

THONATAL MEDICIN

AN INTERNATIONAL SYMPOSIUM HONORING PROF. RICHARD B. JOHNSTON, MD, DENVER WÜRZBURG, GERMANY, APRIL 26 - 28, 2020

# ABSTRACTS



SCIENTIFIC ORGANIZATION PROF. CHRISTIAN P. SPEER, MD, FRCPE

Sunday, April 26, 2020, 13<sup>15</sup> h

- I RESPIRATORY CARE, PULMONARY DISEASES AND BPD – Part 1 Chair: G. Dimitriou, Patras, Greece; R.K. Pejaver, Bangalore, India
- II NUTRITION / GROWTH Chair: C. Härtel, Lübeck, Germany; William W. Hay Jr., Denver, USA
- III BRAIN AND NEURODEVELOPMENTAL OUTCOME Chair: C. Bührer, Berlin, Germany; N. Marlow, London, UK

Monday, April 27, 2020, 12<sup>45</sup> h

- IV RESPIRATORY CARE, PULMONARY DISEASES AND BPD – Part 2 Chair: L. van Marter, Boston, USA; C. Wright, Denver, USA
- V INFECTIONS AND INFLAMMATION Chair: R. Ramanathan, Los Angeles, USA; D. Singer, Hamburg, Germany

### VI MISCELLANEOUS TOPICS

Chair: T.W.R. Hansen, Oslo, Norway; E. Özek, Istanbul, Turkey

### ESTIMATING THE ENDOTRACHEAL TUBE INSERTION LENGTH IN NEWBORN INFANTS USING WEIGHT OR GESTATION: A RANDOMIZED CONTROLLED TRIAL

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**Background.** Current recommendation for estimation of endotracheal tube (ETT) insertion length is based on weight based formula to place the tip of the endotracheal tube in the mid-trachea. Among all the methods studied in newborns, none has been found accurate and the ETT tips are often incorrectly positioned. Estimating the insertion length is very important as inaccurately placed tip of ET tube has significant impact on ventilation of the newborn and secondary complications like lung collapse.

**Objective.** To determine whether estimating the endotracheal tube insertion length using gestation compared to weight results in more correctly placed ET tube tip.

**Study Design.** A Randomized controlled trial. Study setting: Tertiary care level-III neonatal unit. Participants: Neonates (corrected gestation between 25-43 weeks) without congenital malformations who were intubated orally.

**Methods.** 103 newborn infants required intubation were randomized to predict their endotracheal tube insertion length using weight [weight (kg) + 6] (n=51) or gestation [length determined from a table] (n=50). Primary outcome: Correct ET tube tip position, defined as the tip located between the upper border of the first thoracic vertebra (T1) and the lower border of the second thoracic vertebra(T2) on a chest Xray. it was determined by a radiologist who was masked to group assignment.

**Results.** 103 infants were included and the two groups were well comparable. The proportion of correctly placed ET tube tips was significantly higher in gestational age based group [Gestation, 37/50(74%), versus weight 27/51(52.9%), p=0.02]. We found no significant differences in the secondary outcomes.

**Conclusions.** Estimating the endotracheal tube insertion length in newborns using gestational age resulted in more correctly placed ET tube tips compared to weight.

### THE COMPARISON OF TWO DIFFERENT WEANING METHODS FOR CONTINUOUS POSITIVE AIRWAY PRESSURE

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**Background.** There are still many different strategies of weaning preterm infants from nasal continuous positive airway pressure (nCPAP).

**Objective.** The aim of our study was to compare two weaning methods for nCPAP: sudden and gradual.

**Methods.** We included 41 preterm infants < 30 weeks' gestational age who required nCPAP for at least 24 h. Neonates were randomized to a sudden (G1) or a gradual (G2) weaning group.

G1: the nCPAP was finished at once after achieving predefined stability criteria for  $\geq$  12 hours.

G2: nCPAP was gradually weaned with prolonging nCPAP time off in predefined scheme for two days after achieving stability criteria for  $\geq$  12 hours. After nCPAP was finished, we assessed predefined criteria for three more days and then stated that nCPAP was finished successfully.

**Results.** The duration of nCPAP therapy was 18 days in G1 (min. 5, max. 48) and 21 days in G2 (min. 5, max. 77; p=0.69). The duration of weaning from nCPAP was 2 days in G1 (min. 0, max. 20) and 7 days in G2 (min. 2, max. 34; p=0.06). The length of stay in the NICU was 17 days in G1 (min. 6., max. 49) versus 23 days in G2 (min. 6, max. 64; p=0.43). The duration of hospital care was 62 days in G1 (min. 41, max. 95) and 66 days in G2 (min. 40, max. 103; p=0.76).

The neonates were successfully weaned at 30+4 weeks of gestational age (min. 28+4, max. 36+6) and 31+1 weeks (min. 28+6, max. 35+6) in G1 and G2 (p=0.40); the weight was 1295 g (min. 894 g, max. 2210 g) and 1348 g (min. 975 g, max. 2244 g) (p=0.360) in G1 and G2, respectively.

**Conclusion.** As expected, the sudden weaning strategy of nCPAP was associated with a shorter weaning time. However, there were no statistically significant differences in length of NICU and total hospital stay, age of corrected gestational age and weight at the time point of weaning.

# THORACIC FLUID CONTENT AND RESPIRATORY DISTRESS IN PRETERM INFANTS: A LONGITUDINAL BIOREACTANCE STUDY

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**Background.** Thoracic fluid content (TFC) is an indicator of total lung fluid and is measured non-invasively using thoracic impedance technology. TFC is calculated as 1000/Z0 (k $\Omega$ -1), where Z0 (impedance) is inversely proportional to thoracic fluid. Bioreactance is a modified bioimpedance technology with less signal:noise ratio. Bioreactance has been shown to predict respiratory distress in term infants but no data is available in preterm infants.

**Objective.** To determine (1) changes of TFC over first 72 hours of life and (2) the effect of CPAP and surfactant on TFC in preterm ( $\leq$  32 weeks) infants.

**Methods.** This was a retrospective descriptive study at Tygerberg Hospital, Cape Town, South Africa in preterm infants ( $\leq$  32 weeks), admitted within 3 hours of life. Infants with congenital cardiac and pulmonary disease (except PDA), requiring invasive ventilation, inotropic support and those not expected to survive 72hours were excluded. NICOM® Reliant (Cheetah Medical, Massachusetts) monitor was used to measure TFC continuously for 72hours after birth. Various clinical parameters were correlated with TFC and TFCd (TFC change over time) at predetermined time points (0, 6 & 72hrs). Changes of TFC and TFCd were evaluated 6-hourly. Standard institutional neonatal RDS management guidelines were followed.

**Results.** 36 infants were included in the study: average 29.8 (±1.7) weeks and 1367 (±307)g. 57% infants had mild-moderate RDS on a CXR. 80% required CPAP initially and 22% required surfactant replacement therapy (SRT). Average TFC was 46.6±10.5 k $\Omega$ -1. TFC decreased over time and differed significantly at all time points. Respiratory support method and SRT requirement significantly affected TFC values. TFCd changes only differed over the first 18hours of life. Only time (p=0.000) and CPAP (p=0.002) significantly affected TFC after multivariate regression. TFC centiles were constructed for the first 72hrs of life. ROC analysis showed that a TFC>55k $\Omega$ -1 at time 0 predicted SRT requirement (sensitivity 38%, specificity 92%).

**Conclusion.** This is the first study of TFC in preterm neonates utilizing bioreactance technology. TFC is dependant on time and the degree of pulmonary disease. TFC monitoring may be able to predict SRT requirement, prolonged (>48hrs) CPAP requirement. More research is required to confirm these findings.

### EFFECTS OF FREQUENCY (F) AND TIDAL VOLUME (VT) ON CO<sub>2</sub> REMOVAL (VCO<sub>2</sub>) DURING HIGH FREQUENCY OSCILLATORY VENTILATION (HFOV) OF HEALTHY NEONATAL PIGLETS

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**Background.** HFOV may limit lung injury using small Vt  $\leq$  dead space. Mechanisms of CO<sub>2</sub> removal likely differ from conventional (CMV) and spontaneous ventilation, and mathematical relationships with F and Vt remain unclear. Previous animal studies suggest VCO<sub>2</sub> proportional to F and Vt<sup>2</sup> but there are no studies with clinical ventilators or neonatal animals.

**Methods.** VCO<sub>2</sub> was measured in 12 healthy, anesthetized, paralyzed neonatal piglets (2.5-4 kg). Stabilized on CMV to end-tidal CO<sub>2</sub> (EtCO<sub>2</sub>) of 40±2 Torr before each measurement, HFOV (Sensormedics 3100A) was initiated. Continuous sidestream CO<sub>2</sub> concentration from circuit outflow limb (Qubit Infrared CO<sub>2</sub> Analyzer) multiplied by circuit gas flow rate (TSI Mass Flowmeter) yielded VCO<sub>2</sub>. Each measurement was extrapolated to HFOV start time to avoid effects of over/underventilation. Measurements were obtained at various F (6-14 Hz) and Vt (0.5-6 mL/kg) combinations using Florian hotwire anemometer and fitted to equations VCO<sub>2</sub> =  $\alpha$ Vt<sup>x</sup> at fixed F, and VCO<sub>2</sub> =  $\beta$ F<sup>y</sup> at fixed Vt. VCO<sub>2</sub> presumably equaled CO<sub>2</sub> production if EtCO<sub>2</sub> was unchanged after HFOV.

**Results.** Values for x, y,  $\alpha$ , and  $\beta$  showed large variability both between animals at equal F's/Vt's and with each animal at varying F's/Vt's. Values of x were always > 1 (extremes of 1.1 to 3.0 for different animals/F values; interquartile range 1.4 to 2.1), and y from 0.8 to 1.3. Thus data combined for all animals at each F and Vt showed more variability than with individual animals; combined exponents were near x=2 and y=1.

**Conclusions.** HFOV Vt is small but relative size is important since  $CO_2$  removal depends on a power of Vt > 1. Large VCO<sub>2</sub> variability between animals suggests factors other than F and Vt, (e.g. differences in metabolic  $CO_2$  production/storage, V/Q relationships, dead space, airway dynamics) may contribute strongly to determining degree of ventilation. Considering VCO<sub>2</sub> proportional to F and Vt<sup>2</sup> is a good starting point but variability is sufficient to indicate monitoring.

### A SINGLE CENTRE EXPERIENCE ON CONGENITAL DIAPHRAGMATIC HERNIA ENHANCING COMPREHENSION OF RISK FACTORS FOR MORTALITY

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**Background.** Despite current progress in research of congenital diaphragmatic hernia (CDH), management is still challenging, requiring an interdisciplinary team for optimal treatment and mortality remains high. We aimed to improve comprehension of predictors for mortality.

**Methods.** A 16 year retrospective review of all infants diagnosed and treated with CDH, at the Medical University of Vienna, was performed. We compared medical parameters between survivors and non-survivors until discharge from the paediatric or neonatal intensive care unit.

**Results.** During the observational period 66 patients were diagnosed with CDH. Overall survival was 84.6%. The majority of patients were inborn, with a mortality of 14.6%. Fifty-one patients (78.5%) had left-sided hernia with a mortality of 7.8%. In comparison, right-sided hernia occurred less frequently (n=12), however, showed higher mortality (33.3%). Critically instable patients were provided with veno-arterial ECMO (32.3%, n=21). Survival rate among these infants was 66.7%. Right-sided CDH, treatment with iNO over 15 days and the use of ECMO over 10 days were significant risk factors for mortality.

**Conclusions.** This retrospective single-centre analysis of patients with CDH enhances understanding of risk factors for mortality, helping to improve management and enabling further evaluation in prospective clinical trials.

### RESPIRATORY FAILURE IN A PRETERM NEONATE WITH A COMBINATION OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR GENE MUTATIONS: A CASE REPORT

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**Background.** Cystic Fibrosis (CF) is an autosomal recessive disease caused by transmembrane conductance regulator (CFTR) gene mutations. The diagnosis may be suspected following prenatal screening, while respiratory manifestations are rare during the neonatal period.

**Objectives.** We aim to report the clinical and imaging findings in an unusual case of fatal neonatal CF and to discuss diagnostic and therapeutic challenges.

**Methods/Results.** A male neonate born at 30 weeks gestation presented with severe ventilator-dependent respiratory distress. Initial radiographic appearances were consistent with RDS. Subsequent radiographs disclosed extensive areas of consolidations and atelectasis despite surfactant therapy together with unilateral pulmonary interstitial empysema (PIE). Thick tracheal secretions were routinely aspirated. Positive cultures of the endotracheal tube were treated with repeated antibiotic courses. There was no pancreatic insufficiency and bowel movements were normal. CT at a later stage disclosed extensive areas of consolidation and atelectasis alternating with areas of ground glass, subpleural luscencies and unilateral PIE. Fatal respiratory failure occurred despite oscillator therapy. Mutation analysis with next generation sequencing revealed three heterozygote CFTR vaiants: c.1265C>Tin exon 10, c.1312A>Gn exon 10 and c.1408G>A in exon 11, each one previously described as neutral when present in isolation.

**Conclusions.** The diagnosis of CF needs to be considered in neonates with respiratory failure. Imaging appearances are non-specific with an overlap between RDS, bronchopulmonary dysplasia complicated by PIE and infection. Rare CFTR mutations are increasingly recognized as next generation sequencing becomes widely available. Description of cases of new genotype-phenotype associations contributes to better understanding of CF pathogenesis and future prenatal screening.

### THE EFFECT OF POSTNATAL CORTICOSTEROID ON BROWN ADIPOSE TISSUE IN NEONATAL RATS

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**Background.** Corticosteroids have been used to prevent or treat bronchopulmonary dysplasia in preterm infants. Early postnatal exposure to dexamethasone (Dex) has been shown to increase the risk of adverse neurodevelopmental outcomes. Dex was also shown to disrupt brown adipose tissue (BAT) thermogenesis in adult mice. The effect of immediate postnatal exposure to Dex on brown adipose tissue in neonatal rat is not known.

**Methods.** Rat pups were administered Dex or normal saline (Con) on postnatal day (PD) 1 to 3. Body weight, BAT weight, BAT histology and UCP1 protein levels were examined on PD4. BAT function was evaluated by cold exposure under 12°C for 6 hours. The impact of Dex on BAT mitochondrial morphology, membrane potential, fusion and fission were also analyzed.

**Results.** Dex-treated rat pups, compared with Con, showed growth retardation, whitening of interscapular BAT, and higher mortality rate under cold environment. The expression of UCP1 protein was not significantly different between Con and Dex groups. Dex-treated BAT mitochondria showed decreased membrane potential. Under electron microscope, mitochondria were elongated in shape, showed electron-increased density and loss of normal cristae pattern. The expression of both mitochondria fission (DRP1 and MFF) and fusion proteins (OPA1, MFN1, and MFN2) were increased after Dex treatment. Dex treatment also increased translocation of fission (DRP1, MFF, and FIS1) and fusion proteins (OPA1 and MFN2) to the mitochondria. These results suggest that Dex treatment has a great impact on mitochondrial dynamics.

**Conclusions.** Postnatal exposure to Dex led to alternation of morphology and impairment of function of BAT mitochondria, resulting in BAT whitening and cold intolerance. Whether these effects persisted into adulthood and led to metabolic derangements requires further researches.



### SHORT-CHAIN FATTY ACID CONCENTRATIONS IN HUMAN MILK CONSUMED BY INFANTS BORN AT DIFFERENT GESTATIONAL AGES AND THE VARIATIONS IN CONCENTRATION PER LACTATION STAGE

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**Background.** Numerous articles have reported global fatty-acid (FA) profiling of human milk; however, few have reported the short-chain fatty acids (SCFAs) concentration because of the unique physical-chemical properties of the SCFAs. Compared with long-chain FAs, SCFAs are more water soluble and are easily evaporated with organic solvents, resulting in selective loss via the most widely used gas chromatography (GC) analysis methods (GC-flame ionization detector [FID] and GC-mass spectrometry [MS]). In addition, because of the low SCFA content, it is easy to be ignored in the spectrum due to selective loss. Different detection methods and individual differences between human milk samples can affect the SCFA content in human milk, and the methyl esterification methods must be compared.

**Objective.** This study aimed to quantify the SCFAs in human milk and investigate the SCFA concentrations in human milk consumed during lactation by infants born at different gestational ages.

**Methods.** One hundred eighty milk samples from mothers of 30 full-term, 10 early-preterm ( $\leq$ 32 wk), 10 mild-preterm (32–34 wk), and 10 near-term (34–37 wk) infants were collected from colostrum, transitional, and mature milk. The human milk triacylglycerols (TAGs) were transferred into fatty-acid methyl esters via potassium methoxide in methanol and determined using gas chromatography (GC).

**Results.** Total SCFA concentrations (4:0, 6:0, and 8:0) were highest in the mature milk (1.47  $\pm$  0.66 mg/g fat from full-term infant milk) and were approximately 42.18% higher than those in transitional milk. Significantly higher SCFA concentrations were found in full-term milk than in preterm milk (p = 0.001). The milk TAGs were analyzed using UHPSFC-Q-TOF-MS, which showed that the SCFAs were mainly esterified with three long-chain fatty-acid groups (16:0, 18:1 n-9, and 18:2 n-6) at the glycerol backbone. The infants' daily SCFA intake from human milk was estimated and was increased during lactation. The SCFA intake from mature milk for full-term infants (~82 mg/d) was approximately twofold that for preterm infants (~35 mg/d).

**Conclusions.** The correlation between dietary SCFAs in human milk and nutrition in newborns, especially in the gut microbiotas of preterm infants, requires further study.

### CHANGES IN HUMAN MILK MACRONUTRIENT, LYSOZYME AND LACTOFERRIN COMPOSITION DURING MILK PROCESSING IN VILNIUS DONOR HUMAN MILK BANK

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**Background.** Donor human milk is considered a preferred alternative to mother's milk for feeding premature infants. Donor milk undergoes a number of procedures from donation to feeding sick babies, which include freeze-thaw cycles, transferral to different containers and pasteurisation. Holder pasteurisation currently is the most commonly used method in donor human milk banks for the microbiological safety of donated milk. Undergoing procedures can alter nutritional and biological properties of milk, however, available data remains controversial.

**Objective.** The aim of our study was to evaluate the changes of macronutrient in human milk, energy and bioactive proteins (lactoferrin and lysozyme) during milk processing in the Vilnius donor human milk bank.

**Methods.** The study was conducted at the Neonatal Centre of Vilnius University Hospital Santaros Klinikos between October 2017 and July 2018. Human milk samples were collected in a volume of 70 mL from forty-two hospitalized women within 14–16 days after delivery. The macronutrients (protein, fat, carbohydrate) and energy concentration in the each sample were first evaluated in fresh milk and again after the milk samples were frozen at -40 °C, then thawed and pasteurised. Mid-infrared spectrophotometry (MIRIS Human Milk Analyser) was used to evaluate the content of macronutrients and energy in human milk samples. An ultrasonic homogenization of the milk samples was performed with a Miris Sonicator before analysis of macronutrient. Lactoferrin and lysozyme concentrations in each milk sample were also evaluated in thawed unpasteurised milk and after Holder pasteurization by ELISA assays.

**Results.** Forty-two paired human milk samples were analysed. The macronutrient and energy content in human milk did not differ in fresh and pasteurized human milk samples (p > 0.05). The average loss of lysozyme after pasteurisation was 35% and lactoferrin was reduced by > 99%.

**Conclusions.** While the processing of human milk did not affect the macronutrient content, it did result in a significant loss of lysozyme and lactoferrin concentrations. Milk processing in donor human milk banks should be revised and new methods introduced in order to minimise the loss of the bioactive components in human milk.

### LACTOBACILLUS ACIDOPHILUS/BIFIDOBACTERIUM INFANTIS PROBIOTICS ARE BENEFICIAL TO EXTREMELY LOW GESTATIONAL AGE INFANTS IN THE CONTEXT OF HUMAN MILK EXPOSURE

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**Background.** Numerous studies on the therapeutic effects of probiotics in preterm infants have been performed, however, the results remain inconclusive due to a high variability in study protocols, target populations and endpoints, probiotic formulations and the context of nutrition.

**Objective.** To evaluate the distinct effect of prophylactic Lactobacillus acidophilus/ Bifidobacterium infantis probiotics on outcomes of preterm infants < 29 weeks of gestation in the context of human milk exposure.

**Methods.** We performed an observational study of the German Neonatal Network (GNN) between January 1st 2013 until December 31st 2018. Prophylactic probiotic use of Lactobacillus acidophilus/Bifidobacterium infantis was evaluated in preterm infants < 29 weeks of gestation (n= 7516) in subgroups stratified to human milk exposure: (I) Exclusively expressed breastmilk (EBM) of own mother and/or donors (EBM group, n=1568), (II) EBM of own mother and/or donor and formula (mix group, n=5221) and (III) exclusive exposure to formula (formula group, n=727). The effect of probiotics on primary outcomes and growth was tested in univariate models and adjusted in linear/logistic regression models.

**Results.** 5954 (76.5%) infants received Lactobacillus acidophilus/ Bifidobacterium infantis. Probiotic use was associated with improved growth measures in the EBM group (e.g. weight gain velocity in g/d: effect size B = 0.224; 95% CI: 2.82 - 4.35; p <0.001) but not the formula group (effect size B = -0.06; 95% CI: -3.05 - 0.28; p= 0.103). The EBM group had the lowest clinical sepsis risk (34.0%) as compared to the mix group (35.5%) and formula group (40.0%). Only in the mix group probiotic supplementation proved to be protective against clinical sepsis (OR 0.69; 95% CI: 0.59-0.79; p<0.001).

**Conclusions**. Our observational data indicate that the exposure to Lactobacillus acidophilus/ Bifidobacterium infantis probiotics may compensate for the growth disadvantage of exclusively EBM fed infants as compared to formula fed infants. To exert a sepsis-preventive effect, probiotics seem to require the nutritional context of human milk.

### IMPACT OF PDA ON POSTNATAL GROWTH AND COGNITION OF VERY LOW BIRTHWEIGHT INFANTS

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**Background.** The management of a hemodynamically significant patent ductus arteriosus (PDA) in preterm infants with clinical signs and a diameter of > 1.5 mm is still a controversial topic. Previously prophylaxis with ibuprofen has been practiced in some units. Nowadays, a conservative strategy, medical treatment with ibuprofen or surgical treatment are utilized. We aim to determine the impact of a hemodynamically significant PDA on the short term growth and cognitive outcomes of very low birth weight (VLBW) infants managed at a tertiary unit in Singapore.

**Methods.** A retrospective study on growth and cognitive was conducted from the outpatient follow up clinic. We aimed to determine the impact of hemodynamically significant PDA on the short term growth and cognitive outcomes of very low birth weight (VLBW) infants managed at a tertiary unit in Singapore from 2014 till 2018

**Results.** 61 children were analyzed at a median age of 34.5 (IQR 18-52) months, with equal gender distribution. Interestingly those infants who had a hemodynamically significant PDA requiring treatment (n= 38) were more mature (29.9 vs 27.5 weeks) and heavier 1305g vs 985g (P < 0.01) at birth compared to VLBWs without PDA (n=23). Despite their maturity and also larger weight, those who required treatment were more likely to have been mechanically ventilated 66.7% vs 33.3% (p < 0.01).As such, more who required PDA treatment had chronic lung disease (CLD) at 36 weeks (83.8% vs 60.8%%,p<0.05) and more required inhaled medications on follow-up. Growth failure of VLBWs without PDA was more evident until 6 months corrected age and was associated with increased length of stay (79.5 vs 59.0 days, P <0.01). Median cognitive scores were similar 97(IQR 85-105) vs 92(IQR 81-101). No differences were seen in the hearing loss or cerebral palsy rates.

**Conclusions.** In our cohort, the presence of a hemodynamically significant PDA requiring treatment was associated with a higher incidence of CLD needing long term medication but no impairment of cognition and growth at follow-up.



#### 12 SEVERE UPPER GI BLEEDING IN NEWBORNS WITH DIFFERENT ETIOLOGIES

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**Background.** Upper gastrointestinal (UGI) bleeding commonly presents with hematemesis and/or melena. In newborns, etiology includes swallowed maternal blood, coagulation disorders, cow milk intolerance, stress gastritis, sepsis, and trauma. However, severe UGI bleeding is rare.

**Methods.** In 2019, three neonates presented with life threatening UGI bleeding and required hemodynamic and medical stabilization with multiple Packed Red Blood Cell (PRBC), Fresh Frozen Plasma (FFP) transfusions, Vitamin K (Vit-K) and Proton Pump Inhibitor (PPI) treatments. After the stabilization, all had endoscopic evaluation. Their etiology, clinical course, endoscopic findings and prognosis are highlighted in this presentation.

Results. All neonates were outborn and were admitted with life-threatening UGI bleeding. Case 1 was a 3-day-old male newborn with sudden and severe UGI bleeding with 50 ml/kg blood loss. He received multiple PRBC and FFP transfusions and was treated by PPI and Vit-K. Endoscopy showed a widespread erosion through out the stomach. Case 2 was a 2-day-old male newborn with severe UGI bleeding which started around 24 hours of life. Mother had acetyl salicylic acid treatment during the pregnancy. His blood loss was around 55 ml/kg. He received similar stabilization treatment and regular Vit-K administration. Endoscopy revealed erosive pangastritis. Case 3 was a 19-dayold preterm female infant with severe UGI bleeding which started after 3rd dose of oral lbuprofen treatment. She stabilized with multiple PRBC transfusions. Endoscopy showed erosive areas at the lower esophagus. In our cases clinical presentation was similar but the etiology was guite different. In consequence, they presented with severe form of stress gastritis, Vit-K deficiency and a medication side effect. Endoscopy was helpful to rule out other reasons (ie, hemangioma) and to show extension of the damage. Hemodynamic stability was the key for good outcome. Vit-K and PPIs were used successfully. All infants were healed and discharged without any complication.

**Conclusions.** Although severe UGI bleeding is usually seen in sick premature infants, clinician should remember that healthy preterm and term infants can also have this life-threatening condition. Rapid evaluation, hemodynamic stabilization, and resuscitation are the key factors for good outcome. When babies are stabilized, endoscopic evaluation should be performed.



### 13 ARE LATE PRETERM INFANTS AT RISK FOR METABOLIC BONE DISEASE?

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**Background.** Metabolic bone disease (MBD) is the failure of the newborn skeleton to provide sufficient mineralization compared to the in utero fetus with high cumulation rate. As bone mineralization mainly occurs in the last trimester of pregnancy, preterm babies are prone to MBD.

The aim of this study is to determine the prevalence of metabolic bone disease in late preterm infants.

**Method.** The study was conducted between June 2018 and May 2019. Thirty one late preterm and 39 term babies were included in the study. Serum calcium (Ca), phosphorus (P), magnesium (Mg), vitamin D [25(OH)D], parathormone (PTH), osteocalcin levels and alkaline phosphotase (ALP) activity were studied from umbilical cord blood samples and at the fourth month of life. At birth, the levels were compared between term and late preterm babies, but at the fourth month they were compared with reference values.

**Results.** Cesarean delivery rate was 82% in the late preterm and 68% in the term group; 64.5% of late preterms, 36% of term babies were girls. The mean gestational week and birth weight of late preterms and term babies were 35.8 $\pm$ 0.7 weeks and 2704 $\pm$ 444 grams, 39 $\pm$ 0.8 weeks and 3280.1 $\pm$ 331 grams, respectively. The mean umbilical cord blood Ca, P, Mg, ALP levels in late preterm and term babies (9.40 $\pm$ 0.98mg/dL vs 9.72 $\pm$ 0.69mg/dL, 5.20 $\pm$ 1mg/dL vs 5.12 $\pm$ 0.55mg/dL, 1.95 $\pm$ 0.64mg/dLvs 1.70 $\pm$ .23mg/dL and 150.1 $\pm$ 46.1U vs 124.1 $\pm$ 32.6 U/L) were not statistically different between the groups (p>0.05). Vitamin D levels (18.4 $\pm$ 10.2 vs 27.1 $\pm$ 8.3 µg/L) were significantly lower in late preterms during birth, but were within normal levels at the 4th month of life.

**Conclusions.** The blood levels of the biochemical markers used for metabolic bone disease did not show an increased risk for MBD in late preterm babies.

### DAILY AMPLITUDE OF CEREBRAL REGIONAL OXYGEN SATURATION AS A PROGNOSTIC TOOL FOR CARDIOPULMONARY STABILITY IN NEWBORNS WITH RESPIRATORY DISORDERS: A PROSPECTIVE OBSERVATIONAL STUDY

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**Background.** Respiratory disorders are a common problem in newborns with considerable mortality. It is a heterogeneous group of diseases with varying incidence, underlying etiology, clinical course and outcome. Regional cerebral oxygen saturation (crSO2) measured by near-infrared spectroscopy (NIRS) might facilitate early detection of newborns at risk of serious complications. Our objectives were to determine the relationship between crSO2 amplitude during the first day of life ( $\Delta$ crSO2) in near term/term newborns admitted to the NICU and the time to cardiopulmonary stability (weaning from inotropes/vasopressors and mechanical ventilation) and to compare validity of  $\Delta$ crSO2 versus other vital signs in predicting the time to cardiopulmonary stability in this group of patients.

**Methods.** In this prospective observational study, 41 newborns with respiratory disorders requiring mechanical ventilation (gestational age  $36,3\pm2,6$  weeks; birth weight 2999 $\pm689$  grams, Apgar score at 1 min – 8 (6-8)) admitted to the NICU were enrolled within 1 h from the birth. Cerebral oxygenation was monitored during the first week of life by Invos TM 5100C Cerebral/Somatic Oximeter Monitor (Covidien) via Pediatric SomaSensor (SAFB-SM) applied in the center of the forehead.

**Results.** Nine patients had  $\triangle$ crSO2 more than 20% and only 3 of them were stabilized during the first week of life. Thirty two patients with  $\triangle$ crSO2 less than 20% and only 3 of them did not reach cardiopulmonary stability during the same period of time (p = 0,001). Cox regression analysis showed that "high"  $\triangle$ crSO2 (hazard ratio (HR) = 3,25; 95% confidence interval (CI) 1,52–6,95; p = 0,002) was independently associated with prolonged cardiopulmonary compromise in newborns. The discrimination of area under ROC curve for  $\triangle$ crSO2 values and time to cardiopulmonary stability were 0,769, (p = 0,013). In contrast, other variables such as maximum lactate levels on the first day of NICU admission (HR = 1,41; 95% CI 0,68–2,94; p = 0,357) were not associated with the time to cardiopulmonary stability.

**Conclusions.** Our findings suggest that amplitude of cerebral rSO2 fluctuations during the first day of life in newborns with respiratory disorders could serve as a prognostic tool for estimating the time to reach cardiopulmonary stability at the end of the first week of life.

### APOPTOSIS AND CONSECUTIVE BLOOD BRAIN BARRIER BREAKDOWN AS A POTENTIAL KEY MECHANISM IN UREAPLASMA-DRIVEN NEUROINFLAMMATION

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**Background.** Although *Ureaplasma* species (spp.) are generally considered as low-virulent commensals of the adult genitourinary tract, they can induce chorioamnionitis, contribute to preterm birth, and may furthermore cause sepsis, pneumonia and meningitis in neonates. Underlying pathomechanisms in *Ureaplasma*-driven neuroinflammation are largely unknown. Inflammation is a meticulously orchestrated process involving cytokines and chemokines, cell death, and, in neuroinflammation, the blood brain barrier (BBB). The BBB protects the central nervous system (CNS) from external influences, and barrier breakdown is associated with several neuroinflammatory diseases.

**Objective.** The current study addressed *Ureaplasma*-induced cell death in human brain microvascular endothelial cells (HBMEC) and its influence on cell barrier properties.

**Methods.** Native or bacterial lipopolysaccharide-primed HBMEC were exposed to serovar 3 of *Ureaplasma (U.) parvum* or serovar 8 of *U. urealyticum*. Numbers of dead cells and key agents in apoptosis, pyroptosis, and necroptosis were assessed using flow cytometry, qRT-PCR, and RNA sequencing. The xCELLigence technique was employed to continuously monitor cell adhesion properties.

**Results.** Ureaplasma spp. induced cell death in HBMEC (p < 0.05). Agents involved in apoptosis were up-regulated upon Ureaplasma exposure, including caspase 7 and caspase 9 mRNA levels (p < 0.01) as well as caspase 3 mRNA expression (p < 0.05) and activity (p < 0.01). Ureaplasma isolates reduced mRNA levels of the inflammatory caspases 1 (p < 0.01) and 4 (p < 0.05) as well as mRNA expression of NOD-like receptor pyrin domain-containing 3 (p < 0.05) and receptor-interacting protein kinase 3 (p < 0.05) as additional participants in inflammatory cell death. Endothelial barrier properties were significantly reduced upon Ureaplasma exposure of HBMEC (p < 0.01).

**Conclusions.** We presume a major role of *Ureaplasma*-induced BBB breakdown in meningitis, but possibly also in several other inflammation-associated neonatal CNS diseases. *Ureaplasma*-driven apoptosis in HBMEC, main BBB constituents, may initiate barrier breakdown and allow *Ureaplasma* entrance into the CNS. An additional mitigation of inflammatory cell death may further impair immune defense mechanisms. Both may ultimately allow invasive CNS infections and chronic neuroinflammation by *Ureaplasma* spp.

### SURGICAL NECROTIZING ENTEROCOLITIS BUT NOT SPONTANEOUS INTESTINAL PERFORATION IS ASSOCIATED WITH ADVERSE NEUROLOGICAL OUTCOMEAT SCHOOL AGE

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**Background.** Gastrointestinal complications during the neonatal period, i.e. necrotizing enterocolitis (NEC) and spontaneous intestinal perforation (SIP), are associated with adverse short-term outcome in very-low-birthweight infants (VLBWI, < 1500g birth weight). However, little is known about the neurological outcome of survivors at school age.

**Objective.** To analyse the effect of NEC and SIP on neurological outcome at the age of six years.

**Methods.** Data of 2241 infants followed-up at the age of 6 years were included. To determine the effect of NEC and SIP on cognitive outcome in consideration of other important confounding factors, we used multivariable logistic regression models. In addition, infants with surgical diagnosis of NEC (n=43) or SIP (n=41) were compared to NEC (n=43) or SIP (n=41) negative controls using Mahalanobis distance matching.

**Results.** Infants with a history for NEC had a three times increased risk (RR 3.0 [1.8-4.2], p < 0.001) to develop IQ scores < 85 while history of surgical SIP did not increase the relative risk for lower IQs at school age (RR 1.0 [0.4-2.1], p = 1.000). In a matched-cohort analysis, we confirmed that infants with surgical NEC had lower mean IQ results than unaffected controls [SD] (85[17] vs. 94[14], p = 0.023) while no differences were found for history of SIP.

**Conclusions.** Our results reflect that the different aetiology and inflammatory extent of NEC and SIP may lead to disparate neurodevelopment trajectories. Hence, our data suggest a potential role of early gut-brain axis distortion in infants with NEC which needs to be further explored.

### DEVELOPMENT OF NATIONAL GUIDELINES ON NEONATAL ANALGESIA FOR THE KENYAN HEALTHCARE SYSTEM BASED ON A SYSTEMATIC REVIEW AND META-ANALYSIS OF THE LITERATURE, AND SUBSEQUENT GRADE ANALYSIS

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**Background.** Increasing numbers of neonates are undergoing painful procedures in low- to middle-income countries, with potentially significant negative neurodevelopmental sequelae. Engagement of paediatricians in the joint surgical care of these newborns is necessary for adequate pain management. In collaboration with paediatricians in Kenya, the present study sought to establish the first evidence-based guidelines for procedure-related neonatal pain that take account of the low-resource context of Kenyan district general hospitals.

**Methods.** An expert panel determined the scope of procedures (including heelprick, intramuscular/subcutaneous injections, bladder catheterisation, vene/arterial puncture, intravenous cannulation, CPAP, and lumbar puncture) and analgesics (including expressed breastmilk, breastfeeding, non-nutritive sucking, skin-to-skin, swaddling, music, oral sugar, local anaesthesia, paracetamol, morphine, ibuprofen, ketamine) to be reviewed. A PROSPERO registered systematic review following PRISMA guidelines was conducted on studies identified from MEDLINE, Embase, CINAHL & CENTRAL databases from 1953 to March 2019. We included data from RCTs using PIPP, NIPS, NFCS, DAN, heart rate and oxygen saturation as pain outcome measures. We conducted a narrative synthesis of all studies and conducted meta-analysis where appropriate. A panel of Kenyan experts followed GRADE guidance to assess the certainty of evidence supporting interventions and inform judgements on clinical recommendations.

**Results.** Of 2782 studies assessed for eligibility, data from 152 were analysed (79 contributed to meta-analyses). Drawing on narrative findings and metaanalyses, the panel recommended breastfeeding for all babies, or if unable to breastfeed, 1-2 mL of expressed breastmilk as first-line, or 1-2 mL of >10% oral sugar as second line based on a "High" certainty of superiority of these analgesics over placebo and taking account of the low-resource Kenyan healthcare setting. The panel also recommended parental presence during painful procedures with adjunctive provision of skin-to-skin or non-nutritive sucking.

**Conclusions.** We have generated the first procedure-related neonatal analgesic guidelines in Kenya by employing rigorous systematic review to inform decision-making by local experts able to account for context when making recommendations. These guidelines will improve periprocedural care of thousands of neonates throughout Kenya, and may be applied to surgical patients in the tertiary hospital setting.

### IMPLEMENTATION OF TELEMEDICINE SCREENING FOR RETINOPATHY OF PREMATURITY IN RURAL AREAS IN GUATEMALA

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**Background.** ROP is one of the most common preventable cause of childhood blindness in the world, it is responsible for up to 60% of blindness in children in some countries. Because of inadequate neonatal hospital care, the burden of ROP blindness has shifted to the moderately developed countries of Latin America.

**Methods.** There are 39 national hospitals with neonatal care in Guatemala, only 7 of those have an ophthalmology department and/or a ROP screening program. Most of the other centers refer the patients to ophthalmology clinics after detecting that children have obvious signs of poor vision, which usually means that the disease is in the most advanced stages and the treatment options are limited.

Preterm newborns were screened according to the guidelines established by the Guatemalan National Health Department. These guides suggest to screen for ROP in all newborns with a birthweight of less than 2000 grams and/or younger than 36 weeks of gestational age. Patients were screened for the first time at 4 weeks of age or at 32 weeks of post gestational age, while hospitalized or in the outpatient clinic. The technicians selected for the project were enrolled in a 3 month training program, which included: basic eye anatomy, fundamentals of ROP, manipulation of preterm infants and the use of the portable camera (Pictor Plus). Images and patient information (risk factors and medical history) was uploaded to a data base. A pediatric ophthalmologist with experience in ROP management analyzed the data base and gave indications regarding follow up and/or treatment needed.

**Results.** 487 premature neonates from 6 hospitals were included. All of them were followed using telemedicine from April to November 2019, with the screening criteria mentioned above. Mean gestational age of the neonates was 34.48 weeks (+SD), mean birth weight was 1747.93 gr (+SD) and 3.58% required treatment.

**Conclusions.** Although the gold standard for ROP diagnosis is indirect ophthalmoscopy done by an ophthalmologist with experience in ROP, the reality in most low/middle income countries like Guatemala does not allow this to happen. This is why there is a need to develop strategies to give coverage to this at-risk population and one of those strategies can be telemedicine based screening programs.

### **RESPIRATORY DISTRESS SYNDROME IN PRETERM INFANTS: POSSIBLE IMPACT OF SURFACTANT APPLICATION TECHNIQUES**

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**Background.** Respiratory failure caused by respiratory distress syndrome (RDS) is still a major problem in neonatology, and RDS is the most common cause of morbidity of premature infants. Surfactant substitution has been a major breakthrough in the treatment of RDS.

**Objective.** The aim of the study was to compare the effectiveness and outcome of individual surfactant application techniques in the treatment of RDS.

**Methods.** A retrospective analysis of three different surfactant application techniques of preterm infants with RDS was performed. The study group consisted of 198 neonates and was divided into three groups:

1. Premature neonates with mechanical ventilation and surfactant administration through a traditional intubation tube (average gestational age 27,6 weeks; average birth weight 1020g). n = 103

2. Premature neonates with exogenous surfactant administration via InSurE method (average gestational age 28,4 weeks; average birth weight 1124g). n = 59

3. Premature infants with exogenous surfactant supplementation through MIST (average gestational age 29,8 weeks; average birth weight 1425g) n = 33

**Results & Conclusions.** 1. In our retrospective study non-invasive methods of surfactant administration using MIST and InSurE methods seem to be safe and effective in the treatment of RDS.

2. Patients who received surfactant using MIST had a lower incidence of BPD compared to the other methods (33% vs 44% in the MV group and 49% in the InSurE treated group) and less severe intraventricular bleeding and a lower incidence of premature retinopathy. 4% of patients that were treated using MIST had severe IVH (stage 3 or 4), compared to 11% in the InSurE group and 20% in the MV group.

3. Prophylactic supply of surfactant with non-invasive methods already in the delivery room seems to be beneficial and seems to reduce the need for subsequent therapeutic doses of surfactant.

4. Patients with InSurE had statistically significantly fewer pulmonary haemorrhages, while necrotizing enterocolitis was more common.



### 20 DD-SURF: SURFACTANT ADMINISTRATION IN BETWEEN INSURE AND LISA

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**Background.** Whereas surfactant was traditionally administered via an endotracheal tube during mechanical ventilation, it is known that volutrauma damages the lung and ventilation should be prevented. Therefore the concept of INSURE (intubation with ventilation, surfactant administration and extubation) tried to minimize ventilation. The less or minimal invasive surfactant administration (LISA or MIST) avoids mechanical ventilation by giving surfactant intratracheally via a small catheter. Whereas recent studies have shown a benefit of LISA, that intervention has several disadvantages: lack of practice in neonatal intubation, need for secondary intubation due to respiratory deterioration, discontinuation of positive airway pressure, blocking the small tracheal diameter by the surfactant catheter.

**Objective.** To test an alternative approach of surfactant administration (DD-SURF) that combines the advantages of LISA and INSURE: surfactant administration in spontaneously breathing infants via the side-port of an endotracheal tube under continuous CPAP administration.

**Methods.** All newborns below 1500g birth weight, admitted to our neonatal intensive care unit (NICU) between 01/16 and 12/18 were included in this retrospective analysis. Success of DD-SURF was defined as surfactant administration in the delivery room (DR) with no subsequent ventilation during the first 72 hours of life.

**Results.** During the three years period 211 out of 292 included VLBW-infants received at least one dose of surfactant within the first 72 hours. A total of 194 received surfactant in the DR, either as DD-SURF (N=156) or during conventional mechanical ventilation (n=38). All infants with DD-SURF were transferred on CPAP to the NICU after an uneventful DR-management. 19% (30/156) required a re-intubation within the first 72 hours. Newborns requiring intubation after DD-SURF were more immature, smaller and had lower APGAR scores at 1 and 5 minutes. Since DD-SURF was restricted to the DR, a total of 126 VLBW-infants were successfully treated with DD-SURF, representing 60% of all infants receiving surfactant during the first 72 hours of life.

**Conclusions.** DD-SURF is a promising alternative to INSURE and LISA, combining advantages of both procedures. The success rate is comparable to LISA studies. Since neonatal endotracheal intubation is becoming rarer, DD-SURF offers an opportunity to remain proficient in this skill. DD-SURF still has to be evaluated in a randomized, controlled trial before widespread use can be recommended.

### EVALUATION OF RIGID AND FLEXIBLE CATHETERS FOR LESS INVASIVE SURFACTANT ADMINISTRATION IN PRETERM INFANTS WITH RESPIRATORY DISTRESS SYNDROME

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**Background.** Less invasive surfactant administration via thin catheters is the current standard for treating respiratory distress syndrome due to surfactant deficiency in preterm infants. The most commonly used catheter system is a flexible nasogastric tube inserted intratracheally with Magill forceps. Recently, a Less invasive surfactant administration specific, more rigid tool has been launched, the LISAcath®. This study compared a conventional nasogastric tube with the LISAcath® in terms of procedure duration and subjective preference in handling.

**Methods.** 40 medical students, 40 nurses and 12 neonatologists from the University Hospital in Salzburg took part in this study. The time to successfully place either catheter in the trachea of a preterm simulator has been recorded and monitored via video-laryngoscopy. Measurements were separated by groups and method used, resulting in three groups – students, nurses and doctors – with two subgroups for the methods.

**Results.** For the groups "medical students" and "nursing staff", the median procedure time was significantly shorter when using the LISAcath®. They took 79.2 and 69.5 seconds with the nasogastric tube compared to 25.0 and 28.2 seconds with the LISAcath® (p < 0.0001). In the doctors' group, the median time difference between both catheters was also visible but not significant. They required 34.6 seconds with the nasogastric tube and 18.3 seconds with the LISAcath® (p = 0.1320). The majority of each group ranked the LISAcath® to be easier in handling compared with the nasogastric tube.

**Conclusions.** The LISAcath®, specifically developed for less invasive surfactant administration, required shorter procedure times compared to a nasogastric tube used with Magill forceps and is subjectively easier to use.

### PIGTAIL CATHETERS VERSUS TRADITIONAL CHEST DRAINS FOR PNEUMOTHORAX TREATMENT IN TWO NICUS

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**Background.** Pneumothorax in newborns can be life-threatening. The traditional treatment of pneumothorax is chest drain placement. Recently, modified pigtail catheter has been proposed as a less traumatic approach despite limited experience in infants.

**Objective.** The aim of this study was to compare the effectiveness and safety of pigtail catheters versus traditional straight chest drains in term and preterm infants with pneumothorax, in two tertiary neonatal units: Policlinico Hospital in Bari, IT and John Radcliffe Hospital in Oxford, UK.

**Methods.** We retrospectively reviewed medical records of 47 newborns with pneumothorax admitted to the two units between October 2009 and June 2017, and treated with either pigtail catheters or straight chest drains.

**Results.** Three newborns (6.7%) were excluded from the study because they were treated with both types of drains. The remaining 44 neonates were included in the analysis. Overall, 56.8% (n = 25/44) of pneumothoraces were drained with pigtail catheters and 43.2% (n = 19/44) with straight drains. No differences in gestational age and birth weight were found. The success rate, defined as complete radiological resolution of the pneumothorax after drainage, was significantly higher in the pigtail group (96.0% versus 73.7%; p < 0.05). Days of drainage, length of hospital stay and duration of respiratory support were not significantly different. Subcutaneous emphysema and drain dislodgement/malfunction occurred only in the straight drain group (0.0% versus 11.1%; p = 0.18). No significant differences in mortality between the two groups were found (28.0% pigtail group versus 26.3% straight drain group; p > 0.05).

**Conclusions.** Pigtail catheters are a safe and effective alternative to traditional chest drains for infants with pneumothorax.



### 23 PREDICTION OF BRONCHOPULMONARY DYSPLASIA AT BIRTH BY MACHINE LEARNING ANALYSIS OF CLINICAL AND DIGITAL SPECTRAL DATA

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**Background.** Bronchopulmonary dysplasia (BPD) is a long lasting and serious complication in premature infants with high mortality and morbidity. The major causes include chorioamnionitis and preterm birth. The condition may be aggravated by various influences including volutrauma and oxidative stress in combination with invasive mechanical ventilation. No curative treatments are currently available.

**Objective.** The aim was to develop a predictive machine learning algorithm for BPD with the purpose to optimize the existing symptomatic treatments and to develop more effective treatments.

**Methods.** Recently we have developed an algorithm to measure lung maturity on gastric aspirates by mid-infrared spectroscopy as lecithin-sphingomyelin ratio (L/S) (doi:10.1111/apa.14896 and 14831). Infants in the clinical part of the studies were followed for 5 days to diagnose RDS. Sixty-one infants with gestational age 24-31 weeks from the clinical L/S-study were included in the actual multicenter non-interventional study. The study time was now expanded to discharge from hospital to diagnose BPD. The main BPD-diagnosis was need of oxygen day 28 with follow up assessment at 36 weeks postmenstrual age. To build the algorithm, chemometrics, a machine learning method to extract information from chemical, spectroscopical and clinical parameters by data-driven means was used. Mid-infrared spectra from gastric aspirates at birth combined with birth weight, gestational age and treatment with surfactant +/-were used to develop the algorithm. Support vector machine (SVM) classifier procedure and partial least square-regression (PLS) analysis were supplemented with cross-validation and other chemometric methods.

**Results.** Twenty-six infants (43%) had BPD and 35 (57%) no BPD. The algorithm predicted BPD early after birth with a sensitivity of 88% and a specificity of 91%.

**Conclusion.** We have developed a clinical predictive machine learning algorithm for BPD early after birth. A blind test of the algorithm is planned.

### EARLY-ONSET SEPSIS IN PRETERM INFANTS: DIAGNOSTICS AND TREATMENT DIFFERENCES IN 2011 AND 2016

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**Background.** Early - onset sepsis (EOS) is a blood infection that occurs in neonates within 72 hours after birth. Preterm delivery is an important risk factor with higher incidence of sepsis at smaller gestational ages.

**Objective**. The aim of this study was to identify confirmed and suspected EOS in preterm infants and to compare the presence of risk factors, clinical and laboratory signs, empiric antibiotic therapy as well as initiation and duration of antibiotic therapy in Hospital of Lithuanian University of Health Sciences Kauno Klinikos Department of Neonatology (HLUHS KK DN) in 2011 and 2016.

**Methods.** Suspected episodes of EOS in HLUHS KK DN of 2011 and 2016 were retrospectively reviewed. Collected data included demographics, results of clinical and laboratory tests, antibiotic therapy and diagnosis. We compared the amount of confirmed diagnoses of EOS in preterm infants, risk factors, clinical and laboratory signs, also information about treatment between the years (2011, 2016).

**Results**. There were 141 out of 557 patients (25,3%) in 2011 and 77 out of 486 patients (15,8%) in 2016 to whom antibiotic therapy was initiated during the first 72 hours. Birth weight was higher in 2016 with an average of 1771 g (SD 840 g) compared with 1506 g in 2011 (SD 634 g) (p=0,017). Presence of risk factors was higher in 2011 – 12,1% compared with 2016 – 3,9% (p=0,044). Presence of clinical signs did not differ between the years (p=0,61). There was no statistically significant difference in the time points of initiated antibiotic therapy (p=0,46). The length of antibiotic therapy did not differ between the cohorts. Duration of treatment was as follows: <72 hours 79 (56%) and 46 (59,7%); 73-119 hours 9 (6,4%) and 2 (2,6%); >120 hours 53 (37,6%) and 29 (37,7%) in 2011and in 2016 respectively. There was no difference between the years comparing the incidence of confirmed EOS diagnoses (22% in 2011 and 24,7% in 2016).

**Conclusions.** There was no statistically significant difference in presence of risk factors, clinical and laboratory signs and the use of antibiotics. No differences were found comparing confirmed cases of EOS.



### 25 ROAD TO THE NEW WORLD OF EARLY-ONSET SEPSIS PRACTICE

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**Background.** Early-onset neonatal sepsis (EONS) is defined as blood or cerebrospinal fluid (CSF) culture-proven infection within 72 hours after birth. U.K Hospital use either NICE or RCOG Guidelines or a hybrid version of these two guidelines which fails to consider the "wellness" at birth and how that modifies the risk of EONS. Kaiser Permanente Sepsis group from Northern California used Bayesian approach to create a multivariate model for predicting the risk for EOS. The algorithm uses: Population risk, intrapartum risk, infants' clinical condition at birth, wellness after birth and derives a computational risk score. KPSC does not consider "C" reactive protein

**Methods.** We used Kaiser Permanente Neonatal Sceptic Calculator on retrospective data on the use of empirical antibiotics in our postnatal ward care. We projected KPSC on 76 late preterm and term infants  $\geq$  34/40 weeks at birth over period of five months who received empirical antibiotics to prevent EOS.

**Results.** If we have used KPSC as it is in this cohort of babies, we would have given antibiotics to only 24 babies out of 76 babies (31.6%). This would have prevented 52 babies (68.4%) from getting antibiotics. If we take an extremely cautious approach as we should - any baby with any symptom or sign on first clinical examination to be included in "Equivocal" group -, we would have still given antibiotics to 54 babies in this cohort (71%) and have prevented 22 babies from getting antibiotics (29%). In addition, it would have reduced antibiotic exposure by 66 days, presence of Junior medical staff by 44 hrs, working time of NICU nursing staff by 396 hrs and maternal separation by 528 hrs.

**Conclusions.** Judicious adoption of KPSC could potentially reduce interventions and antibiotic use and promote bondage without missing additional cases of early-onset neonatal sepsis.

### GENETIC PREDISPOSITION TO EARLY-ONSET NEONATAL SEPSIS DEPENDING ON GESTATIONAL AGE

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**Background**. Early-onset neonatal sepsis remains one of the major causes of neonatal mortality. Genetic association studies may help to detect molecular mechanisms that are causally related to the disease occurrence. A number of potential functional candidate gene variants have been described but the data remain variable and in some points controversial most likely due to heterogeneity and small number of patients.

**Objective.** To investigate genetic polymorphisms in neonates according to GA, in order to find genes potentially involved in response to infection.

**Methods.** The study included 379 neonates (24-41 weeks of gestation) < 72 hours of life. All neonates had signs of respiratory distress and required respiratory support. Peripheral blood samples for genotyping DNA were taken in all patients at the same time of sepsis-workup. We examined SNP in several groups of genes. Genotyping was performed by the specific PCR product melting curve analysis elaborating "kissing" (adjacent) probes (DNA-technology, Moscow, Russia).

In a retrospective analysis all patients were divided into 2 main groups depending on the reason of respiratory distress (infectious or non-infectious): Group 1: 161 neonates with RDS or transient tachypnea of neonate (TTN), Group 2: 218 neonates with early-onset neonatal sepsis (EOS). Based on the gestational age, the neonates of the 2 main groups were divided into 4 subgroups according to gestational age (GA): 24-28 wks, 29-32 wks, 33-36 wks, ≥37wks.

**Results**. We identified statistically significant differences in the distribution of alleles and genotypes in neonates having infectious and non-infectious cause of respiratory distress for various genes depending on GA. The distribution of the following genotypes and alleles was statistically different: in subgroup of preterm infants 29-32 wks - NOS3-786, NOS3-894, IL1b; in neonates 33-36 wks - AGTR2, IL4R1902, IL8, GNB825, HTR2A; in neonates ≥37 wks - IL8, ADD1, ADRB3.

**Conclusion.** The development of early-onset infection is not only associated with the genes of innate immunity, but also with genes regulating vascular tone and energy metabolism, indicating a complex mechanism of the process. Detected genetic associations vary among neonates in association with GA and may be related with maturation patterns of different systems.

### 27 SEPSIS MORTALITY OF EXTREMELY PRETERM INFANTS IN GERMANY AFTER THE INTRODUCTION OF COLONIZATION SCREENING

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**Background.** According to German infection surveillance guidelines updated in 2013, a weekly screening followed by extended hygiene precautions for infants colonized with drug-resistant or highly epidemic organisms is mandatory for neonatal intensive care units (NICU). The scientific evidence of this recommendation is limited.

**Objective.** We aimed to evaluate the sepsis incidence and pathogen specific fatality rates before and after the guideline update in a large population-based cohort of preterm infants.

**Methods.** The German Neonatal Network (GNN) is a prospective cohort study including data from 62 German level III NICUs. Preterm infants born between 2011 and 2018 with a gestational age between 22+0 and 28+6 weeks were included in this study. We compared infants born before (2011-2013) and after publication of the updated guideline (2014-2018). The primary outcome was sepsis-related mortality.

Results. In-hospital mortality of extremely preterm infants was 12.9% (1654/12823). 277 non-survivors (16.7%) were classified as sepsis related deaths. Infants discharged between 2014 and 2018 (n=8903) had a lower total mortality (12.5% vs. 13.8%, p=0.036) and reduced rates for clinical sepsis (31.4 vs. 42.8%, p<0.001) and cultureproven sepsis (14.4% vs. 16.5%, p=0.003) as compared to infants discharged in 2011-2013 (n=3920). Nine pathogens were significantly associated with sepsis related mortality. Pseudomonas aeruginosa had the highest case-fatality rate [8/16, 50%, OR 47 (17-126), p<0.001)] followed by Candida albicans [13/55, 24%, OR 15 (7.8-28), p<0.001], E. coli [19/181, 10-5%, OR 5.6 (3.5-9.2), p<0.001)], extended spectrum ßlactamase (ESBL) E. coli [4/37, 11%, OR 5.6 (2.0-16), p=0.01] Klebsiella spp. [9/83, 11%, OR 5.4 (2.6-11.2), p<0.0001], Streptococcus agalactiae [8/88, 9.1%, OR 4.7 (2.2-9.7), p=0.001] Enterococci [9/114, 7.9%, OR 4.0 (2.0-8.0), p=0.001], Enterobacter [6/108, 5.6%, OR 2.7 (1.2-6.2), p<0.0001] and Staphylococcus haemolyticus [12/220, 5.5%. OR 2.7 (1.5-4.8), p=0.003]. Discharge after guideline update had no effect on pathogen-specific case fatality. In addition, total sepsis-related mortality (2.1% vs. 2.3%, p=0.54) and culture-proven sepsis rates with pathogens detected by colonization screening remained unchanged. While the exposure of GNN infants to cefotaxime declined over time (31.1 vs. 40.1%, p<0.001), the treatment rate with meropenem increased (31.6 vs. 26.3%, p<0.001).

**Conclusions.** Sepsis remains an important cause of death in extremely preterm infants. Weekly colonization screening is associated with reduced sepsis rates, but has no effect on sepsis-related mortality and sepsis with screening-relevant pathogens. The increasing exposure to meropenem should be a target of antibiotic stewardship programs.

### BACTERIOLOGICAL PROFILE AND ANTIBIOGRAM OF A NEONATAL UNIT IN A TERTIARY HOSPITAL IN SINGAPORE

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**Background.** Neonatal sepsis is one of the leading causes of morbidity and mortality in newborns. It is defined as a clinical syndrome characterized by signs and symptoms of infection which may or may not be accompanied by bacteraemia within the first month of life. We aim to identify common bacteriological isolates and antimicrobial susceptibility pattern in our neonatal unit. We also aim to formulate an antibiogram specific to our own neonatal unit.

**Methods.** This is a 3-year retrospective review of all bacteriological isolates obtained from neonates who were admitted to the neonatal high dependency and intensive care units in Singapore General Hospital between January 2015 to December 2017. Those with the same pathogen that was isolated within 10 days of the first isolate from the same patient was considered as a duplicate and excluded from the analysis.

**Results** Total of 206 neonates were recruited into the study, predominantly males (57.8%). Of these, 105 (51.0%) patients had late onset sepsis. Total of 383 bacterial cultures were isolated. Majority of the bacterial isolates were gram negative (60.6%), predominantly Escherichia coli (n=59, 15.4%), followed by Enterobacter species (n=54, 14.1%) and Klebsiella species (n=42, 11.0%). Both Escherichia coli and Klebsiella species demonstrated good antimicrobial susceptibility to Gentamicin (81.4% and 83.3% respectively) and Amikacin (98.3% and 95.2%, respectively). However, Enterobacter showed poor antimicrobial susceptibility to Gentamicin (29.6%) but good susceptibility to Amikacin (92.6%). Among the gram-positive cultures, Staphylococcus aureus was the commonest organism isolated (n=51, 13.3%) followed by coagulasenegative Staphylococcus (n=33, 8.6%) and Enterococcus species (n=24, 6.3%). Staphylococcus aureus demonstrated good antimicrobial susceptibility to Cloxacillin (100%) and Vancomycin (100%) but poor sensitivity to Penicillin (14%) and Ampicillin (13%). Both Enterococcus and Group B Streptococcus are highly susceptible to both Penicillin and Ampicillin. In this study, 39.4% were multi-resistant strains: 35 (9.1%) expressed Extended Spectrum Beta-Lactamase (ESBL) and 17 (4.4%) were Methicillin-Resistant Staphylococcus aureus-strains (MRSA).

**Conclusions.** Bacteriological profile and antimicrobial susceptibility pattern can vary within or across institutions. Hospital antibiogram is useful in the identification of common bacterial isolates and antimicrobial susceptibility rates within each institution. It can also be utilised as a reference tool in the selection of empirical antibiotic therapy and in monitoring antimicrobial resistance trend. Thus, we recommend that each neonatal unit should formulate their own antibiogram to optimise the management of neonatal sepsis within their institution.

### EPIDEMIOLOGY OF STAPHYLOCOCCUS AUREUS INFECTION IN THE NEONATAL PERIOD: A 12-YEAR SINGLE CENTER EXPERIENCE

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**Introduction/Objectives.** Staphylococcus aureus (S. aureus) is a common cause of neonatal infections worldwide. Aim of this study was to evaluate the incidence, clinical manifestations and resistance patterns of culture proven S. aureus infections in neonates admitted to a tertiary-care neonatal intensive care unit over a 12-year period.

**Methods.** We performed a retrospective cohort study in neonates with cultureproven, invasive and non-invasive, methicillin resistant (MRSA) or susceptible (MSSA) S. aureus infections admitted to a tertiary neonatal intensive care unit from January 2008 to December 2019. CDC criteria were used to define Community-acquired (CA), community-onset healthcare associated (COHA) and hospital-acquired (HA) infection. One isolate per patient was included.

**Results.** Overall 71 clinical isolates were identified (57 CA, 13 HA, 1 COHA). Mean birth weight was 3259 gr [range 1000-5050], mean gestational age was 38 weeks and median age at diagnosis was 11 days. Skin and soft tissue infections were the most common (22/71, 30.9%), while invasive infections were rare (5/71, 7%). Twenty-two isolates were MRSA (30.9%). Erythromycin and clindamycin resistance occurred in 20.9% (13/62) and 14.4% (10/69) of isolates respectively. Resistance to rifampicin and trimethoprim/sulfamethoxazole was found in 1.5% (1/67) and 2.9% (2/68) of the strains. No resistance to vancomycin, teicoplanin and linezolid was noted. No mortality occurred. The incidence of S. aureus infections increased during the study period from 3.58 per 1000 admissions in 2008-2013 to 27.53 per 1000 in 2014-2019. The number of CA infections increased and a significant rise of MSSA was noted from 1.9 to 14.8/1000 in the years 2014-2019.

**Conclusions.** The burden of S.aureus infections is considerable in the neonatal period. Over a 12-year period, we observed rising trends of CA infections along with an increase in methicillin sensitive strains.

### EPIDEMIOLOGICAL STUDY OF HOSPITAL-ACQUIRED CONJUCTIVITIS IN A LEVEL III NEONATAL UNIT

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**Background.** Hospital-acquired conjunctivitis (HAC) is one of the most common infections encountered in neonatal intensive care units (NICUs) and a significant cause of ocular morbidity if not adequately treated.

**Objectives.** To determine the etiology and antimicrobial susceptibility of pathogens causing HAC in a tertiary care reference NICU over a 3-year period.

**Methods.** Hospital databases were retrospectively searched for neonates with culture-proven HAC. Antimicrobial susceptibility testing data according to EUCAST guidelines were identified for all isolated microorganisms from January 2017 to December 2019. HAC cases were defined using the ECDC criteria as described in the HAI-Net ICU protocol, version 2.2 after reviewing the patient's chart. Cultures were not routinely tested for Chlamydia.

**Results.** HAC occurred in 151 hospitalized neonates (151/1278, 11.8%). The most common pathogens were gram-positive bacteria (67.3%), followed by gram-negative bacteria (29.8%) and fungi (2.9%). Among gram-positive pathogens, CoNs were the predominant organisms (66.3%), while Enterococcus spp, viridans streptococci, and S. aureus were less frequent (15.0%, 10.7%, and 5.9%, respectively). The most common gram-negative pathogens were Pseudomonas aeruginosa (28.9%) followed by Klebsiella (22.9%) and Enterobacter species (15.7%). Resistance rate to tobramycin, empirically prescribed as 1st line treatment, was significant (58.8%), while none of the isolates were resistant to chloramphenicol.

**Conclusions.** HAC is common in NICU. Continuous surveillance and physician awareness are required to prevent treatment failure with potentially serious sequelae for neonatal health, especially in premature neonates. Given the observed resistance patterns, tobramycin resistance should be considered in selecting empiric antibiotic treatment. It is worth emphasizing the importance of the implementation of strict infection control measures to prevent the dissemination of resistant strains.

### NO MATTER WHAT TOLL-LIKE RECEPTOR: STIMULATION TRIGGERS ROBUST PROINFLAMMATORY BUT DIMINISHED ANTI-INFLAMMATORY IMMUNE RESPONSES IN CORD BLOOD MONOCYTES

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**Background.** Particularities of early life immune responses are thought to place preterm and term infants at risk of severe infections and inflammation-related morbidities. Qualitative and quantitative differences in monocyte function as well as toll-like receptor (TLR) expression and signaling have been described. However, there is conflicting data on the responsiveness of neonatal monocytes. A number of studies point to stimulus-specific patterns.

**Objective.** To evaluate early immune responses in neonatal monocytes to stimulation with TLR1/2 (Pam3CSK4), TLR2/6 (zymosan), TLR3 (polyinosinic-polycytidylic acid; poly(I:C)), TLR4 (lipopolysaccharide; LPS), TLR5 (flagellin) and TLR9 ligand (CpG oligonucleotide) compared to adult cells.

**Methods.** Primary cord blood and adult monocytes were stimulated with TLR agonists. Using qPCR, flow cytometry and bead-based immunoassay, expression of pro- and anti-inflammatory cytokines and chemokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-8, IL-10, IL-1RA, IP-10, CXCL10) and interferons (IFN- $\alpha$ 2/- $\beta$  and IFN- $\gamma$ ) was assessed. Ratios of monocyte subsets and phosphorylation of TLR downstream molecules were analyzed by means of flow cytometry. TLR1-5 expression was evaluated at the transcriptional and translational level.

Results. Independent of stimulus, neonatal monocytes mounted proinflammatory cytokine and chemokine responses comparable to adult responses, both at the level of mRNA and protein expression. IL-6 and IL-8 release partly exceeded adult levels (Pam3CSK, zymosan: p<0.05; flagellin: p<0.01). However, TLR-stimulated cord blood monocytes released lower amounts of IFN-y (poly(I:C): p<0.01; LPS, flagellin, CpG: p<0.05), immunoregulatory IL-12 as well as anti-inflammatory IL-10 (Pam3CSK4, zymosan, poly(I:C), flagellin: p<0.05 versus adult) and IL-1RA (poly(I:C), LPS, CpG: p<0.05) and revealed higher ratios of proinflammatory to anti-inflammatory cytokines (TNF-α/IL-10: p<0.05, TNF-α/IL-1RA: p<0.05, IL-6/IL-10: p<0.05 and p<0.01, IL-6/IL-1RA: p<0.05. IL-8/IL-10: p<0.05 and p<0.01. IL-8/IL-1RA: p<0.05). While basal ratios of monocyte subsets correlated with those in adults, stimulus-induced levels of CD14++CD16- and CD14+CD16+ monocytes were markedly higher in neonates (zymosan, LPS, CpG; p<0.05; poly(I;C); p<0.01), Activation of the p65, p38, ERK1/2 and IRF3 signaling pathways as well as up-regulation of TLR2 and down-regulation of TLR-5 was comparable among neonates and adults. In contrast, poly(I:C)-induced expression of TLR3 mRNA was 4-fold higher in neonatal monocytes (p<0.01). TLR1 and TLR4 mRNA were up-regulated only in adult cells.

**Conclusions.** Our data confirm robust proinflammatory immune responses in cord blood monocytes, but show diminished immunoregulatory and anti-inflammatory responses, independent of stimulus, coming along with unfavorable cytokine ratios. The higher presence of non-classic pro-inflammatory CD14+CD16+ subsets in stimulated neonatal monocytes may further promote imbalanced inflammation. Particularities in stimulus-induced TLR expression may render neonates susceptible to a second hit.

# PATHOGENESIS OF NECROTIZING ENTEROCOLITIS: PEPTIDOMIC PROFILING OF RAT'S INTESTINE

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**Background.** Necrotizing enterocolitis (NEC) is a devastating inflammatory disorder of mostly preterm neonates. The incidence of NEC for neonates with a birth weight of 500-1500g is approximately 7%. It has been speculated that abnormal intestinal peptides might be involved in the development of necrotizing enterocolitis. Its underlying mechanism has not been elucidated yet.

**Methods.** In this study, we have established a rat model of NEC and have identified a different pattern of peptides between the NEC and control group.

**Results.** In the NEC-group 176 peptides derived from 91 proteins were differentially expressed, including 73 down-regulated and 103 up-regulated. A bioinformatic analysis of differentially expressed peptides was performed to predict the potential function of peptides. Our results indicate that glucose metabolism and amino acid metabolism might play important role in NEC.

**Conclusions.** We have identified peptide changes within intestinal cells of NEC which might contribute to a better understanding of the pathogenesis of NEC.



### 33 IS NT-PROBNP ASSOCIATED WITH POSTPARTUM ADAPTATION?

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**Background.** Reference values of NT-proBNP level in newborns may vary depending on Apgar scores and postnatal age. However, it is still unclear if the type of delivery affects NT-proBNP levels or not. In this study, we aimed to compare NT-proBNP levels in healthy term newborns born after vaginal delivery (n=28) or caesarean section (n=28).

**Methods.** Healthy babies with a gestational age of 38 weeks and older born in the hospital of the University of Kırıkkale were included in the study. The blood samples were taken in the first hours of life. The cases (n=56) were grouped according to the type of delivery, and the relationship between type of delivery and Apgar scores at the first and fifth minutes, hematological parameters, LDH and CPK levels, as well as NT-proBNP levels were investigated.

**Results.** Both groups were comparable in terms of gender, gestational age, body weight, and Apgar scores. NT-proBNP levels were 3145 (372-7231) pg/ml in babies born vaginally and 783 (401-6563) pg/ml in babies born by C-section (p <0.05). In addition, CPK and LDH levels were [483 U / L (116-1410), 343 U / L (40-1438)] in infants born vaginally, whereas those in born by caesarean section were [625 U / L (210- 926), 378 U / L (219-1000)] (p <0.05). Finally, the white blood cell counts of the patients born vaginally were higher (p<0.05), and a positive correlation between NT-proBNP values and white blood cell counts was found (r=0.6, p=0.000).

**Conclusion.** NT-proBNP levels of newborns born vaginally are in the range of predefined reference levels and increased four times compared to those born by C-section. The difference between the markers and white blood cell counts suggests that vaginal delivery causes physiological stress and this may be related to postnatal adaptation.

### CORRELATION OF REGIONAL OXYGENATION WITH RED BLOOD CELL PARAMETERS AND ARTERIAL BLOOD GAS DATA IN NEONATES

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**Background.** Since its introduction, near-infrared spectroscopy (NIRS) has drawn extensive interest as a potential tool for monitoring newborn haemodynamics. Current studies demonstrate that cerebral oxygenation correlates well with venous saturation in newborns, as well as with partial oxygen pressure in pediatric patients. However, studies on the relationship of NIRS data with red blood cell parameters and arterial blood gases (ABG) in newborns are lacking. Our objectives were to determine the relationships between regional oxygenation and red blood cell parameters, as well as ABG data in neonates.

**Methods.** In this prospective observational study 107 neonates with gestational age of 37 [35; 39] weeks were included. Twenty nine patients (27,1%) did not have an arterial line, thus they were not included in the ABG measurements. Patients were monitored using NIRS (Invos TM 5100C Cerebral/Somatic Oximeter Monitor; Covidien) during one week. The cerebral NIRS sensor (Pediatric SomaSensor - SAFB-SM) was applied in the center of the forehead, or at the midline of the abdomen, above the pubic area in the case of abdominal oxygenation. Statistically significant positive and negative correlations (p value <0,05) were noted between regional oxygenation and the studied blood parameters.

**Results.** The relationships between abdSO2 and levels of Hb and HCT was only observed only when respiratory disorders were present: (p=0,014). Weak positive correlations were found in the pairs: pCO2 and crSO2 (r=0,25, p<0,001), pH and cerebral fractional tissue oxygen extraction (cFTOE) (r=0,22, p<0,001), and negative: pH and crSO2 (r=0,25, p<0,001), pCO2 and cFTOE (r=0,29, p<0,001). It was noted that premature patients had a stronger correlation of red blood cell parameters with crSO2 and cFTOE. Reduction of pCO2 in arterial blood by 5 mmHg was accompanied by an increase in cFTOE by 0,02. The correlation coefficients between the level of pCO2 and crSO2 with cFTOE in the subgroups of term and preterm neonates did not differ significantly. No statistically significant correlations were found between PaO2 and SaO2 on the one hand and crSO2 on the other (r=0,01 p=0,983 for PaO2, r=0,10 p=0,058 for SaO2, respectively).

**Conclusions.** Our findings showed a statistically significant relationship between regional oxygenation and certain red blood cell parameters and ABG data in neonates.

### AN OBSERVATIONAL STUDY ON THE USE OF PERIPHERAL LINES VERSUS CENTRAL LINES IN NEONATAL INTENSIVE CARE UNITS

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**Background.** There is a debate regarding the best choice of the intravenous (IV) access for preterm infants – peripheral or central (umbilical or peripherally inserted central catheter). Each has its own advantages and disadvantages.

**Objective**: To study practices regarding selection of vascular access devices and outcomes related to them.

**Methods.** Prospective data collection on all IV lines used in a cohort of all the preterm infants born in Bnai Zion Medical Center's NICU over a seven month's period. Data was also collected on patients' demographics and outcomes related to IV access, including nutritional and infectious outcomes.

**Results.** The cohort included 120 infants, 94 of whom required IV line. Preterm infants born at  $\leq$  32 weeks gestation, or with head circumference  $\leq$  29 cm were more likely to require two or more IV lines or a central line for administration of parenteral nutrition or medications for longer periods. However, central lines were not associated with better nutritional status at discharge based on weight z-scores. Only one episode of infection - central line associated bloodstream infection in a peripherally inserted central catheter - was recorded, and no other line associated complications.

**Conclusions.** Our data supports the use of central IV access for preterm infants born at  $\leq 32$  weeks or with head circumference  $\leq 29$  cm. Our findings should encourage other NICUs to study their data on the use of central vs. peripheral IV lines and outcomes, in order to draw their own practice guidelines with recommendations for best choice for IV access in preterm infants.

### 36 40 YEARS OF EXPERIENCE IN A PRIVATE NICU IN GREECE

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**Background.** The MITERA NICU, a tertiary Center and the first private NICU in Greece began its operation in April 1979, as part of the newly founded MITERA Maternity Hospital.

**Objective.** To evaluate perinatal/neonatal mortality, survival rate and disease incidence of babies born at MITERA and admitted to the NICU from January 1980 up to December 2018.

**Methods.** Our data were retrospectively collected and analyzed from clinical archives and annual reports by the MITERANICU. We report summary statistics of total births, NICU admissions, prematurity rate, perinatal/neonatal mortality, disease specifics and overall survival.

**Results.** Years 1980-2018: Total births in Greece 4193263, births at MITERA 462111 (11.03%). Total NICU admissions 82269, total neonatal deaths 1844, neonates survived at MITERA 460567, survival rate at MITERA 99.60% and at MITERA NICU 97.76%. Perinatal/Neonatal Mortality: Significant decrease of PNM from 13.3% in 1980 to 4.23% in 2018 and impressive decrease of NM from 8.1% in 1980 to 0.38% in 2018.

The prematurity rate gradually increased from 6.0% in 1980 to 14% in 2018. Survival rate of babies with RDS significantly increased from 68% in the presurfactant era 1980-1992 to 100% in 2018. The survival rate according to birth weight increased impressively, especially in the VLBW and ELBW, up to 98.71%. Survival according to gestational age increased up to 95-100%. The incidence of BPD in the last 7 years was very low (4.99%). The incidence of early onset sepsis was very low 1,48 cases/ per 1000 live births, in the last 8 years and that of late onset sepsis 4.51%, mostly due to CoNS. No deaths were attributed to sepsis in our NICU within the last 8 years.

**Conclusions.** Our results indicate a substantial overall decrease in perinatal and neonatal mortality, significant increase in survival rates and low incidence of BPD and neonatal sepsis of babies born at MITERA and admitted to MITERA NICU during the years 1980-2018.

### NEONATAL OUTCOMES IN PATIENTS WITH HEMOLYTIC DISEASE OF THE NEWBORN AFTER INTRAUTERINE TRANSFUSIONS: A 7- YEAR SINGLE-CENTER EXPERIENCE

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**Background.** Due to major advances in the management of hemolytic disease of fetus and newborn (HDFN) immune hydrops - a severe and potentially lethal condition – has nearly disappeared in developing countries. Nevertheless, the problem of HDFN – associated morbidity and mortality is still highly relevant in populations with limited access to high quality medical care.

**Objective.** To investigate the course of HDN in neonates after IUTs and to identify strategies for further improvement.

**Materials and Methods.** This single-center retrospective study included 52 neonates with Rh-antiD-alloimmunization who underwent IUTs and were born in our Center in 2012-2019. The mothers were referred to the Center from distant regions of Russia mainly after telemedicine consultations.

**Results.** 1-st trimester antibody screening was performed in 94% of admitted women; anti-D-Ig prophylaxis was absent in 96% of women. Median GA at the time of maternal admission was 29 weeks (min-max 20-35). 25 fetuses (48%) presented with hydrops at the time of first IUT. Median number of IUTs was 2 (min-max 1-5). Intrauterine reversal of hydrops was achieved in 32% of fetuses (8/25) and most of these patients (7/8) did not have severe HD postnatally; only 1 patient required exchange transfusion (ET). All neonates were born prematurely and admitted to our NICU. Median GA at birth was 32,5 weeks (min-max 29-36,5), body weight - 2170g (min-max 1430 - 3350g). ET was required in 61,5% (32/52) of cases. Neurologic complications were registered in 3,8% (1 antenatally diagnosed PVL, 1 postnatal IVH  $\ge$ III). Overall survival was 91% (47/52), survival among neonates with hydrops -71% (12/17).

**Conclusions.** Our data show, that in a specific population of patients, managed with IUTs, all neonates were born prematurely and required intensive care. The high percentage (48%) of hydrops before 1<sup>st</sup> IUT indicates late referral to a tertiary center. Despite a fairly goodscreening rate for HDFN and introduction of IUTs, the incidence of fetal hydrops was relatively high; moreover, reversal of fetal hydrops was achieved in only 1/3 of patients. Extension of proper immunoglobulin prophylaxis and timely referral to tertiary centers appear to be the key factors for further improvement.

# IS PHOTOTHERAPY ASSOCIATED WITH FUTURE CANCER RISK? A SYSTEMATIC REVIEW AND META-ANALYSIS OF 6,637,417 CHILDREN

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**Background.** Phototherapy is the main treatment option for neonatal jaundice to prevent bilirubin encephalopathy. While generally believed to be safe, some studies have pointed out its possible association with childhood cancer. We aimed to assess the effect of neonatal phototherapy on the future cancer risk.

**Methods.** In December 2018, a comprehensive search in 13 databases was carried out to identify studies reporting childhood cancer development after exposure to phototherapy. A meta-analysis was done and Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated and pooled. Quality assessment was performed using the NIH tool for included studies.

**Results.** Ten studies were included and were eligible for qualitative and quantitative analysis. The studies had a considerably good level of quality. We found a statistically significant association between phototherapy exposure and any type of cancer [(OR = 1.23, 95% CI = (1.07-1.42), p = 0.004)], kidney cancer [OR = 2.52, 95% CI = (1.38-4.58), p = 0.003], any leukemia [(OR = 1.73, 95% CI = (1.31-2.30), p < 0.001], and myeloid leukemia [OR = 2.89, 95% CI = (1.80-4.63), p < 0.001].

**Conclusions.** Phototherapy may carry the risk of childhood cancers, especially kidney cancer, any leukemia and myeloid leukemia. Thus, it should be used only when indicated and searching for more conservative guidelines may be appropriate.

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