**Week 1: Clinical Trials and General Neonatology**

**Neonatal Clinical Trials II**

**Thursday, June 11 2:30-4:00 pm EDT**

**Moderators**
Eric Eichenwald  
Afif EL-Khuffash

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Note: Schedule subject to change based on presenter availability.
CONTROL ID: 3381743
TITLE: Early use of Azithromycin on the prevention of Ventilation-Induced Lung Injury by release of proinflammatory cytokines: A Double-blind Randomized Clinical Trial
PRESENTER: Renato S Procianoy
AUTHORS (LAST NAME, FIRST NAME): Silveira, Rita C.1; Nunes, Cristiane R.1; Corso, Andrea L.1; Procianoy, Renato S.2
R.S. Procianoy, Neonatology, Universidade Federal do Rio Grande do Sul/Hospital de Clinicas de Porto Alegre, Porto Alegre, BRAZIL;
CURRENT CATEGORY: Neonatology
CURRENT SUBCATEGORY: Neonatal Clinical Trials
KEYWORDS: preterm, proinflammatory cytokines, Azithromycin.
SESSION TITLE: Neonatal Clinical Trials II | Neonatal Clinical Trials II
SESSION TYPE: Webinar|Platform
ABSTRACT BODY:
Background: Macrolide antibiotics have anti-inflammatory properties and are assumed to be capable of inhibiting inflammation at multiple points in the inflammatory cascade. Macrolides have been used to treat Ureaplasma spp. infections with the intention of preventing BPD, being Azithromycin the choice.

Objective: Evaluation of the anti-inflammatory effect of azithromycin on the prevention of ventilation-induced lung injury (VILI) in preterm infants through the dosing of cytokine pre- and post-use of medication. In addition, to establish an association between the presence of Ureaplasma in preterm newborns and the response to azithromycin.

Design/Methods: Double-blind, placebo-controlled, randomized controlled trial (NCT03485703) including preterm infants who underwent mechanical ventilation (MV) within the first 72 hours of life. They received intravenous azithromycin (at a dose of 10/mg/kg/ day for 5 days) or placebo (saline solution 0.9% for 5 days) within the first 12 hours of MV onset. Two blood samples were collected (pre- and post-intervention) for interleukin (ILs) levels and Ureaplasma PCR. Patients were followed during hospitalization for outcomes of death and BPD. Major congenital malformations, chromosomal syndromes, STORCH, and who had mothers with HIV were excluded.

Results: Eighty randomized preterm infants were analyzed. After three deaths, they were divided into the group which received azithromycin (38) and placebo group (39). Birth weight and gestational age were similar. Serum levels for IL2 before and after azithromycin were 1.67 ± 0.17 pg / ml and 1.64 ± 0.14 pg / ml (p = 0.002), respectively; for IL-6 pre was 2.41 ± 0.73 pg / ml and post 2.06 ± 0.41 pg / ml (p = 0.001); and for IL8 pre, 3.24 ± 0.44 pg / ml and post 3.03 ± 0.34 (p = 0.003). In the placebo group levels of IL-β (1.29 ± 0.39 pg / ml and 1.44 ± 0.23 pg / ml, 0.007) and IL-8 (2.90 ± 0.61 pg / ml and 3.16 ± 0.36 pg / ml) increased significantly after 5 days of administration. Bronchopulmonary dysplasia was present in 43.8% of the azithromycin group and 75.9% in placebo (p=0.018). There was a reduction in the incidence of BPD / death in preterm infants receiving azithromycin (52.4% versus 84.6% in the placebo group; p= 0.003).

Conclusion(s): Azithromycin has anti-inflammatory effects reducing cytokine levels after 5 days of use. Thus, reducing BPD / death outcome in ventilated preterm infants.

(No Image Selected)
**Multicentre, Randomized Trial.**

**PRESENTER:** Xavier Durrmeyer

**AUTHORS (LAST NAME, FIRST NAME):** Rozé, Jean-Christophe³; Cambonie, Gilles⁴; Le Thuaut, Aurelie¹; FLAMANT, Cyril¹; Debillon, Thierry³; Durrmeyer, Xavier⁷; Boubred, Farid⁷; Gascoin, Geraldine⁶; PATKAI, Juliana⁵; Beuchee, Alain⁸; Favrais, Geraldine⁹

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**CURRENT CATEGORY:** Neonatology  
**CURRENT SUBCATEGORY:** Neonatal Clinical Trials  
**KEYWORDS:** Ductus arteriosus, Echocardiography, Ibuprofen.

**SESSION TITLE:** Neonatal Clinical Trials II | Neonatal Clinical Trials II  
**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** After more than 40 years of research, no strategy concerning patent ductus arteriosus (PDA) has proven long-term benefit, although early echocardiography-based targeted treatment of DA might improve some short-term outcomes.

**Objective:** To compare rates of survival without cerebral palsy at 2 years in extremely preterm infants with a large DA between those treated with ibuprofen or placebo in the first 12 hours after birth.

**Design/Methods:** Neonates less than 28 weeks of gestation with no contra-indication to ibuprofen were enrolled in a multicenter, double blind, randomized, controlled trial in 11 French NICUs from April 2012 to December 2016. All participants had a standardized echocardiographic measure their DA's size and were classified as having a “small” or “large” DA based on a validated threshold: 2.26 - (0.078 x post natal age in hour) mm, Kluckow M et al, 2008. Infants with a “large” DA were randomized to receive Ibuprofen (10 mg/kg on first day, then 5 mg/kg/day the next 2 days) or placebo before 12 hours after birth. The primary outcome was survival without cerebral palsy at 2 years. Secondary outcomes included neonatal mortality and morbidities. Intention-to-treat analysis using mixed models was performed, as well as per-protocol and sensitivity analyses using multiple imputations.

**Results:** Among the 337 enrolled infants, 228 (67.7%) were classified as having a large DA and were randomized (see Table). Pulmonary hemorrhage during the first 3 days after birth occurred in 2/114 (1.8%) versus 9/114 (7.9%), p=0.049, in ibuprofen and placebo groups, respectively, absolute risk reduction [aRR], 0.06; 95%CI, 0.004 to 0.13. The primary outcome was assessed in 108/114 (94.7%) and 102/114 (89.5%) in patients allocated to Ibuprofen or placebo, respectively. Survival without cerebral palsy occurred in 77/114 (71.3%) versus 73/114 (71.6%), p=0.96, in Ibuprofen and placebo groups, respectively, aRR, 0.00; 95%CI, -0.12 to 0.12. Per-protocol and sensitivity analyses using multiple imputations confirmed main analysis.

**Conclusion(s):** Early echocardiography targeted treatment of PDA did not change the rate of survival without cerebral palsy at 2 years, but might reduce the rate of early pulmonary hemorrhage. (EUDRACT: 2011-003063-30, ClinicalTrials.gov Id: NCT01630278). This study is dedicated to the memory of the late Prof. Véronique Gournay, main investigator of this trial.
Neurodevelopmental outcomes at 2 years corrected age of neonates premedicated with atropine-propofol versus atropine- atracurium-sufentanil for nonemergency intubation: follow-up of a randomized controlled trial

Manon TAUZIN

TAUZIN, Manon; Marchand-Martin, Laetitia; Lebeaux, Cécile; BREINIG, Sophie; Claris, Olivier; Tourneux, Pierre; Alexandre, Cénéric; Lévy, Corinne; Jung, Camille; Dechartres, Agnès; Durrmeyer, Xavier

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Neonatology

Neonatal Clinical Trials

Propofol, Neurodevelopmental outcome, Neonates.

Neonatal Clinical Trials II | Neonatal Clinical Trials II

Session Title: Neonatal Clinical Trials II | Neonatal Clinical Trials II

Abstract Body:

Background: Premedication for nonemergency intubation in neonates is recommended but there is no consensus on drugs to be used. We conducted a randomized controlled trial of premedications with atropine-propofol versus atropine- atracurium-sufentanil showing no significant difference in the frequency of prolonged desaturation between the 2 groups (PRETTINEO trial). Considering the concerns for neurotoxicity of common anesthetics and analgesics in neonates, we performed a neurodevelopmental follow-up.

Objective: To compare neurodevelopmental outcome at 2 years corrected age between infants treated with 2 different regimens before intubation.

Design/Methods: Planned follow-up of the PRETTINEO multicenter, double blind, randomized controlled trial conducted in 6 French Neonatal intensive care units between 2012 and 2016. Neonates were randomized to receive a premedication with atropine-propofol or atropine- atracurium-sufentanil. Neurodevelopmental outcome was assessed with the Age and Stages Questionnaire (ASQ). The primary outcome was survival with no ASQ domain below threshold at 2-years corrected age. Secondary outcomes included survival and ASQ scores at age 2. Outcomes were analyzed in the as treated population after multiple imputation for missing data.

Results: Of the 173 randomized neonates (mean gestational age, 30.6 weeks; mean birth weight, 1502g), 166 were included in the follow-up study with 85 treated with atropine-propofol either as allocated (n=83) or open-label (n=2) and 81 treated with atropine- atracurium-sufentanil either as allocated (n=79) or open-label (n=2). Survival with no ASQ score below threshold at 2-years corrected age occurred in 45/85 (52.9%) patients in the atropine-propofol group versus 38/81 (47.3%) patients in the atropine- atracurium-sufentanil group (adjusted risk difference 5.2, 95% CI -11.3 to 21.7, p=0.54). At 2 years corrected age, survival rates were 81/85 (95.3%) versus 74/81 (91.4%) (p=0.44) and mean (SD) total ASQ scores were 219.7 (56.1) versus 218.7 (59.9) (p=0.90) in the atropine-propofol and atropine- atracurium-sufentanil group, respectively.
Conclusion(s): In this follow-up study of a randomized controlled trial in neonates requiring intubation, premedication with atropine-propofol was not significantly associated with impaired neurodevelopmental outcome or death at 2 years compared to atropine- atracurium-sufentanil.

ClinicalTrials.gov Identifier: NCT01490580
The MOBYDuck trial was designed to determine whether maternal DHA supplementation during the neonatal period improves bronchopulmonary dysplasia-free survival at 36 weeks of postmenstrual age in breastfed infants born before 29 weeks of gestation.

**Design/Methods:** The MOBYDuck Trial was a two-arm, randomized, double-blind, placebo-controlled, multicenter trial involving 16 Neonatal Intensive Care Units (NICU) in Canada. Consenting, lactating mothers who delivered prematurely before 29 weeks of gestation were assigned to take 1.2g DHA daily or a placebo from 72 hours post-delivery until 36 weeks of post-menstrual age. Primary outcome was bronchopulmonary dysplasia-free survival in infants at 36 weeks of post-menstrual age. Relative risks stratified by sites were estimated using a log-binomial regression model with generalized estimating equations accounting for multiple infants per pregnancy.

**Results:** Trial enrollment stopped early because the treatment effect favored the placebo group: 461 mothers, and 523 of their 528 infants were included in an intention-to-treat analysis. DHA percentage of total fatty acids in breast milk reached 0.95±0.44% in the DHA versus 0.34±0.20% in the placebo groups (P<0.001). Overall, 147 of 268 (54.9%) infants in DHA and 157 of 255 (61.6%) infants in placebo groups survived without bronchopulmonary dysplasia (relative risk, 0.91; 95% CI, 0.80 to 1.04; P=0.18). Bronchopulmonary dysplasia rates were 41.7% in DHA versus 31.4% in placebo groups (relative risk, 1.36; 95% CI, 1.07 to 1.73; P=0.01). Severe bronchopulmonary dysplasia rates were 34.9% in DHA versus 25.3% in placebo groups (P=0.02). Mortality was 6.0% in DHA versus 10.2% in placebo groups (P=0.12).

**Conclusion(s):** Maternal DHA supplementation during the neonatal period did not improve bronchopulmonary dysplasia-free survival among infants born under 29 weeks of gestation. (Clinicaltrials.gov Identifier: NCT02371460; funded by the Canadian Institutes of Health Research).

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**CONTROL ID:** 3369161

**TITLE:** Early PARacetamol (EPAR) trial: a randomized controlled trial of early paracetamol (acetaminophen) to promote closure of the ductus arteriosus in preterm infants

**PRESENTER:** Timothy Schindler

**AUTHORS (LAST NAME, FIRST NAME):** Schindler, Timothy¹; Smyth, John¹; Bolisetty, Srinivas¹; Michalowski, Joanna¹; Mallitt, Kylie-Amr²; Singla, Abhijeet¹; Lui, Kei²

**AUTHORS/INSTITUTIONS:** T. Schindler, J. Smyth, S. Bolisetty, J. Michalowski, A. Singla, Royal Hospital for Women, Randwick, New South Wales, AUSTRALIA; K. Mallitt, K. Lui, School of Women's and Children's Health, University of New South Wales, Randwick, New South Wales, AUSTRALIA;

**CURRENT CATEGORY:** Neonatology

**CURRENT SUBCATEGORY:** Neonatal Clinical Trials

**KEYWORDS:** Preterm Infants , Patent Ductus Arteriosus, Paracetamol.

**SESSION TITLE:** Neonatal Clinical Trials II | Neonatal Clinical Trials II

**SESSION TYPE:** Webinar|Platform

**ABSTRACT BODY:**

**Background:** The management of patent ductus arteriosus (PDA) in preterm infants is an area of controversy. The medications typically used to treat PDA are associated with a number of unwanted adverse effects. Paracetamol (acetaminophen) is a medication with an excellent safety profile in infants and has been suggested as a safe medication in situations where other medications have failed or are contraindicated. There are limited data on the use of early paracetamol in preterm infants.

**Objective:** This study aimed to investigate whether early treatment with paracetamol reduces the number of infants requiring intervention for PDA.

**Design/Methods:** This was a double-blind, parallel, randomized, placebo-controlled trial in preterm infants <29 weeks’ gestation. At 6 hours of life, infants with a ductus arteriosus >0.9 mm were randomized to receive either (1) intravenous paracetamol at a dose of 15 mg/kg initially, followed by every 6 hours at a dose of 7.5 mg/kg for 5 days; or (2) intravenous 5% dextrose every 6 hours for 5 days. The primary outcome was the need for any intervention for
management of PDA up to 5 days. Secondary outcomes included closure of the ductus arteriosus at 5 days, size of the ductus arteriosus at 48 hours, ductal reopening, mortality and significant morbidities.

**Results:** Of 58 infants randomized, 29 were allocated to the intervention and 29 to the control group. The trial was stopped for benefit at 50% recruitment after reaching pre-specified stopping criteria. Less infants in the intervention group required intervention for management of PDA up to 5 days (6 [21%] vs 17 [59%] infants [p=0.003]; relative risk reduction 0.65 [95% CI 0.23 – 0.84; NNT 2.6]). The intervention group had a higher rate of ductal closure at 5 days (20 [69%] vs 8 [28%] infants [p=0.002]; relative risk reduction 0.57 [95% CI 0.23 – 0.76; NNT 2.4]) and smaller ductal size at 48 hours (1.0 mm [SD 0.8] vs 1.4 mm [SD 0.9]; p=0.04). There were no differences in ductal reopening, mortality and significant morbidities (including intraventricular hemorrhage). Three deaths occurred (two in the intervention group; one in the control group), which were not attributed to the intervention. No other adverse events or side effects were reported.

**Conclusion(s):** Early paracetamol reduced the number of infants requiring intervention for PDA. Australian New Zealand Clinical Trials Registry number, ACTRN12616001517460. Funded by Running for Premature Babies (registered charity).
presented by cluster 2, characterized by typical strains of later gestational ages including *Bifidobacterium* sp and *Blautia* sp (Fig 2), probiotics use enhanced richness and β diversity in Cluster1 (p=0.001). Probiotics use was associated with significant increase in fungal microbiome β diversity during treatment only (Fig 3).

**Conclusion(s):** Probiotics supplementation in ELBW infants resulted in significant increase in bacterial and fungal richness and diversity. These changes continued after 2 weeks of treatment cessation for bacterial component and during treatment for the fungal component. Further analyses of metabolomics and stool samples at 6 and 12 months of age are pending.

**Figure 1:**
A. qPCR: Mean and SD of log value for cell concentration Cell/ml.
B. 16S rRNA: Probiotics impact on bacterial species richness (Chao1) and β diversity (Principal Coordinate analysis: PCoA).

**Figure 2:** 16S rRNA, A. Principal coordinate analysis and B. Heat map represent Dirichlet multinomial mixtures (DMM); a probabilistic modelling of microbial metagenomics data identified two distinct microbial clusters, cluster 1 represented in the early samples and characterized by Staphylococcus sp, Enterobacteriaceae, and Clostridium sensu stricto 1, while subsequent samples are presented by cluster 2, characterized by typical strains of later gestational ages such as *Bifidobacterium* sp. and *Blautia* sp.

C. Most relative abundance genera in study groups

**Figure 3:** ITS2 gene sequencing
A. Fungal species richness changes (Chao1).

B. Probiotics impact on fungal β diversity (Principal Coordinate analysis: PCoA).

**IMAGE CAPTION:**

Figure 1:

A. qPCR: Mean and SD of log value for cell concentration Cell/ml.

B. 16S rRNA: Probiotics impact on bacterial species richness (Chao1) and β diversity (Principal Coordinate analysis: PCoA).

Figure 2: 16S rRNA, A. Principal coordinate analysis. and B. Heat map represent Dirichlet multinomial mixtures (DMM); a probabilistic modelling of microbial metagenomics data identified two distinct microbial clusters, cluster 1 represented in the early samples and characterized by Staphylococcus sp, Enterobacteriaceae, and Clostridium sensu stricto 1, while subsequent samples are presented by cluster 2, characterized by typical strains of later gestational ages such as Bifidobacterium sp. and Blautia sp.

C. Most relative abundance genera in study groups

Figure 3: ITS2 gene sequencing

A. Fungal species richness changes (Chao1).

B. Probiotics impact on fungal β diversity (Principal Coordinate analysis: PCoA).