Week 3: Neonatal Cardiopulmonary

Neonatal Pulmonology: Interventions and Human Studies

Tuesday, June 23  4:30-5:45 pm EDT

Moderators
Brenda Poindexter
Michele Walsh

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<td>Less Invasive Surfactant Administration (LISA) – pulmonary outcome of preterm infants at early school age from the German Neonatal Network</td>
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Note: Schedule subject to change based on presenter availability.
CONTROL ID: 3374912

TITLE: Less Invasive Surfactant Administration (LISA) – pulmonary outcome of preterm infants at early school age from the German Neonatal Network

PRESENTER: Wolfgang Göpel

AUTHORS (LAST NAME, FIRST NAME): Göpel, Wolfgang 1; Kribs, Angela 2; Mehler, Katrin 2; Härtel, Christoph 3; Herting, Egbert 1

AUTHORS/INSTITUTIONS: W. Göpel, E. Herting, Pediatrics, University of Lübeck, Lübeck, GERMANY; A. Kribs, K. Mehler, University of Cologne, Cologne, GERMANY; C. Härtel, University of Lübeck, Lübeck, GERMANY;

CURRENT CATEGORY: Neonatology

CURRENT SUBCATEGORY: Neonatal Pulmonology

KEYWORDS: preterm infant, surfactant, spirometry.

SESSION TITLE: Neonatal Pulmonology: Interventions and Human Studies | Neonatal Pulmonology: Interventions and Human Studies

SESSION TYPE: Webinar|Platform

ABSTRACT BODY:

Background: Surfactant is a standard treatment for preterm infants with respiratory distress syndrome. “Less invasive surfactant administration (LISA)” describes a recently developed method of surfactant administration via a small diameter tube while the preterm infant is breathing spontaneously. Few long term outcome data of infants treated with less invasive surfactant administration are published.

Objective: Analysis of pulmonary, neurocognitive and other outcome data at early school age in a large cohort of preterm infants stratified for less invasive surfactant treatment. In addition, we analysed the effect of gestational age and fraction of inspired oxygen (FiO\textsubscript{2}) within the first 12 hours of life (which are frequently used as thresholds for surfactant therapy) on forced expiratory volume within one second as % of expected values (FEV1%).

Design/Methods: Multicenter prospective cohort study of preterm infants with a birth weight below 1500 grams who were born <= 30 weeks + 6 days of gestation. Follow up assessment of children born preterm and control children born at term was done by a single team from the University of Lübeck. Measurements at follow-up included spirometry, 3-minute running test, standardized intelligence and motor-function tests.

Results: A total number of 2492 preterm infants from 45 centers had follow up assessment at a mean age of 5.8 ± 0.4 years. 173 control children born at term were tested. Children born at term had significantly better pulmonary outcome data with the exception of FEV1/FVC (table). No significant differences with regard to baseline data at birth were observed between 711 children born preterm and treated with LISA and 1781 children born preterm without LISA-treatment. At follow-up LISA-treated children had significantly higher rates of FEV1 > 80% and significantly higher FEV1% and FVC% levels (table). FiO\textsubscript{2} between 21% and 90% and gestational age between 26 and 30 weeks were not associated with altered FEV1% at 5 years (figure 1 and 2). The predictive value of bronchopulmonary dysplasia for FEV1% at 5 years was limited (figure 3).

Conclusion(s): Lung function of children born preterm is poor if compared to control children born at term. Gestational age and FiO\textsubscript{2} within the first hours of life, which are both frequently used to decide if surfactant should be administered, are not predictive for FEV1% at 5 years. In this observational study, LISA was associated with improved FEV1% and FVC% at early school age.
Fig. 1: FEV1% at early school age and gestational age.

* Mean FEV1% significantly lower if compared to infants with gestational age 30 weeks (unpaired T-test, p<0.05)

Fig. 2: FEV1% at early school age and supplemental oxygen within the first 12 hours of life.

* Mean FEV1% significantly lower if compared to infants without supplemental oxygen within the first 12 hours of life (unpaired T-test, p<0.05)

Fig. 3: Duration of respiratory support or supplemental oxygen and FEV1% at early school age

Thresholds for FEV1 s > 80 % are indicated by dashed line and thresholds for BPD at 36+0 weeks postmenstrual age are marked by dotted line. Children who were discharged with supplemental oxygen and/or respiratory support are indicated by x. Data are limited to 2116 preterm children with successful spirometry and reported duration of respiratory support / supplemental oxygen. 585 of these children had FEV1s < 80%. Only 179 children with FEV1 < 80% had a diagnosis of BPD. Accordingly, sensitivity of BPD at 36 weeks for FEV1 < 80% was only 0.31 and specificity 0.87. The positive predictive value of BPD was 0.47 and negative predictive value was 0.77.

**IMAGE CAPTION:**
Fig. 1: FEV1% at early school age and gestational age.
Mean FEV1% significantly lower if compared to infants with gestational age 30 weeks (unpaired T-test, p<0.05)

**Fig. 2: FEV1% at early school age and supplemental oxygen within the first 12 hours of life.**

Mean FEV1% significantly lower if compared to infants without supplemental oxygen within the first 12 hours of life (unpaired T-test, p<0.05)

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**CONTROL ID:** 3372871

**TITLE:** Modulation of CPAP-induced airway hyperreactivity by the calcium sensitive receptor (CaSR)

**PRESENTER:** Catherine A. Mayer

**AUTHORS (LAST NAME, FIRST NAME):** Mayer, Catherine A.¹; Pabelick, Christina²; Prakash, Y.S.²; Martin, Richard J.¹; MacFarlane, Peter M.¹

**AUTHORS/INSTITUTIONS:** C.A. Mayer, R.J. Martin, P.M. MacFarlane, Pediatrics, Case Western Reserve University, Rainbow Babies & Children's Hospital, Cleveland, Ohio, UNITED STATES; C. Pabelick, Y. Prakash, Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, UNITED STATES;

**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Pulmonology

**KEYWORDS:** CPAP, CaSR, airway reactivity.

**SESSION TITLE:** Neonatal Pulmonology: Interventions and Human Studies | Neonatal Pulmonology: Interventions and Human Studies

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** CPAP has become the mainstay of neonatal respiratory support for preterm infants, although consequences of its use on respiratory morbidity are unknown. We developed a mouse model of neonatal CPAP and showed that it causes long-term airway hyperreactivity. The calcium sensitive receptor (CaSR) has been shown to be sensitive to mechanical stretch and is associated with various respiratory morbidities, but its effects on airway hyperreactivity following neonatal CPAP have not been studied.

**Objective:** To test the hypotheses that CaSR modulates airway hyperreactivity in a mouse model of neonatal CPAP.

**Design/Methods:** 1) In vivo mouse model of neonatal CPAP: neonatal mice received CPAP (6cm H2O) for 3 hours/day for the first 7 postnatal (P) days. Control mice experienced the same conditions as experimental animals only with no CPAP. Two weeks after CPAP ended (P21), mice were sacrificed and airway reactivity to increasing doses of methacholine (0.25μM-8μM) was measured using the precision cut lung slice method. Changes in airway smooth muscle actin and CaSR expression were assessed in the lung using rtPCR and immunohistochemistry. 2) Airway reactivity following neonatal CPAP (as described in 1) was also assessed in smooth muscle CaSR(-/-) mice.

**Results:** In wild type mice, CPAP increased AW reactivity in response to methacholine compared to control mice (Maximum contraction from baseline lumen area: CPAP: 42.6%, control: 14.7%; p≤0.006). Additionally, we observed
increased expression of both CaSR and smooth muscle actin mRNA and protein in the lungs of CPAP exposed mice. Compared to control mice, AHR was not increased in CPAP exposed CaSR\(^{(-/-)}\) mice suggesting resistance to CPAP treatment (Maximum contraction from baseline lumen area: CPAP: 22.6%, control: 16.0%, \(P=0.19\)).

**Conclusion(s):** We conclude that lung CaSR is an important modulator of increased airway reactivity in response to CPAP exposure in neonatal mice. These data have important implications for the way CPAP may contribute to the pathophysiology of wheezing disorders commonly seen in former preterm infants.

(No Image Selected)
Table 1

**Two SNP interaction model**

**Intragenic SNP interaction**

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<tr>
<th>Gene</th>
<th>SNP1</th>
<th>SNP2</th>
<th>Effect</th>
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<th>adj p-value</th>
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<td>rs1590707</td>
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**Intergenic SNP interaction**

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<td>SFTPA2</td>
<td>rs1136450</td>
<td>a1</td>
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<td>SFTPA2</td>
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<td>SFTPA2</td>
<td>rs1059047</td>
<td>a2</td>
<td>0.0001</td>
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P<0.05, * adjusted for gestational age and sex, FDR correction

Table 2. The two SNP interactions model showed significant intragenic and intergenic interactions with additive effect (a1 or a2) among the SFTPA1 and SFTPA2 SNPs associated with RDS.

Table 3. The three SNP interaction model showed significant (p<0.01) interactions with additive (a) effect among only SFTPA1 and SFTPA2 SNPs associated with RDS.

Figure 1. Among the three SNP interactions, only SFTPA1 and SFTPA2 had intragenic interactions and were included in all the intergenic interactions associated with RDS when compared with other SFTP SNPs. SFTPB and SFTPD SNPs had no intergenic interactions whereas SFTPC had no inter or intragenic SNP interactions associated with RDS. (P<0.05)

**Image Caption:**

Table 1

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BACKGROUND: The Neonatal Research Network (NRN) has used 3 epidemiologic definitions for bronchopulmonary dysplasia (BPD): 1) a clinical definition based on supplemental oxygen at 36 weeks postmenstrual age (PMA) (clinBPD), 2) a physiologic definition inclusive of a room air challenge (RAC) at 36 weeks (physBPD), and 3) a pragmatic definition based on any respiratory support at 36 weeks (pragBPD). PragBPD has been shown to be strongly correlated with long term respiratory outcomes.

OBJECTIVE: Evaluate variations in prevalence of the 3 BPD definitions at NRN centers and over time, and compare outcomes for infants that pass or fail the RAC

DESIGN/METHODS: Cohort study of infants <29 weeks gestational age born at NRN centers from 2012-2017. We excluded infants who died before 36 weeks PMA or who had congenital anomalies. ClinBPD was defined as any oxygen supplementation at exactly 36 weeks PMA. PhysBPD was determined at 36 ± 1 weeks PMA as either: 1) mechanical ventilation, positive pressure or >30% supplemental oxygen, or 2) ≤ 30% oxygen via hood or nasal cannula with failure of the RAC (oxygen saturation <90% for 5 minutes, or <80% for 15 consecutive seconds). PragBPD was defined as any respiratory support at 36 weeks PMA categorized into 3 severity grades. We compared demographics and clinical characteristics among infants with the 3 BPD types, and infants who passed or failed the RAC. We compared prevalence of the BPD types over time and by center. For infants <27 weeks GA, we examined associations between RAC results and death, long-term respiratory morbidity, or moderate-severe neurodevelopmental impairment at 22-26 months PMA.

RESULTS: Of 8026 infants included, 1074 completed the RAC and 554 of these completed 22-26 month follow-up. Demographic and clinical characteristics were not significantly different between infants who passed or failed the RAC, other than receipt of steroids (Table 1). In pairwise comparisons between the 3 BPD definitions, Kappa coefficients ranged from 0.50-0.88 among baseline characteristics (Table 1) and 0.52-0.97 among centers (Table 2). The prevalence of each definition of BPD has significantly changed over time (Figure 1). The RAC results were not associated with long-term morbidities (Table 3).

CONCLUSION(S): Prevalence of all 3 BPD definitions increased over time; pragBPD was higher in every center assessed. Because RAC results were not predictive of long-term morbidities, pragBPD may be a more useful BPD definition for trials and quality improvement benchmarking.
Table 1. Comparison of infants diagnosed with physiologic, clinical and/or pragmatic BPD > grade 1, and those who passed or failed the room air challenge.

Table 2. Rate of infants with physiological vs clinical vs pragmatic BPD > grade 1, by site.

Table 3. Long-term serious respiratory outcomes and neurodevelopmental impairments at 22-26 months postmenstrual age of infants <27 weeks gestational age, who passed or failed the room air challenge and died or underwent follow-up.

Figure 1. Prevalence of infants with physiological, clinical, and pragmatic BPD > grade 1 over time.

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Figure 1. Prevalence of infants with physiological, clinical, and pragmatic BPD > grade 1 over time.
**CONTROL ID:** 3374386

**TITLE:** Budesonide with surfactant decreases lung and liver responses in mechanically ventilated LPS-exposed preterm lambs

**PRESENTER:** Noah Hillman

**AUTHORS (LAST NAME, FIRST NAME):** Hillman, Noah; Kemp, Matthew W.; Fee, Erin L.; Rittenschober-Boehm, Judith; Royse, Emily; Salomone, Fabrizio; Musk, Gabrielle; Jobe, Alan H.

**AUTHORS/INSTITUTIONS:** N. Hillman, Pediatrics, Saint Louis University, St. Louis, Missouri, UNITED STATES; J. Rittenschober-Boehm, University of Vienna, Vienna, AUSTRIA; M.W. Kemp, University of Western Australia, Perth, Western Australia, AUSTRALIA; E. Royse, Pediatrics, Saint Louis University, Saint Louis, Missouri, UNITED STATES; A.H. Jobe, Pediatrics, Cincinnati Childrens, Cincinnati, Ohio, UNITED STATES; E.L. Fee, Obstetrics and gynaecology, University of Western Australia, Crawley, Western Australia, AUSTRALIA; G. Musk, Animal Care Services, University of Western Australia, Perth, Western Australia, AUSTRALIA; F. Salomone, Preclinical, Chiesi Farmaceutici S.p.A., Parma, ITALY.

**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Pulmonology

**KEYWORDS:** budesonide, lung inflammation.

**SESSION TITLE:** Neonatal Pulmonology: Interventions and Human Studies | Neonatal Pulmonology: Interventions and Human Studies

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** Mechanical ventilation is associated with bronchopulmonary dysplasia (BPD) in preterm infants, and the addition of budesonide (Bud) to surfactant therapy decreased the rates and severity of BPD. In preterm sheep, Bud 0.25 mg/kg in 200 mg/kg poractant alfa decreased injury responses in the lung, liver and brain. Chorioamnionitis is associated with increased rates of BPD in ventilated preterm infants.

**Objective:** To test the hypothesis that the addition of Bud to surfactant at delivery will decrease the injury from mechanical ventilation in preterm lambs exposed to intra-amniotic (IA) LPS relative to surfactant alone.

**Design/Methods:** Lambs at 126 + 1 day GA received E. Coli LPS 10 mg IA 48 hours prior to surgically deliver and mechanical ventilation with injurious ventilation for 15 minutes. After 15 minutes, lambs were assigned to either poractant alfa 200 mg/kg mixed with: 1) saline or 2) Bud 0.25 mg/kg. Physiology, blood gases, and plasma Bud levels were determined for a 4 h ventilation. Lung and liver tissues were evaluated for indicators of injury and compared to controls euthanized at birth.

**Results:** Compared with surfactant alone, Bud improved blood pressures, compliance and ventilation (Table 1), while decreasing mRNA for pro-inflammatory cytokines in the lung and liver (Table 2). Both groups had increases in mRNA for toll-like receptor 4 and surfactant protein B compared to controls.

**Conclusion(s):** In preterm lambs exposed to IA LPS and ventilated from birth, the addition of Bud to surfactant improved physiology and markers of lung and systemic inflammation.
Background: Preeclampsia (PE) is a major risk factor for preterm birth and is strongly associated with the subsequent
development of bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity. We have previously shown
that antenatal (AN) exposure to soluble fms-like tyrosine kinase 1 (s-FLT), an endogenous VEGF antagonist that is
markedly increased in maternal blood and amniotic fluid in PE, causes abnormal lung structure and function in infant
rats. Clinical studies suggest that maternal vitamin D deficiency is a risk factor for severe PE, however, whether AN
vitamin D (VD) treatment can restore lung structure and function after exposure to AN s-Flt is unknown.

Objective: To determine if early VD (1,25-(OH)\textsubscript{2}D\textsubscript{3}) treatment will preserve lung structure and function in infant rats
after antenatal exposure to s-Flt.

Design/Methods: Fetal rats were exposed to recombinant human sFlt-1 (1ug), recombinant human s-Flt (1ug) + 1,25-
(OH)\textsubscript{2}D\textsubscript{3} (1ng/ml), 1,25-(OH)\textsubscript{2}D\textsubscript{3} (1ng/ml) or saline via intra-amniotic (IA) injection at E20 and delivered two days later.
At 14 days of age, lung function including total respiratory system compliance (Crs) and resistance (Rrs) was determined
by Flexivent and lung structure was assessed for radial alveolar counts (RAC) and pulmonary vessel density (PVD) by
standard morphometric analysis. Infant hearts were assessed for right ventricle hypertrophy (RVH) by the ratio of
RV/LV+S (Fulton’s Index).

Results: IA s-Flt decreased RAC and PVD by 28% and 43%, respectively, and increased RVH by 32% as compared to
controls (p<.001). IA s-Flt increased lung resistance by 30% and decreased compliance by 30% compared to controls
(p<.01). IA 1,25-(OH)\textsubscript{2}D\textsubscript{3} treatment in s-Flt exposed animals restored lung structure, function, and prevented RVH when
compared to controls (p=ns). IA 1,25-(OH)\textsubscript{2}D\textsubscript{3} (1ng/ml) treatment alone did not alter lung resistance or compliance.

Conclusion(s): IA VD improved infant lung structure and function and prevented right ventricular hypertrophy after s-
Flt exposure in vivo. We speculate that 1,25-(OH)\textsubscript{2}D\textsubscript{3} may preserve lung growth and function through enhanced
angiogenesis in experimental PE.

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