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Antioxidants and Other Novel Treatments for BPD

This month eNeonatal Review is unveiling our new look as well as several new features:

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In This Issue...

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that primarily affects premature infants who are treated with supplemental oxygen and ventilatory support for a primary respiratory disorder^[1-4], and is primarily characterized by abnormalities of lung growth, including angiogenesis and alveolarization. Although multifactorial in origin, reactive oxygen species (ROS) from hyperoxia and inflammation, volutrauma, and genetic predisposition are thought to play important roles in the development of BPD^[3,5-9]. The condition is associated with significant long-term complications, including wheezing, asthma, repeated respiratory infections, and neurodevelopmental impairments. Recently, an NIH /FDA consensus panel reviewed pharmacologic interventions that need to be studied in very low birth weight (VLBW) infants^[10].

In this issue, we review novel therapeutic strategies for the prevention and treatment of BPD, including inhaled nitric oxide (iNO) directed at decreasing pulmonary vasoconstriction as well as ameliorating intrapulmonary and systemic inflammation, explorations into vitamin A, recombinant human superoxide dismutase (rhSOD), and anti-transforming growth factor beta (TGF-β) antibodies to specifically reduce the oxidant injury and inflammation associated with BPD.

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Edward F. Lawson, MD

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Edward E. Lawson, MD
Professor
Department of Pediatrics - Neonatology
The Johns Hopkins University
School of Medicine

Christoph U. Lehmann, MD
Assistant Professor
Department of Pediatrics - Neonatology
The Johns Hopkins University
School of Medicine

Lawrence M. Noguee, MD
Associate Professor
Department of Pediatrics - Neonatology
The Johns Hopkins University
School of Medicine

Mary Terhaar
Assistant Professor
Undergraduate Instruction
JHU School of Nursing

Robert J. Kopotic, MSN, RRT, FAARC
Director of Clinical Programs
ConMed Corporation

GUEST AUTHORS OF THE MONTH



Commentary & Reviews:
Jonathan M. Davis, MD
Professor of Pediatrics
Tufts University School of
Medicine
Chief of Newborn Medicine
Associate Director
Clinical Research Center
The Floating Hospital for
Children
Tufts – New England
Medical Center
Boston, MA

Guest Faculty Disclosure

No faculty member has indicated that they have received financial support for consultation, research or evaluation or has a financial interest relevant to this literature review.

Unlabeled / Unapproved Uses

The following faculty members have disclosed that their presentation will reference unlabeled/unapproved use of drugs or products:

Jonathan M. Davis, MD
Inhaled nitric oxide, caffeine



Commentary & Reviews:
Juliette C. Madan, MD, MS
Assistant Professor of
Pediatrics
Tufts University School of
Medicine
Assistant Pediatrician
Division of Newborn
Medicine
Tufts – New England
Medical Center
Boston, MA

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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 the scientific integrity of this CE activity.

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

- Discuss the uses of inhaled nitric oxide for the prevention of BPD
- Describe the uses of targeted antioxidant and anti-inflammatory therapies to prevent or treat BPD

- Explain the importance of long-term follow-up and evaluation of functional outcomes in determining the efficacy of treatments for BPD

COMMENTARY

Despite intensive study and multiple attempts to develop specific therapies to prevent or ameliorate BPD, little success has actually been achieved. Part of the difficulty involves the optimal definition of BPD. Current definitions include oxygen requirements at 36 weeks corrected gestational age (CGA), which may not adequately predict the later pulmonary and neurodevelopmental outcomes that are of greater importance. For instance, in a 1999 study, administration of vitamin A to VLBW infants was shown to result in a small but significant (7%) reduction in the incidence of BPD at 36 weeks CGA^[11]. However, Ambalavanan and colleagues (reviewed herein) followed these infants to 18-22 months CGA and were unable to demonstrate any improvements in clinical respiratory status from vitamin A. This is surprising in view of the extensive scientific data indicating that vitamin A protects the preterm lung from the damaging effects of hyperoxia and mechanical ventilation. In contrast, we demonstrated (study reviewed herein) that repeated doses of intratracheal recombinant human superoxide dismutase (rhSOD - an important antioxidant enzyme) administered to critically ill VLBW infants did not result in significant differences in pulmonary outcome at 36 weeks CGA (although severe ROP was markedly reduced). However, at one year corrected age, rhSOD-treated infants did show significant improvements in clinical pulmonary status, with the most dramatic changes seen in infants <27 weeks gestation).

While the beneficial effects of iNO have been established in full term infants with severe respiratory failure, its use in preterm infants is more controversial. Three recent trials studied different iNO intervention strategies (different dosing, timing, and duration of exposure) to prevent BPD (the Kinsella and Ballard trials are reviewed herein). However, each of these trials used a different definition of BPD (oxygen requirements at 36 weeks CGA, either alone or with/without a physiologic oxygen challenge test or radiographic criteria). A previous study was unable to demonstrate any beneficial effects of iNO in a population of seriously ill VLBW infants^[12], Kinsella and associates (using an early, low dose treatment component) demonstrated a significant reduction in BPD in larger infants, although iNO significantly reduced severe neurologic injury in the entire cohort. In contrast, Ballard and colleagues (using a later, higher dose treatment strategy) demonstrated a significant reduction in the incidence of BPD in their entire birth cohort, with infants enrolled between 7-14 days of age having a significantly better outcome than infants enrolled between 15-21 days. Although longer term outcome studies still need to be completed, it appears that the early use of low dose iNO may prevent severe brain injury, while higher doses started by one week of life may be efficacious in the prevention of BPD.

While caffeine is routine for treatment of apnea of prematurity, Schmidt and associates demonstrated that the early use of caffeine significantly reduced death or BPD in VLBW infants^[13] (a study reviewed in the October 2006 issue of [eNeonatal Review](#)). The long term follow-up from this trial will be of utmost importance in determining whether pulmonary and neurodevelopmental outcomes associated with caffeine are also significantly improved. Finally, multiple growth factors and cytokines affecting lung development are present in the fetal lung. This delicate balance may be significantly altered in response to preterm birth, infection, hyperoxia and mechanical ventilation. Nakanishi and colleagues (reviewed herein) administered anti-TGF- β to mice exposed to chronic hyperoxia (a model with similar characteristics to BPD) and found that these antibodies significantly reduced inflammation and lung injury while improving lung growth and clinical outcome. This important study demonstrates both the importance of TGF- β signaling in the pathogenesis of hyperoxic injury in the newborn lung and



its relationship to disrupted terminal lung development.

BPD continues to be an important cause of long-term pulmonary dysfunction in VLBW infants. While several therapies, both novel and more established, have the potential to significantly ameliorate this condition, we need to be cautious in our interpretation of preliminary data until longer-term results are available (e.g., wheezing, asthma, respiratory infections, hospitalizations). This is especially true since these studies employed a slightly different definition of BPD (defined above) and 36 weeks CGA represents just a single moment in time. While we need to revisit these studies to more fully understand the efficacy of some treatments, there is justifiable optimism regarding future development of others.

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EARLY INO THERAPY FOR THE PREVENTION OF BPD

Kinsella JP, Cutter GR, Walsh WF, Gerstmann DR, Bose CL, Hart C, Sekar KC, Auten RL, Bhutani VK, Gerdes JS, George TN, Southgate WM, Carriedo H, Couser RJ, Mammel MC, Hall DC, Pappagallo M, Sardesai S, Strain JD, Baier M, Abman SH. **Early inhaled nitric oxide therapy in premature newborns with respiratory failure**. N Engl J Med 2006; 355:354-64.

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Comment in: [N Engl J Med. 2006 Jul 27;355\(4\):404-6](#).

Kinsella and colleagues recently completed a multicenter, randomized trial involving 793 newborns who were 34 weeks gestation or less at birth and had

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respiratory failure requiring mechanical ventilation. Premature newborns, stratified into 3 birthweight categories (500-749 grams, 750-999 grams, or 1000 to 1250 grams), randomly received either iNO (5 ppm) or placebo gas within 48 hours of birth for 21 days or until extubation. Primary outcome was a combination of death or BPD at 36 weeks CGA; secondary outcomes included severe IVH (grades III or IV), PVL, or ventriculomegaly.

The results in the entire cohort of 500-1250 gram infants showed no difference in the overall risk of the combined outcomes. However, iNO significantly decreased the risk of BPD by 50%, and the combined risk of death or BPD by 40% in the subgroup of patients with birthweights of 1000-1250 grams (BPD 29.8% in the iNO group vs. 59.6% in the placebo group). Of note, the secondary outcomes of brain injury (IVH, PVL, ventriculomegaly) were decreased in the overall population of 500-1250 gram infants (brain injury 17.5% in iNO group vs. 23.9% in placebo group, $p=0.03$). Importantly, iNO therapy was not associated with increased risks of pulmonary hemorrhage or other adverse events.

This important study addresses concerns about early iNO therapy in the VLBW population related to the potential risk for neonatal brain injury, pulmonary hemorrhage, and death. While iNO has beneficial vasoactive and anti-inflammatory effects, it is thought to adversely affect platelet adhesion. The authors theorize that iNO may reduce neutrophil accumulation in infants with RDS, and may also reduce oxidant stress by modulating inflammatory cytokines and cell apoptosis. They also hypothesize that iNO may modulate systemic circulation of cytokines that can injure distant organs through reduction in lung-derived cytokines. Of particular note is the authors' finding that the use of iNO, with median iNO exposure of 14 days, appears safe in this VLBW population, even when used within the first 48 hours of life when risk for neurologic injury is highest.

iNO THERAPY AT 7-21 DAYS

Ballard RA, Truog WE, Cnaan A, Martin RJ, Ballard PL, Merrill JD, Walsh MC, Durand DJ, Mayock DE, Eichenwald EC, Null DR, Hudak ML, Puri AR, Golombek SG, Courtney SE, Stewart DL, Welty SE, Phibbs RH, Hibbs AM, Luan X, Wadlinger SR, Asselin JM, Coburn CE for the NO CLD Study Group. **Inhaled nitric oxide in preterm infants undergoing mechanical ventilation.** *N Engl J Med* 2006; 355:343-53.

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Ballard and colleagues conducted a randomized, stratified, double-blind, placebo-controlled trial of iNO at 21 centers involving infants of birthweights of 1250 grams or less who required ventilatory support between the ages of 7 and 21 days. iNO was started at 20 ppm for 48-96 hours, then decreased weekly to 10, 5 and 2 ppm for a minimum duration of 24 days (as long as infants required intubation). The primary study outcome of interest was survival without BPD at 36 weeks gestation; secondary outcomes included duration of oxygen therapy/duration of hospitalization. Of particular interest were the long term pulmonary outcomes including need for rehospitalization and respiratory support (mechanical ventilation/CPAP and oxygen supplementation) at 40, 44, 52, and 60 weeks postmenstrual age.

Among 294 infants receiving iNO and 288 receiving placebo, the iNO group had a significantly increased rate of survival without BPD at 36 weeks gestation (43.9% vs. 36.8% in placebo group, $p<0.05$). The infants who received iNO also were discharged sooner and received supplemental oxygen for a shorter period of time. There were no short term safety concerns relative to rates of NEC, sepsis, PDA requiring therapy, ROP, or neurologic findings on ultrasound.

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Subgroup analysis demonstrated that iNO was more beneficial in infants enrolled between ages 7 to 14 days compared to those infants enrolled between days of life 15 to 21.

The decision was made to delay enrollment in the study until 7 days of life secondary to concerns about potential brain injury with early use. The authors believed that later and more prolonged therapy would prevent lung injury from hyperoxia and improve surfactant function, lung growth, angiogenesis, and alveolarization.

Further long-term neurodevelopmental follow-up to the Kinsella and Ballard trials will provide important information for practitioners regarding the long-term safety of this specific treatment.

CYTOKINE-DIRECTED THERAPIES

Nakanishi H, Sugiura T, Streisand JB, Lonning SM, Roberts Jr. JD. **TGF- β neutralizing antibodies improve pulmonary alveologenesis and vasculogenesis in the injured newborn lung.** Am J Physiol: Lung Cell Mol Physiol. 2007 Apr 13; [Epub ahead of print].

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Pulmonary injury, associated with the disruption of alveologenesis in the developing lung, is known to cause BPD in premature infants. TGF- β is an important regulator of cellular differentiation and early lung development, and levels of TGF- β are increased in various forms of lung injury. Although the role of TGF- β in the pathogenesis of BPD has been studied, its role in inhibiting terminal lung development is not well understood. In this study, the authors theorized that oxygen-induced injury in the maturing lung is associated with TGF- β mediated disruption of alveologenesis and microvascular development. They tested the hypothesis that TGF- β neutralizing antibodies would attenuate TGF- β signaling, and promote alveolar development using a newborn mouse model of BPD.

Upregulation of TGF- β signaling results in increased nuclear localization of a protein called phospho-Smad2. In this study, the investigators found that treatment with TGF- β neutralizing antibodies attenuated nuclear localization of phospho-Smad2 in response to hyperoxia in pulmonary cells. Of note, the use of TGF- β neutralizing antibodies also improved quantitative indicators of alveologenesis, extracellular matrix assembly, and microvascular lung development in the injured and developing lung. Interestingly, the use of these antibodies demonstrated improved overall somatic growth in hyperoxic mouse pups, with no increase in inflammatory markers.

The changes demonstrated in this hyperoxia model of BPD included: improved microvascular development, alveolar septal elastin organization, and improved overall alveologenesis. This important animal study demonstrates the potential benefit of anti-TGF- β antibodies in preventing lung injury in developmental diseases of the lung in premature infants.

ANTIOXIDANT THERAPIES: VITAMIN A

Ambalavanan N, Tyson JE, Kennedy KA, Hansen NI, Vohr BR, Wright LL, Carlo WA and the NICHD NRN. **Vitamin A supplementation for extremely low birth weight infants: outcome at 18 to 22 months.** Pediatrics 2005; 115: e249-e254.

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VLBW infants are often deficient in vitamin A (retinol), which may increase the risk for BPD. While randomized controlled trials and a systematic review have indicated that vitamin A supplementation decreases BPD and/or death^[1,2,3], the long-term effects of vitamin A supplementation had not been reported previously. Goals of the present study investigated the longer-term risks and benefits of vitamin A supplementation, including rates of death, neurodevelopmental impairment (NDI), pulmonary complications, and re-hospitalizations at 18-22 months CGA among infants who were previously enrolled in the NICHD vitamin A trial^[1]. The primary outcome for this study was NDI (defined as one or more of the following conditions: MDI or PDI <70, CP, blindness, or hearing impairment) or death. The follow-up visit evaluated information regarding number of re-hospitalizations, respiratory medication use, and the need for oxygen at home or in a chronic care facility.

A total of 807 infants participated in the original vitamin A trial. 85% of the survivors were assessed at 18-22 months CGA. For all measurements of NDI, no significant differences between the treatment groups were found. Of note, there were no differences and no evidence of benefit from vitamin A supplementation on long-term pulmonary morbidity after discharge. The patients who developed BPD at 36 weeks CGA were more likely to have NDI at follow-up, with rates of 54% in the BPD group vs 37% in infants who did not have BPD (RR: 1.48, CI: 1.22-1.80, p <0.001).

The prior vitamin A randomized controlled trial had shown clear benefit to an intervention directed toward decreased rates of BPD (55% vs. 62%, RR 0.89, 95% CI 0.80-0.99)^[1]; however, in Ambalavanan's long-term follow-up study, the pulmonary benefits were not evident. In fact, the trends related to pulmonary morbidity demonstrated a borderline significant result, with the vitamin A group being more likely to require diuretics at follow-up (RR 2.80, CI: 0.91-8.64, p = 0.06). In addition, there were more patients from the vitamin A group who required oxygen for home use, were still receiving oxygen therapy at >6 months of age, and still required oxygen at the 18-22 month follow-up. These findings reinforce the importance of direct long-term pulmonary morbidity and neurodevelopmental outcomes evaluation as opposed to evaluating the outcome of a diagnosis of BPD at 36 weeks' corrected age.

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ANTIOXIDANT THERAPIES: RECOMBINANT SOD

Davis JM, Parad RB, Michele T, Allred E, Price A, Rosenfeld W; for the North American Recombinant Human CuZnSOD Study Group. **Pulmonary outcome at one year corrected age in infants treated at birth with recombinant human superoxide dismutase**. Pediatrics 2003;111:469-76.

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Preterm infants have been shown to be relatively deficient in pulmonary



antioxidant enzyme activity with a maturation pattern similar to pulmonary surfactant, of particular importance since preterm infants are routinely exposed to hyperoxia (even room air is hyperoxic compared to in utero oxygen tensions) and damage from reactive oxygen species have been implicated in the pathogenesis of BPD. To examine whether treatment of premature infants with recombinant human superoxide dismutase (rhSOD) reduces BPD and improves pulmonary outcome at 1 year corrected age, 302 infants (600-1200 grams birth weight) were randomized to receive either intratracheal rhSOD (5 mg/kg in 2 mL/kg saline) or placebo every 48 hours (as long as intubation was required) for up to 1 month of age.

There were no differences between groups in the incidence of death or the development of BPD – defined as oxygen requirement with an abnormal chest radiograph at 28 days of life (required by the FDA) or at 36 weeks CGA. However, in follow-up at a median of 1 year CGA, 37% of placebo-treated infants had repeated episodes of wheezing or other respiratory illness severe enough to require treatment with asthma medications, such as bronchodilators and/or corticosteroids, compared with 24% of rhSOD-treated infants, a 36% reduction ($p < 0.05$). In a subset of infants < 27 weeks gestation, 42% treated with placebo received asthma medications compared with 19% of rhSOD treated infants, a 55% decrease. Infants < 27 weeks gestation who received rhSOD also had a 55% decrease in emergency department visits and a 44% decrease in subsequent hospitalizations.

These data indicate that treatment at birth with rhSOD may reduce early pulmonary injury, resulting in improved clinical status when measured at 1 year corrected age. Future trials are currently being planned to examine the impact of prophylactic, intratracheal administration of rhSOD in VLBW infants on clinical pulmonary outcome at 1 year corrected age.

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

- Discuss the uses of inhaled nitric oxide for the prevention of BPD
- Describe the uses of targeted antioxidant and anti-inflammatory therapies to prevent or treat BPD
- Explain the importance of long-term follow-up and evaluation of functional outcomes in determining the efficacy of treatments for BPD

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- **Edward E. Lawson, MD** 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.
- **Christoph U. Lehmann, MD** has indicated no financial relationship with commercial supporters.
- **Lawrence M. Noguee, MD** has received grant support from the National Institute of Health.
- **Mary Terhaar** has indicated no financial relationship with commercial supporters.
- **Robert J. Kopotic, MSN, RRT, FAARC** has indicated a financial relationship with the ConMed Corporation.

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