preterm infants at risk for BPD are sorely needed.

Mechanical ventilation and resuscitation injury are important factors in the pathogenesis of lung inflammation and BPD.<sup>7,17</sup> Centers with liberal use of nasal continuous positive airway pressure (nCPAP) rather than mechanical ventilation have a lower incidence of BPD.<sup>18</sup> Therefore, the results of the first large randomized study evaluating these modalities was keenly awaited. Morley et al<sup>19</sup> (reviewed in this issue), report that preterm infants randomized to nCPAP or mechanical ventilation had an equivalent incidence of BPD or death. While the infants randomized to nCPAP had increased incidence of pneumothorax, they had less oxygen use.

Despite many studies, so far only vitamin A<sup>20</sup> and caffeine<sup>21</sup> have been shown to reduce BPD in large clinical trials. The role for routine use of iNO to reduce BPD is being evaluated. Presently, using either nasal CPAP or intubation followed by early extubation are both acceptable treatment choices for the initial management of the preterm infant. The COIN trial demonstrated that use of nasal CPAP is safe and feasible.

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## UMBILICAL CORD BLOOD *UREAPLASMA UREALYTICUM* AND *MYCOPLASMA HOMINIS* CULTURES IN VERY PRETERM NEWBORN INFANTS

Goldenberg RL, Andrews WW, Goepfert AR, et al. **The Alabama Preterm Birth Study: umbilical cord blood *Ureaplasma urealyticum* and *Mycoplasma hominis* cultures in very preterm newborn infants.** *Am J Obstet Gynecol.* 2008;198(1):43.e1-5.

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*Ureaplasma urealyticum* and *Mycoplasma hominis* are among the most frequently isolated organisms from both placental and amniotic fluid in women with chorioamnionitis. In this study, the authors investigated the previously unexplored incidence of positive cord blood cultures for these organisms in preterm infants exposed to chorioamnionitis, and correlated culture status to infant outcome. The infants studied were a subset (351 out of 457 consecutive deliveries) of premature deliveries between 23 and 32 weeks' gestation born in Alabama between 1996 and 2001. Systemic inflammatory response syndrome (SIRS) was defined as clinically suspected sepsis or a band:band+ polymorphonuclear cell ratio of  $\geq 0.15$  in the absence of positive cerebral spinal fluid (CSF) or blood culture.

The investigators found a positive cord blood culture for *U urealyticum* or *M hominis* (or both) present in 23.4% of the preterm infants. Non-white women, women less than 20 years old, and women with spontaneous (vs indicated) deliveries were at increased risk for having positive cultures. Elevated cord IL-6 levels were associated with positive cultures for *U urealyticum* or *M hominis* (OR 5.62, CI 3.82-10.78  $p < 0.001$ ), neonatal SIRS (41.3% vs 25.7%  $p = 0.007$ ), and BPD (26.8% vs 10.1%  $p = 0.001$ ). After adjusting for confounding variables such as gestational age, sex, race, etc, the association between positive cultures and SIRS remained, but that of positive culture and BPD became marginally significant ( $p = 0.087$ ). Positive blood cultures were not associated with increased risk of respiratory distress syndrome, necrotizing enterocolitis, periventricular leukomalacia (PVL), intraventricular hemorrhage, or death. Extremely premature infants (23 to 24 wk gestation) were more than twice as likely to have positive cultures compared with infants with gestational ages of 29 to 32 weeks (44% vs 19%).

This study shows the presence of *U urealyticum* or *M hominis* in the cord bloods of a surprisingly large number of premature infants, and demonstrates a link between the presence of antenatal *Ureaplasma* chorioamnionitis, SIRS, and BPD. Previous studies may have underestimated the incidence of bacteremia with mycoplasma species in preterm infants, since these organisms require specialized culture techniques. Although the precise implication of a large incidence of bacteremia that is assumed to be transient is not known, the study clearly points out that there are subsets of infants with chorioamnionitis in whom outcomes may be different. The authors question whether antibiotics that treat these organisms may have an effect on subsequent neonatal morbidity and mortality.

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# ENDOTOXIN TOLERANCE IN PRETERM FETAL SHEEP EXPOSED TO CHORIOAMNIONITIS

Kallapur SG, Jobe AH, Ball MK, et al. **Pulmonary and systemic endotoxin tolerance in preterm fetal sheep exposed to chorioamnionitis.** *J Immunol.* 2007;179(12):8491-8499.

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About 70% of preterm deliveries less than 30 weeks gestation are exposed to chorioamnionitis, and about 50% of these exposed infants have a systemic inflammatory response. Despite the large number of infants being exposed to inflammation in utero, often for long periods, many of these infants appear clinically normal. The authors used a fetal sheep model of chorioamnionitis with intra-amniotic injection of lipopolysaccharide (LPS). They had previously showed that intra-amniotic LPS directly contacted the fetal lung and caused inflammatory cell influx and expression of inflammatory cytokines.<sup>1</sup> A single injection of LPS in the fetal sheep caused structural changes in the fetal lung resembling BPD. However, in fetal lambs exposed to repeated LPS injections, the lung morphology at term was indistinguishable from controls. The authors hypothesized that repeat intra-amniotic injection of LPS in fetal sheep caused endotoxin tolerance. Endotoxin tolerance denotes a blunted response to a challenge dose of endotoxin (LPS) after a priming endotoxin dose.

Intra-amniotic injections of LPS were given as follows: a single injection at either 2 days, 7 days, or two injections 2 & 7 days prior to delivery at 125 days gestation (term=150 days). Inflammation was assessed in the lung and the systemic tissues. Exposure to a single injection of LPS induced maturation of monocytes, such that they had increased secretion of IL-6 in response to *in vitro* LPS challenge. In response to a single dose of LPS, lung inflammation was detected by: 1) increased BAL cells, 2) expression of iNOS (NOSII - an activation marker in lung inflammatory cells) and 3) increased expression of cytokines IL-1 $\beta$  and IL-8 in the lungs. Interestingly, lambs exposed to 2 injections of LPS had decreased iNOS staining and decreased induction of IL-1 $\beta$  and IL-8 compared with the single LPS injection group. A single intra-amniotic injection of LPS caused induction of serum amyloid A3 (SAA3 - an acute phase reactant), but repeat LPS exposure caused decreased SAA3 expression, demonstrating a decreased systemic response to repeated exposures to intra-amniotic LPS. The authors confirmed the *in vivo* findings of endotoxin tolerance with *in vitro* challenge of isolated lung and blood monocytes. Monocytes isolated from animals exposed to LPS 7 days prior to delivery responded to LPS *in vitro* with increased IL-6 and H<sub>2</sub>O<sub>2</sub> production. Monocytes from animals exposed to repeat LPS injections failed to increase these markers. These results show decreased lung and systemic inflammatory responses to repeat injections of LPS, consistent with endotoxin tolerance.

This translational study importantly demonstrates that exposure to LPS can modulate the innate immune system of a preterm fetus. The fetal consequences of exposure to LPS can be a positive modulation (maturation of monocytes) or a negative modulation (endotoxin tolerance). In preterm infants, chronic or repeat exposure to Gram-negative bacterial chorioamnionitis may limit the lung and systemic injury responses, thus benefiting the infant. However, endotoxin tolerance may also be deleterious, since impaired innate immune host responses to invading pathogens may increase the risk of infection.

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## ACCELERATED THYMIC MATURATION AND AUTOREACTIVE T-CELLS IN BPD

Rosen D, Lee JH, Cuttitta F, Rafiqi F, Degan S, Sunday ME. **Accelerated thymic maturation and autoreactive T cells in bronchopulmonary dysplasia.** *Am J Respir Crit Care Med.* 2006;174(1):75-83. Epub 2006 Mar 30.

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Preterm, 125 day gestation, baboons (term= 180 days) exposed to PRN (as needed) oxygen and mechanical ventilation for 14 to 21 days develop bronchopulmonary dysplasia (BPD) similar to preterm infants. Both premature infants with BPD and baboons with BPD have increased pulmonary neuroendocrine cells containing bombesin-like peptides (BLP) and increased urinary BLP levels. Although clinical observations have suggested a role for the thymus in the development of BPD, adaptive immune changes in BPD are unstudied. The authors hypothesized that thymic architecture and T-cell function are altered in baboons with BPD. Using immunostaining, they studied thymic cell subsets: immature thymocytes (terminal deoxynucleotidyl transferase<sup>+</sup>), T-helper cells (CD4+), cytotoxic T-cells (CD8+), and nurse cells (thymic epithelial cells important in negative selection) in baboons exposed to PRN oxygen for 14 days (14dPRN) or 21 days (21dPRN) with or without the blocking anti-BLP antibody (2A11).

Compared with gestational matched unventilated controls, the 14dPRN and 21dPRN baboons with BPD had the following thymic alterations: a) decreased thymic cortical volume, b) decreased numbers of immature prothymocytes, c) decreased numbers of nurse cells, and d) increased numbers of mature T-cells subsets with CD4+ or CD8+ expression. These changes demonstrate that precocious maturation of thymic cells are associated with BPD. Interestingly, the authors demonstrated that the 14dPRN or 21dPRN baboons treated with anti-BLP antibody 2A11, but not a control immunoglobulin, reversed these changes. In another study,<sup>1</sup> the authors demonstrated that 2A11 blocked the development of BPD in baboons. Furthermore, the mature T-cells in ventilated baboons were autoreactive and increased numbers of CD4+ cells were seen in the lungs. Treatment with 2A11 also ameliorated these changes.

This translational study provides insight into understanding the adaptive immune changes in BPD. The authors concluded that blocking the BLP activity protected the lung by promoting normal thymic development and decreased precocious thymic maturation and the development of auto-reactive T-cells. It will be important to study if similar changes occur in preterm infants developing BPD.

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# NASAL CPAP OR INTUBATION FOR VERY PRETERM INFANTS AT BIRTH

Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB, for the COIN trial Collaborators. **Nasal CPAP or intubation for the very preterm infants at birth: The COIN trial.** *N Engl J Med.* 2008;358:700-708.

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Bronchopulmonary dysplasia (BPD) has been associated with ventilation and oxygen treatment. This is the first of three studies (COIN, SUPPORT, Vermont Oxford Delivery Room) to report the use of nasal continuous positive airway pressure (nCPAP) versus intubation in premature infants (the other two studies are still enrolling subjects). The COIN investigators hypothesized that the use of nCPAP, instead of intubation and ventilation, would reduce the rate of death or BPD. This multinational, randomized, unmasked controlled trial compared the use of nCPAP or intubation in infants (n=610) born between 25 weeks 0 days and 28 weeks 6 days. Consent was antenatal but enrollment was postnatal. Preterm infants spontaneously breathing and needing respiratory support were randomized to nCPAP or intubation at 5 minutes of life. Infants needing intubation in the first 5 minutes were excluded, as were infants in no respiratory distress. nCPAP was started at 8 cmH<sub>2</sub>O and subsequently the pressure was changed as needed. Infants in the nCPAP arm were intubated if they had any one of the following: apnea not responsive to stimulation and methylnanthine (>6 episodes requiring stimulation in 6 hours or >1 episode of positive pressure ventilation), arterial pH <7.25 with a PaCO<sub>2</sub> > 60 mmHg, metabolic acidosis unresponsive to treatment, or needing an FiO<sub>2</sub> >0.60. The use of surfactant or criteria for extubation were not mandated. BPD was defined based on oxygen treatment at 36 weeks' gestation.

The primary outcome of death or oxygen requirement at 36 weeks was not different between intervention groups, with the unadjusted odds ratio of 0.80 (95% CI 0.58 to 1.12, p=0.12) in favor of nCPAP. At 36 weeks, only 8.8% in the intubated group and 9.4% in the nCPAP group required greater than 0.30 FiO<sub>2</sub>, and only 1.3% in the nCPAP group and 1.4% in the intubated group were receiving ventilation or CPAP at this time. At 28 days, nCPAP did show a decreased rate of death or oxygen treatment, OR 0.63 (95% CI 0.46 to 0.88, p=0.006), but this advantage disappeared by 36 weeks' gestation. The intubation rate for the nCPAP treatment was 46%, with 55% at 25 or 26 weeks and 40% at 27 or 28 weeks. The reasons noted for intubations were: FiO<sub>2</sub> >0.60 (53%), PaCO<sub>2</sub> > 60 mmHg (41%), apnea episodes (38%), and metabolic acidosis unresponsive to treatment (21%) (some patients had multiple reasons cited). Surfactant use was halved in nCPAP groups, and infants randomized to nCPAP received significantly less days of ventilation (median 3 days vs 4 days), even though the pneumothorax rates were higher (9% vs 3%).

The authors concluded that there are no differences in outcome of death or BPD between treatment groups, but that starting early nCPAP in the very preterm was not detrimental. No differences were seen between groups in death, grade III or IV intraventricular hemorrhage, PVL, BPD, or other co-morbidities. Limitations of the study included exclusion of sick infants requiring initial intubation and exclusion of outborn infants. BPD is a complex disease and the early use of nCPAP, compared with intubation, did not alter the occurrence of the disease.

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## Learning Objectives — [back to top](#)

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

- Describe to colleagues how the different modalities of respiratory support impact the incidence of BPD in preterm infants
- Discuss with colleagues the contribution of antenatal inflammation to BPD
- Explain to colleagues the changes in immune function in preterm animals exposed to an inflammatory stimulus

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