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CARDIAC PHYSIOLOGY PATHOLOGY

1. MYOCARDIAL FUNCTION IN LATE PRETERM INFANTS DURING THE TRANSITIONAL PERIOD: A COMPREHENSIVE APPRAISAL USING DEFORMATION AND ROTATIONAL MECHANICS

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Background: Reference ranges for myocardial deformation and rotational mechanics are becoming well-established in premature infants < 29 weeks gestation and in healthy term infants > 37 weeks gestation. However, to date, no data exists on later preterm infants between 30–34 weeks. We aimed to describe left (LV) and right (RV) longitudinal strain (LS) and systolic strain rate (SRs) in addition to LV rotational mechanics in this population over the first 48 h of age.

Methods: Late preterm infants born between 30 + 0 and 34 + 6 weeks gestation were considered for this study. Infants were excluded if they developed other morbidities during their hospital stay or if there was evidence of chromosomal anomalies or dysmorphic features. LV and RV LS and SRs in addition to LV apical and basal rotation, twist, twist rate (LVTR) and untwist rate (LVUTR) were measures on Days 1 and 2. Indices of RV mechanics including pulmonary artery acceleration time (PAAT), RV ejection time (RVET), Tricuspid annular plane systolic excursion (TAPSE) and Fractional area change (FAC) were also measured.

Results: Forty-five infants with a mean ± SD gestation of 32.7 ± 1.2 weeks and birthweight of 1894 ± 345 grams were included in this study. Twenty one (47%) were male, 42 (93%) were delivered via cesarean section, 32 (71%) received a complete course of antenatal steroids, and 15 (33%) received magnesium sulphate. There was no change in the majority of LV functional measurements with the exception of LVURT. There was an increase in PAAT, RVET and PAAT:RVET. TAPSE and FAC increased over the study period. RV longitudinal Strain and SRs did not change (Table 1).

Conclusions: This study establishes reference ranges for LV and RV functional parameters in uncomplicated late premature infants. LV function remains relatively preserved over the first 48 h in this population. RV function measurements (TAPSE and FAC) increase in magnitude likely reflecting of the physiological decline in pulmonary vascular resistance with an observed increase in PAAT.

Keywords: Deformation, Rotational Mechanics, Late Preterm Infants, Left ventricle, Right ventricle

Disclosures: None declared

2. DOES PRONE SLEEPING AFFECT CARDIOVASCULAR CONTROL IN PRETERM INFANTS IN NICU?

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Background: Preterm infants are frequently placed prone in the neonatal intensive care unit (NICU) to improve respiratory function. However, prone sleeping is associated with impaired

	Day 1	Day 2	p
Time of Echocardiogram (Hours)	4 [3 – 7]	49 [48 – 52]	<0.01
LV Deformation Imaging			
Global Longitudinal Strain (%)	18.2 ± 2.7	19.3 ± 3.4	0.03
Global Longitudinal Systolic SR (1/s)	1.7 ± 0.3	1.8 ± 0.4	0.11
LV Rotational Mechanics			
Apical Rotation (°)	8.2 [5.7 – 11.6]	7.7 [4.2 – 12.1]	0.80
Basal Rotation (°)	2.8 [0.0 – 6.3]	0.3 [-1.6 – 3.5]	0.27
Twist (°)	6.6 [0.3 – 8.9]	6.2 [2.8 – 9.7]	0.34
Torsion (°/cm)	2.9 [0 – 3.9]	2.8 [1.2 – 4.4]	0.22
Twist Rate (°/second)	89 [60 – 123]	99 [60 – 153]	0.19
Untwist Rate (°/second)	81 [40 – 127]	117 [80 – 170]	<0.01
Event Timing			
Pulmonary artery acceleration time (PAAT, ms)	44 ± 15	61 ± 20	<0.01
Right ventricular ejection time (RVET, ms)	166 ± 25	184 ± 30	<0.01
PAAT:RVET	0.27 ± 0.07	0.33 ± 0.09	<0.01
Deformation Imaging			
Free Wall Longitudinal Strain (%)	19.7 ± 4.2	19.1 ± 4.7	0.54
Free Wall Longitudinal Systolic SR (1/s)	1.8 ± 0.5	2.1 ± 0.6	0.06
RV-Specific Measurements			
Fractional Area Change (%)	23 ± 9	27 ± 9	<0.01
TAPSE (mm)	6.6 ± 1.3	7.3 ± 1.5	<0.01

Values presented as means ± SD or Median [IQR]

[ID54] Table 1 Functional Measurements

cardiovascular control in both term infants and preterm infants after term-corrected age. In term infants, heart rate (HR) is increased and HR variability (HRV) is decreased when infants sleep prone. Currently, there is a paucity of data on the effect of prone sleeping on HRV in preterm infants during their early postnatal weeks in NICU when they are most vulnerable to cardiovascular instability. We assessed the effects of position and sleep state on HRV in preterm infants longitudinally over the first 6 weeks of life.

Methods: Fifty-five preterm infants (born between 24–34 weeks of gestation) were studied weekly for 6 weeks after birth with cardiorespiratory monitoring, including electrocardiogram (ECG). Infants slept for 1 h in both the prone and supine positions and data were analysed for both active sleep (AS) and quiet sleep (QS). Spectral analysis was performed on R-R interval series in a low frequency band (LF, 0.04–0.15 Hz, related sympathetic + parasympathetic changes) and a high frequency band (HF, 0.4–1.5 Hz, related to respiratory and parasympathetic modulation). HRV LF, HF and total power (TP) and LF/HF were calculated. Effects of sleep position, state and postnatal age were analysed using a linear mixed model approach.

Results: Overall, LF, HF and TP were lower when prone compared to supine across the first 6 weeks of life (LF: 76.3 ± 4.7 vs 61.8 ±3.8 ms2, $p < 0.05$; HF: 10.8 ± 2.1 vs 18.5 ± 2.6 ms2, $p < 0.05$; TP; 109.9 ± 8.5 vs 136.3 ± 10.8 ms2, $p < 0.05$), with no interaction between position and postnatal week in any of the parameters. R-R interval was shorter in the prone compared to supine position (379.1 ± 1.5 vs 388.1 ± 1.5 ms, $p < 0.01$). LF and TP were lower during QS compared to AS (LF: 58.6 ± 3.7 vs 81.4 ± 4.9 ms2, $p < 0.001$; TP: 95.9 ± 8.2 vs 150.2 ± 11.2 ms2, $p < 0.001$). TP decreased in the first 3 weeks, being higher at week 1 compared to week 3 (160.1 ± 19.3 vs 92.2 ± 11.7 ms2, $p < 0.05$). LF also decreased initially, being lower at week 3 compared to weeks 2 and 4 (51.1 ± 4.6 vs 77.8 ± 6.5 and 80.6 ± 7.8 respectively, $p < 0.05$ for both).

Conclusions: The prone position was associated with reduced HRV and higher HR in preterm infants in the NICU. These results suggest dampened autonomic activity, which could increase the vulnerability to hypertensive/hypotensive events by limiting the compensatory HR responses. Further studies are required to determine the clinical significance of impaired HRV in the prone position in clinically unstable preterm infants.

Keywords: NICU, preterm infant, heart rate variability, infant positioning

Disclosures: None declared

3. FEASIBILITY AND REPRODUCIBILITY OF LEFT ATRIAL STRAIN IN PRETERM AND TERM NEONATES IN THE FIRST 48 h OF LIFE

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Background: There is evidence of an early diastolic dysfunction in neonates, particularly when born prematurely. Moreover, important changes of left ventricular function and left ventricle filling pressure occur in the transitional period, likely related to changes in loading conditions, patent ductus arteriosus size and pulmonary vascular resistance.

In adult patients, left atrial strain has recently been proposed as a novel marker of diastolic dysfunction due to its strong correlation with left ventricular filling pressure.

Our aims were to assess the feasibility and repeatability of left atrial strain measurement in a cohort of healthy term and preterm neonates in the first 48 h of life.

Methods: This was a multicenter prospective observational cohort study enrolling healthy term and preterm neonates. Preterm infants < 32 weeks of gestational age were excluded if they required FiO2 > 30% or mechanical ventilation. Each infant underwent one echocardiogram in the first 48 h of life. Atrial strain was calculated off-line (Q-Lab 10.2 Philips) from a "standard" 4-Chambers (4C) and 2-Chambers (2C) apical views. Measurements of atrial deformation, namely peak positive (ε pos) and peak negative (ε neg) atrial strain, were calculated for both the standard 4C and 2C views (Figure 1). Intraobserver and interobserver repeatability were calculated according to Bland-Altman and intraclass correlation coefficient (ICC). Images quality was classified according to the Colan grading system. Only images rated as excellent or good were considered applicable.

Results: Twenty-eight patients were studied. Median (range) birth weight and gestational age were 2030 g (620–3690 g) and 34 (25–42), respectively. Atrial strain imaging was feasible from 96% of the acquisitions from both 4C and 2C views.

Peak positive atrial strain from 4C views showed high intraobserver and interobserver repeatability: bias 0.2%, coefficient of variation (CV) 2.17%, ICC 0.97 and bias −0.5%, CV 3.7%, ICC 0.94 respectively. Peak negative atrial strain from 4C views showed high intraobserver and interobserver repeatability: bias −0.5%, CV 3.7%, ICC 0.97 and bias −0.5%, CV 3.7%, ICC 0.94 respectively.

From 2C views both peak positive and peak negative atrial strain showed high intraobserver (bias −0.5%, CV 3.1%, ICC 0.97 and bias 0%, CV 3%, ICC 0,97) and interobserver repeatability (bias −0.4%, CV 4.7%, ICC 0.97 and bias −0.7%, CV 5.7%, ICC 0.97).

Conclusions: This study demonstrates high clinical feasibility and reproducibility of peak positive and peak negative atrial strain measurements from 4C and 2C views by 2D speckle-tracking echocardiography in term and preterm neonates in the first 48 h of life and provide a new promising tool that may be used for the assessment of left diastolic function.

Keywords: Neonatal cardiology; Cardiac ultrasound; Speckle-tracking; Left ventricular diastolic function

Disclosures: None declared

4. CARDIAC PHENOTYPING IN PREMATURITY: COMPARISON OF LEFT VENTRICULAR ROTATIONAL MECHANICS IN TERM AND PRETERM INFANTS

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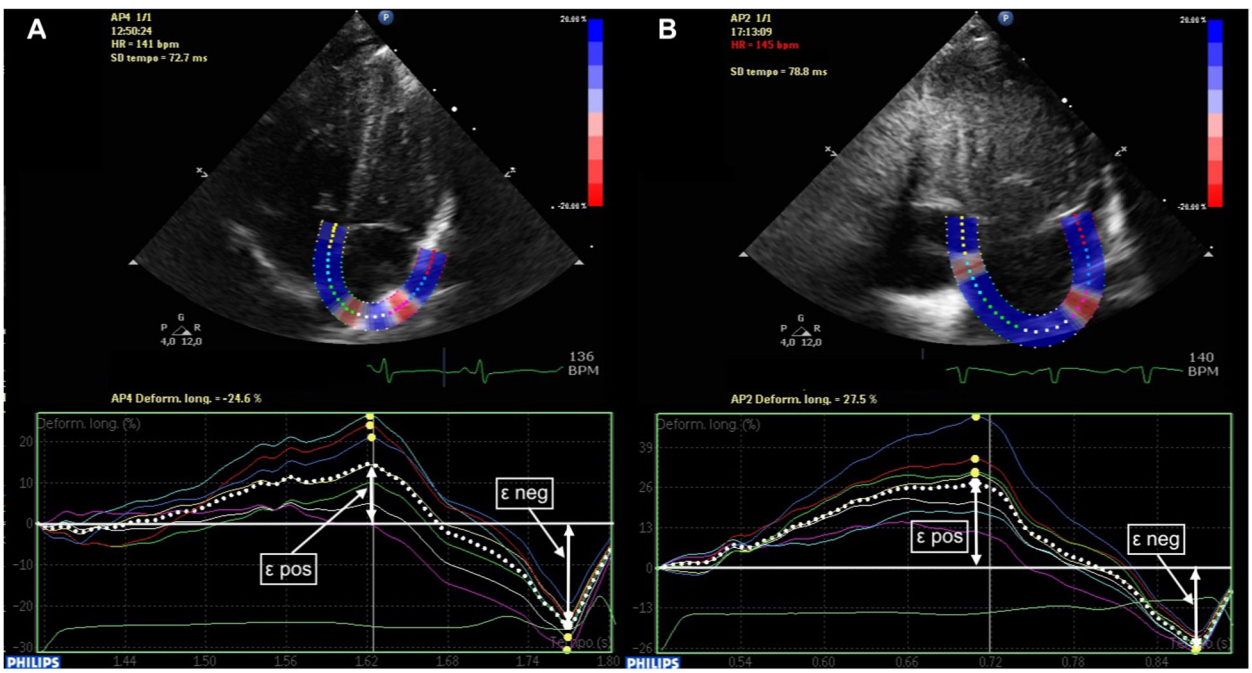
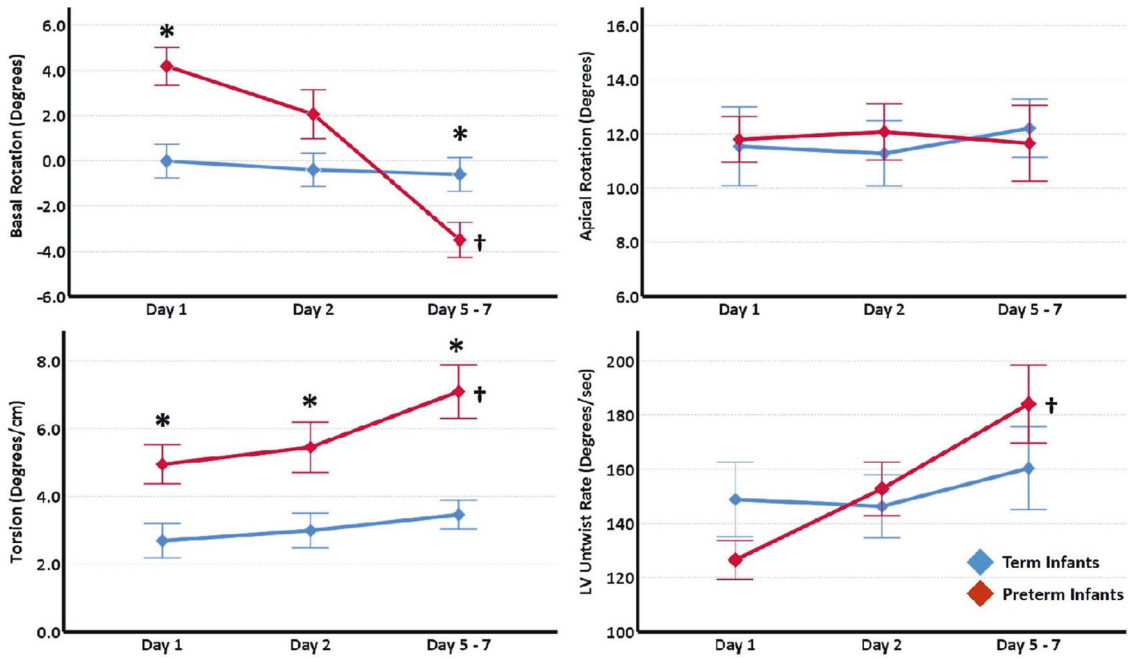


[3] Figure 1 Atrial deformation measured in 4 chambers apical view (A) and in 2 chambers apical view (B). ε pos = (Peak positive atrial strain deformation). ε neg = (Peak negative atrial strain deformation)



[4] Figure 1 Change in rotational mechanic betweem the groups over the first week of age. Values are presented as means (diamonds) and standard error (whiskers). *p < 0.05 between groups at time point. $^{+}$p < 0.05 within group over time

Background: Developmental differences exist in left ventricular (LV) myofibre architecture between term and extremely premature infants. LV rotational mechanics add important information on myocardial structure and function, and describe the wringing motion that occurs due to the twisting of the apex and base of the heart in opposite directions during systole, and the return to the untwisted steady state in diastole. However, there remains a paucity of information comparing rotational mechanics in term and preterm infants. To test the hypothesis that prematurity alters LV twist and torsional physiology in the transitional period, we compared rotational mechanics between extreme preterm infants and term neonates over the first week of age

Methods: We prospectively recruited a cohort of health term infants (37–42 weeks gestation) and compared it to a historical cohort of extremely preterm infants (<29 weeks gestation). Advanced quantitative speckle-tracking echocardiography was performed on Days 1, 2 and 5–7 to measure basal rotation, apical rotation, LV torsion (twist indexed to LV length), and LV untwist rate. Measurements were compared between the two groups and over time.

Results: Thirty term infants (mean ± SD gestation: 39.7 ± 1.1 weeks, birthweight: 3667 ± 443 grams) and 51 preterm infants (gestation 26.7 ± 1.5 weeks, birthweight 1011 ± 233 grams) were included. In preterm infants, basal rotation was positive on Day 1, changing to negative by Day 5–7. Torsion was higher in preterm infants compared to term infants on Day 1 ($P < 0.05$) and continued to increase in preterm infants by Day 5–7 ($P < 0.05$). There was a significant increase in LV untwist in preterm infants over the study period ($P < 0.05$). Apical rotation was similar between the two groups and was persevered over the first week of age. There was no change in term rotational mechanics parameters over the study period with minimal twist (Figure 1).

Conclusions: Extremely preterm infants demonstrate increasing torsion over the first week of age. This is predominantly driven by an increasing negative basal twist. LV untwist is also altered in premature infants. There is no change in rotational parameters in term infants. An augmentation of torsion in premature infants may represent an adaptive response to compromised known longitudinal systolic and diastolic function in the preterm population.

Keywords: Rotational Mechanics; Neonates; Preterm Infants

Disclosures: None declared

5. SHOCK IN THE FIRST 72 h OF LIFE IN VERY LOW BIRTH WEIGHT INFANTS: DOPAMINE OR DOBUTAMINE?

Paulo Martins-Filho[1], Davi Casale Aragon[1], Fábia Pereira Martins-Celini[1], Cristina Calixto[1], Ferreira Cristina Helena Faleiros[1], Adriana Carnevale-Silva[1], Bruno Maiolini[1], Gabriella Almeida de Souza[1], Renata Toffolo[1], Silva Ayla[1], Fukamichi Soraya[1], Souza Thaissa Rodriguez[1], Laryssa De Carli de Almeida Couto[1], Walusa Gonçalves-Ferri[1]

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Background: During the transition to extrauterine life, preterm infants have a higher risk of developing circulatory failure and shock. Different pharmacological agents are used for the management of hemodynamic instability in this transition period. The main drugs used as first choice in the hemodynamic approach in this period are dopamine and dobutamine, but evidence about which inotrope should be used is lacking. The objective is to evaluate the association between dopamine or dobutamine use and unfavorable outcomes in very low birth weight infants with shock in the first 72 h.

Methods: Cohort study. Preterm infants <1500 g born between 2010 and 2018 were included, excluding deaths in the delivery room, malformations, and concomitant use of dopamine and dobutamine.

Patients were divided into 2 groups: Group 1: use of dopamine. Group 2: use of dobutamine. The choice of the first drug in the shock (defined as the presence of hypotension-arterial pressure less than gestational age) was determined by the medical staff.

[5] Table 1. Association between Dopamine or Dobutamine use and unfavorable outcomes

Outcomes	Dopamine Group		Dobutamine Group		Adj RR[a] (CI 95%)
	Yes (%)	No (%)	Yes (%)	No (%)	
Death up to 7 days	21 (42.0)	29 (58.0)	22 (24.7)	67 (75.3)	1.75 (1.04; 2.91)
Pulmonary Hemorrhage	13 (26.0)	37 (74.0)	43 (48.3)	46 (51.7)	2.21 (1.13; 4 .31)
PIVH[b]	7 (14.0)	43 (86.0)	9 (10.1)	80 (89.9)	1.11 (0.32; 3.77)
Leukomalacia	5 (12.8)	34 (87.2)	10 (13.2)	66 (86.8)	1.15 (0.29; 4.57)

[a]Relative Risk with 95% confidence interval, adjusted by early sepsis, SNAPPE II > 20, delivery hemorrhage and gestational age.
[b]PIVH: periintraventricular hemorrhage

Outcomes:pulmonary hemorrhage, death until 7 days, intraperiventricular hemorrhage and leukomalacia were evaluated. In order to estimate the gross and adjusted relative risks, simple and multiple log-binominal regression models were considered. The covariates were sepsis, SNAPPEII, delivery hemorrhage and gestational age. The software used was SAS 9.4 and R3.5.1.

Results: For the study 1268 neonate with birth weight <1500 g were selected and 316 (24.9%) required vasoactive drug. Of these, 22 (6.9%) presented malformations and 155 (49%) used associated dopamine and dobutamine and were excluded from the analysis, completing the study 139 patients. Of these, 50 (35.9%) used dopamine and 89 (64.0%) used dobutamine. The means of gestational age and birth weight of patients who used dopamine and dobutamine were 868.10 g (SD 299.78) and 26.88 weeks (SD 2.82) vs 858.99g (SD 279.24) and 27.50 weeks (SD 2.88). The dopamine use was associated with death until seven days of life (adjusted RR(CI95%) = 1.53 [1.04: 2.77]). However, the use of dobutamine was associated with occurrence of pulmonary hemorrhage (adjusted RR(CI95%) = 2.21, [−1.13: 4.31]). No association was found between the use of dobutamine or dopamine with perintraventricular hemorrhage or leukomalacia.

Conclusions: The use of the dopamine as the first choice in shock in the first 72 h in very low birth weight infant is associated with death until 7 days of life. However, the use of dobutamine is associated with pulmonary hemorrhage. Therefore, according to our data, dobutamine is the drug indicated for the premature patient in the first 72 h; however the use was associated with unfavorable outcomes, so the use should to be done with criteria.

Keywords: Dopamine, Dobutamine, shock, preterm

Disclosures: None declared.

6. INTRA AND INTER-OBSERVER VARIABILITY OF ADVANCED NEONATOLOGIST PERFORMED ECHOCARDIOGRAPHY IN PRETERM INFANTS BELOW 30 WEEKS

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Background: Neonatologist Performed Echocardiography (NPE) is becoming a routine tool in neonatal intensive care as provides non-invasive and real time pathophysiological information on hemodynamics that can be used to guide treatment of sick newborn infants. The evolution of the technique has provided advanced methods to assess ventricular function. However, information regarding their reliability is scarce. We aim to describe the reliability of advanced echocardiographic measurements in preterm infants who underwent NPE for any reason.

Methods: Cardiac Strain using Wall Motion Tracking [Toshiba] and Tisular Doppler Imaging (TDI) were studied. Left ventricular global longitudinal strain (LS) and strain rate (SR) from four-chamber (4C) view, circumferential strain (circS) and circumferential SR (circSR) from basal short axis (SAX) view were assessed. All scans were performed by the same operator who did online first measurement. Intra-observer variability was stablished based on offline second analysis of the scans, at least one week apart. Inter-observer variability was evaluated by offline second analysis by a different investigator. Second reviews were blinded to the first measurements. Intraclass correlation coefficient with 95% confidence interval ICC (95% CI, p) and the repeatability index (RI) were used.

Results: 58 NPE studies were performed in 18 infants [27.9 (1.4) weeks of gestation, 1181 (309) g birth weight] during 4-months period, at day 7 (7.6) of life. Mean (SD), intra and inter-observer ICC and RI are displayed (Table 1).

Conclusions: The reliability of Cardiac Strain using Wall Motion Tracking (Toshiba) and Tisular Doppler Imaging is good or very good in preterm infants below 30 weeks of gestation. These new imaging techniques offer reliable information that can be used to guide treatment in the sick newborn infant.

Keywords:

Disclosures: None declared

7. PRETERM INFANTS' CARDIOVASCULAR RESPONSE TO CARDIO-RESPIRATORY EVENTS DURING TRANSITIONAL PERIOD

Silvia Martini[1], Topun Austin[2], Viviana Perrone[1], Giulia Frabboni[1], Marek Czosnyka[3], Peter Smielewski[3], Silvia Galletti[1], Francesca Vitali[1], Giacomo Faldella[1], Luigi Corvaglia[1]

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Background: Intermittent episodes of hypoxemia and/or bradycardia, also defined as cardio-respiratory events (CRE), are frequent in preterm infants and may result in transient hypoxia and hypoperfusion of target organs; concomitant changes in cardiac output (CO), cardiac contractility (CC) or systemic vascular resistances (SVR) may contribute to affect end-organ perfusion during CRE. In this study we aimed to explore cardiovascular hemodynamic changes determined by different CRE types in preterm infants during the first 72 h (h) after birth, a period characterized by a significant hemodynamic instability with high risk of clinical complications.

Methods: During the first 72 h, non-invasively ventilated newborns (gestational age < 32 weeks, birth weight <1500 g) underwent a continuous, non-invasive pulse oximetry and electrical velocimetry monitoring for the assessment of the following parameters: arterial oxygen saturation (SpO2), heart rate (HR), stroke volume (SV), CO, CC, SVR. The monitoring data were simultaneously recorded via ICM

TDI (left lateral)	mean (SD)
Systolic peak (s') (cm/s)	4.6 (0.9)
Early diastolic (e') (cm/s)	5.5 (1.6)
Late diastolic (a') (cm/s)	5.4 (1.1)
TDI (septum)	**mean (SD)**
Systolic peak (s') (cm/s)	3.5 (0.7)
Early diastolic (e') (cm/s)	4.1 (1.1)
Late diastolic (a') (cm/s)	5.2 (1.1)
TDI (right lateral)	**mean (SD)**
Systolic peak (s') (cm/s)	6.3 (1.1)
Early diastolic (e') (cm/s)	6.4 (1.2)
Late diastolic (a') (cm/s)	9.3 (1.8)
Myocardial Performance Index (MPI)	**mean (SD)**
Left lateral	0.57 (0.17)
Septum	0.54 (0.18)
Right lateral	0.44 (0.16)
Cardiac strain	**mean (SD)**
LS (%)	-15.63 (3.47)
SR (1/s)	-1.54 (0.44)
circS (%)	-17.18 (2.70)
circSR (1/s)	-1.95 (0.50)

	Intra-observer variability		Inter-observer variability	
	ICC (95% CI, p)	RI (%)	ICC (95% CI, p)	RI (%)
MPI (septum)	0.90 (0.81-0.94, 0.000)	30.3	0.89 (0.81-0.94, 0.000)	28.9
(septum) s' (cm/s)	0.98 (0.97-0.99, 0.000)	6.5	0.90 (0.82-0.94, 0.000)	16
LS (%)	0.75 (0.59-0.85, 0.000)	28.6	0.78 (0.65-0.87, 0.000)	29.9
SR (1/s)	0.67 (0.48-0.80, 0.000)	44.3	0.75 (0.59-0.85, 0.000)	39.9
circS (%)	0.88 (0.79-0.93, 0.000)	15.8	0.71 (0.53-0.83, 0.000)	29.13
circSR (1/s)	0.70 (0.52-0.82, 0.000)	37.6	0.64 (0.44-0.79, 0.000)	44.5

[ID746] Table 1 TDI: Tisular Doppler Imaging; MPI: Myocardial Performance Index; LS: Left ventricular global longitudinal strain; SR: Left ventricular global longitudinal strain rate; circS: Circumferential strain; circSR: Circumferential strain rate; SD: standard deviation; ICC; infraclass correlation coefficient; 95% CI: 95% confidence intervals; p: p values; RI: repeatability index

+ software (Cambridge Enterprise Ltd, UK). CRE ≥ 10 s were defined as isolated desaturation (ID, SpO2 < 85%), isolated bradycardia (IB, HR < 100 bpm or <70% baseline) and combined desaturation/bradycardia (DB). Percentage changes (%Δ) of the recorded parameters between pre-event baseline and event nadir were analysed and compared among ID, IB and DB by Kruskal-Wallis test. Significance level was set at $p < 0.05$.

Results: A total of 767 events from 22 neonates (mean gestational age 30 ± 2 weeks) were analysed. Of these, ID were 457 (59.6%), IB 121 (15.8%) and DB 189 (24.6%). SV and CO were indexed for the infants' weight, whereas SVR were adjusted for their body surface area. Changes in cardiovascular parameters during different CRE event types are shown in Figure 1. As expected, %ΔHR decreased significantly during DB and IB compared to ID, but there was no difference between DB and IB. Compared with ID, DB and IB showed significantly increased %ΔSV and %ΔSVR, whereas a greater negative variation was observed for %ΔCO. %ΔCC reached significantly lower values during DB compared with ID and IB.

Conclusions: Cardiovascular responses to CRE differ significantly in relation to the event type, with possible clinical implications in terms of end-organ perfusion. In particular, the occurrence of bradycardia results in a transient CO decrease and SVR increase that, in the presence of concomitant hypoxia, may further reduce O2 delivery to end organs. Moreover, concomitant hypoxia may also play a role in the reduction of CC observed during DB.

Keywords: Cardiorespiratory events, bradycardia, desaturation, preterm infants, cardiac output, stroke volume, systemic vascular resistances, cardiac contractility

Disclosures: None declared

CIRCULATION MACRO MICROCIRCULATION

8. DYNAMIC LIGHT SCATTERING: A NEW NONINVASIVE TECHNOLOGY FOR NEONATAL HEART RATE MONITORING

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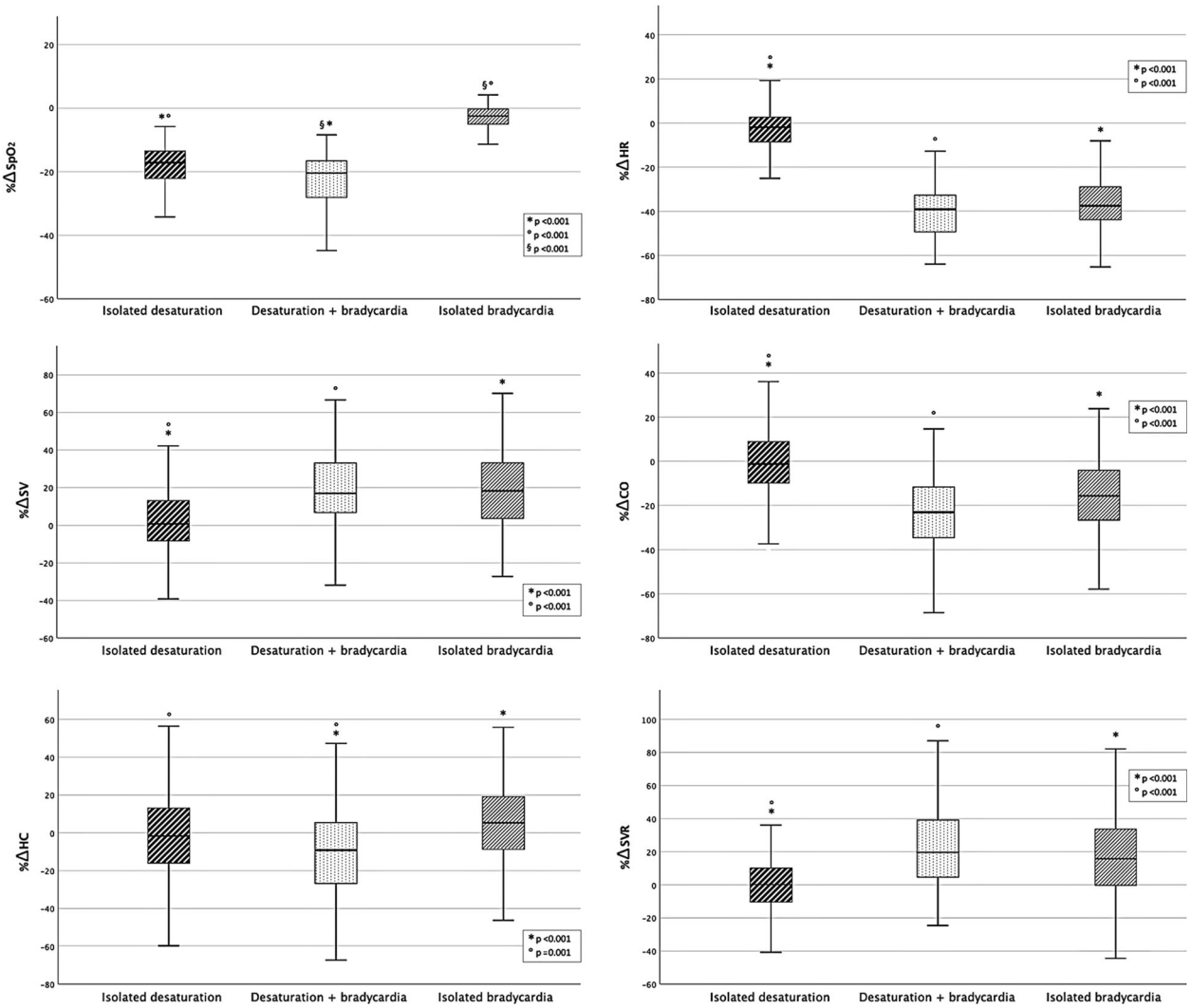
Background: Heart rate (HR) detection in premature infants is challenging due to a low signal amplitude and fragility of the premature skin, necessitating the minimization of skin adhesives. This affects both the current standard of electrocardiography (ECG) and pulse oximetry. Recently the dynamic light scattering (DLS) technique has been miniaturized, allowing noninvasive HR measurements with a single sensor. Hemoglobin motion is detected with a laser diode emitting a small light beam which is scattered by hemoglobin. This creates a time-varying speckle pattern which translates to a pulsatile waveform (Figure 1a). This study evaluates DLS for HR measurement in neonates and compare agreement with ECG.

Methods: Stable infants with a gestational age (GA) of ≥ 26 weeks, monitored with ECG, were eligible for inclusion. HR was measured on 5 different sites (forehead, upper extremity, thorax, lower extremity and abdomen) with the DLS sensor (Elfi-Tech Ltd.,



[7] Figure 1 Percentage changes from baseline of arterial oxygen saturation (%ΔSpO2), heart rate (%ΔHR), stroke volume (%ΔSV), cardiac output (%ΔCO), heart contractility (%ΔHC) and systemic vascular resistances (%ΔSVR) among different types of cardio-respiratory events (isolated desaturation, isolated bradycardia and combined desaturation and bradycardia) and results of pairwise comparison

Israel) for 15 min each. The DLS signal-to-noise ratio (SNR) indicates signal quality and was logged together with DLS HR at a 1 Hz rate. ECG-derived HR from standard of care monitoring was logged at a 1 Hz frequency. To match ECG averaging, every 10th second of DLS HR was compared to ECG HR. For analysis patients were randomly divided into two groups. To determine the optimal SNR value, bias and limits of agreement were calculated for every SNR in the first group. This value was used to assess agreement in the second dataset.

Results: Measurements of HR were performed in thirty-four patients, of which 31 were analyzed. Infants had a median (IQR) GA of 30 3/7 (27 4/7–31 6/7) weeks and median (IQR) weight at measurement of 1400 (1160–1825) grams. A total of 2490, 2477, 2504, 2497 and 2421 paired data points were available at the forehead, upper extremity, thorax, lower extremity and abdomen, respectively. For clinical use, international standards for heart rate detection demand a specified accuracy. In the first group ($n = 15$), out of all sites the forehead showed the best compliance with the IEC 60601–2–27:2011 standard, reaching 100% at a SNR of 4.69 (68% of 1180 data pairs remaining). Application on the second group ($n = 16$) showed an agreement between DLS HR and ECG HR with a bias (lower and upper limits of agreement) of −0.14 (−5.07–4.78) bpm on the forehead (1310 data pairs) (Figure 1b).

Conclusions: DLS is a new and promising technique for noninvasive heart rate detection in neonates, showing good agreement with ECG HR when measured at the forehead. Movement however has a notable influence on accuracy, which can be improved with future iterations of the technology. In addition, DLS has the potential for measuring other hemodynamic parameters such as blood flow, which is an important yet currently unavailable parameter in neonatal care.

Keywords: Dynamic light scattering; heart rate; neonatal monitoring; electrocardiography

9. HEMODYNAMIC STUDY OF NEONATAL PIGS WITH SEPTIC SHOCK TREATED WITH METHYLENE BLUE: NEOPIG STUDY

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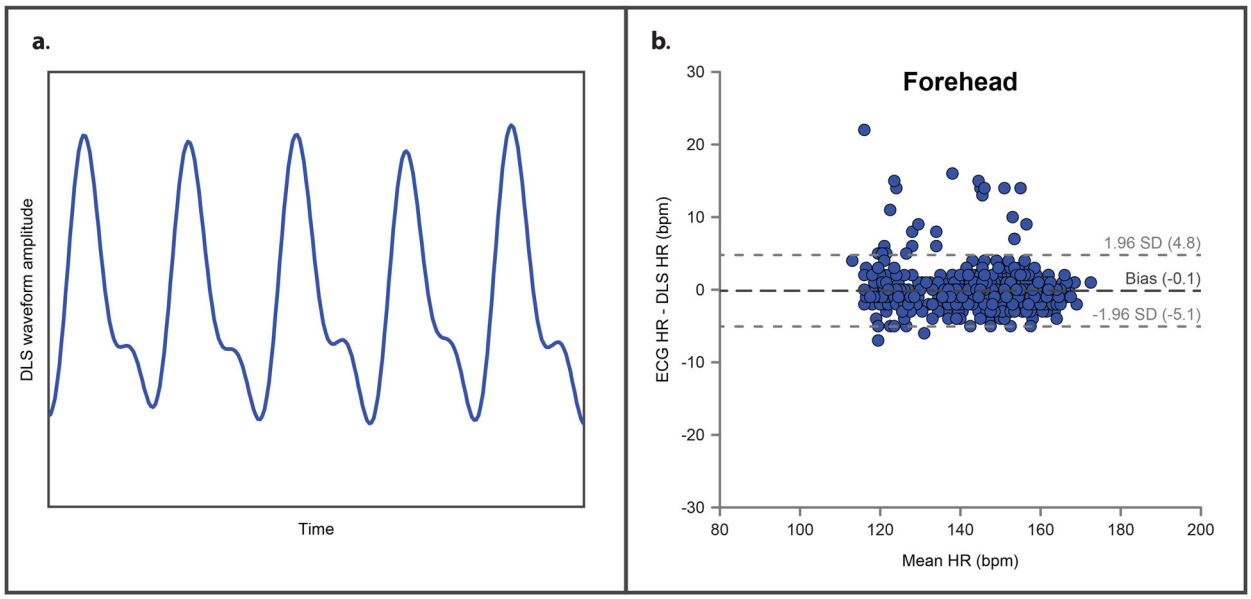

[8] Figure 1 (a) DLS waveform example in a neonate, showing a detailed sphygmogram and (b) Bland-Altman plot of DLS measurement at the forehead, showing the agreement between ECG and DLS heart rate

Background: Introduction: Hemodynamic shock is an independent predictor of early mortality in neonates. The medications currently available for the shock are very aggressive and were associated with sequelaes.

Methylene blue (MB) promove cGMP inhibition and have been advocated for the treatment of refractory shock. There is case reports about MB use in cardiac surgery or thoracic trauma in children, however the use of MB in neonatal patients is still controversial. There are not study with neonate animal model and MB in septic shock. The objective was assesses the methylene blue effects in neonatal animal with septic shock.

Methods: The neonate pigs (3–8 days of life) were separated in 4 groups (n group = 5 animals):

Control: Animals sedated and ventilated (6 h).

Sepsis: Animals sedated, ventilated (6 h) and infusion of LPS Escherichia coli 0.06 mg/kg.

Methylene Blue (sham): Animals sedated, ventilated (6 h) and administration of MB.

Sepsis/ Methylene Blue: Animals sedated, ventilated (6 h) and infusion of LPS Escherichia coli and administration of MB.

Every animal received invasive monitoring for 6 h. Echocardiogram was performed at the start of the experiment, after diagnosis of shock (decrease 20% in mean arterial pressure) and immediately after the installation of MB. Administration of MB: bolus of 2 mg/kg (15 min), after 1 h in continuous infusion at the dose of 0.5–2 mg/kg/h.

Results: 20 neonatal pigs were evaluated.

The treated group had lower nitrate and Cyclic guanosine monophosphate (cGMP) values than the sepsis group, however, these values did not return to normal level (animal control level).

There was an increase in Invasive Arterial Pressure (20%), however, these levels were not maintained in the subsequent hours and did not return to normal level (animal control level).

The bicarbonate values and base excess improved and reached the normal levels (animal control level). (Figure 1).

There was an increase in pulmonary artery pressure although no statistical difference in relation to PO2.

There was no change in ventricular function and vena cava distensibility (Ecochardiography evaluation).

Conclusions: Methylene blue elevates mean arterial pressure, but does not have the effect of reversing hemodynamic shock in neonatal septic animals. However, there was improvement of metabolic biomarkers (bicarbonate and Base excess), probably indicating a possible improvement in tissue perfusion. Studies should be performed to analyze the role of MB as adjuvant therapy in the treatment of septic shock.

Keywords: methylene blue, bicarbonate, base excess, sepsis, shock

Disclosures: None declared

10. THE HYPOTENSION IN PRETERM (HIP) INFANT TRIAL

Eugene Dempsey[1], Keith Barrington[2], Neil Marlow[3], Colm O'Donnell[4], Jan Miletin[5], Gunnar Naulaers[6], Po-Yin Cheung[7], David Corcoran[8], Afif El Khuffash[8], Geraldine Boylan[1], Stranak Zbynek[9], David Van Lere[10], Jozef Macko[11], Hana Widermannova[12], Lisbeth Thewissen[6], Vicki Livingstone[1], Gerard Pons[13]

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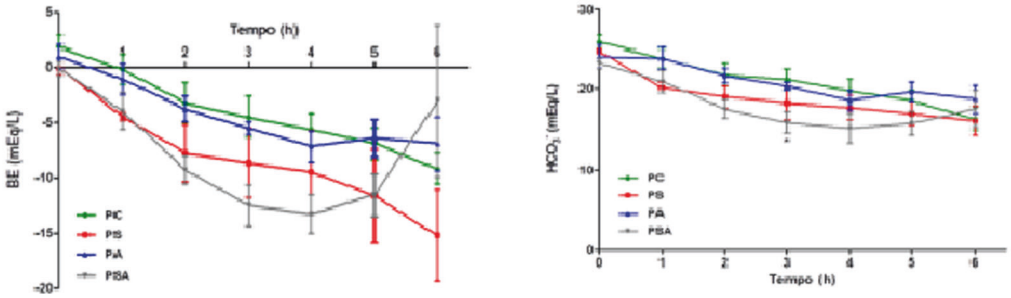
Background: The definition and management of low blood pressure (BP) in immature infants is controversial. A mean BP less than gestational age (GA) is the most common indication for intervention and volume followed by dopamine is the most commonly used treatment (standard approach). We wished to determine whether observational approach compared to this standard approach affects survival without significant brain injury at 36 weeks corrected GA in infants born before 28 weeks' GA.

HCO3- = Bicarbonate; BE = base excess; tempo (h)= time (hours); PC=Control group; PS=Sepsis group; PA=Methylene blue/Sham; PSA= Methylene Blue + sepsis (treatment group). * p <0.05 (PC versus PSA). Two-way ANOVA, Bonferroni post test.



[9] Figure 1 Mean values of blood bicarbonate (HCO3-) and base excess (BE)of the control (PC), sepsis (PS), methylene blue (PA) and methylene blue + sepsis/treatment group(PSA)

[10] Table. 1. Patient Demographics and Outcome

	Standard (n = 29) n (%)	Observational (n = 29) n (%)	P value
[a]Gestational age (weeks)	25.3 (1.5)	25.4 (1.3)	
[a]Birthweight (g)	683 (145)	745 (170)	
[b]Apgar 1 min	4 (2-6)	4 (3-6)	
[b]Apgar 5 mins	7 (5-8)	7 (6-8)	
Male	21 (72)	20(69)	
Multiple	9 (31)	12 (41)	
[b]Lactate at enrolment (mmol/L)	1.9 (1.2-3.1)	2.2 (1.6-4.6)	
[a]Mean BP < GA (mmHg)	−3.6 (2.1)	−3.5 (1.9)	
Primary outcome	18 (62)	20 (69)	0.58
Mortality	6 (21)	8 (28)	0.54
Severe ultrasound abnormality	6 (21)	5 (17)	0.74
Any ultrasound abnormality	16 (55)	13 (45)	0.44
NEC/SIP	4 (14)	7 (25)	0.29

[a]mean (SD)
[b]median (IQR)

Methods: This randomised trial was conducted at 10 sites across Europe and Canada. Infants born before 28 weeks' gestation were eligible for inclusion if they had mean BP less than their GA that persisted ≥15 min in the first 72 h of life, an indwelling arterial line and a cerebral ultrasound free of significant (≥ grade III) intraventricular haemorrhage (IVH). Participants were randomly assigned to standard approach group—saline bolus followed by a dopamine infusion—or to observational approach group—saline bolus followed by a placebo (saline) infusion. Caregivers and outcome assessors were masked to group assignment. The primary outcome was survival to 36 weeks corrected GA without severe brain injury. The study was stopped early due to enrolment difficulties.

Results: 58 infants were enrolled between Feb 2015 and Sept 2017. There were no differences in GA, birth weight, Apgar scores, male sex, multiplicity, mean BP and mean lactate at enrolment between the groups (Table). There was no difference in the rate of the primary outcome between the standard approach group and the observational approach group [18/29 (62%) vs 20/29 (69%), p = 0.58]. There were no differences in the rates of the individual components of the primary outcome, any degree of IVH or NEC /SIP between the two groups (Table 1). Among infants born before 26 weeks, additional treatments for low BP were used less often in the standard approach group [2/19 (10%) vs 12/19 (48%), p = 0.002].

Conclusions: Conducting trials of haemodynamic support in extremely preterm infants is challenging. Though this study lacked power, we did not detect differences in clinical outcomes between standard or observational approaches to treatment. These results will inform future studies in this area; in the interim, either treatment approach appears reasonable.

Keywords: Hypotension; preterm; dopamine
Disclosures: None declared

11. SPLANCHNIC OXYGENATION CHANGES ARE MORE PROFOUND COMPARED TO BRAIN FOLLOWING BLOOD TRANSFUSION

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Background: Blood transfusion improves cerebral (Banerjee et al. Early Human Dev 2016) and gut (Banerjee et al. Vox Sanguinis 2016) tissue perfusion in preterm infants; this has been demonstrated by increased tissue oxygenation index and reduced fractional tissue oxygen extraction. Retrospective and cohort observational studies have indicated that pre-existing anaemia as well as blood transfusion may lead to necrotising enterocolitis (Patel RM et al. JAMA 2016, Paul D. et al. Ped 2011). The objective of this study was to measure the relative changes in cerebral and splanchnic tissue oxygenation following blood transfusion using Near Infra-Red Spectroscopy (NIRS) in preterm infants.

Methods: Preterm infants who required blood transfusion for clinical indication were studied: babies with pre-existing Grade 3 or 4 IVH or gut abnormality such as NEC were excluded. Infants were recruited to three postnatal age groups: 1 to 7 (group 1), 8 to 28 (group 2) and ≥29 days of life (group 3). Simultaneous cerebral and gut oxygenation was measured using NIRS (NIRO 300, Hamamatsu Photonics KK Japan). Tissue Oxygenation Index (TOI) and Fractional Tissue Oxygen Extraction (FTOE) were measured 15–20 min before, during and 15–20 min post-transfusion.

Cerebral oximetry parameters Mean (SD)	Group 1 (1 – 7 days) n = 17†				Group 2 (8 – 28 days) n = 20††				Group 3 (≥29 days) n = 15†††			
	Pre-BT	Post-BT	p value	% change	Pre-BT	Post-BT	p value	% change	Pre-BT	Post-BT	p value	% change
Cerebral tissue oxygenation index (cTOI) %	71.0 (15.8)	74.6 (12.6)	<0.05	5%	66.0 (12.3)	73.7 (11.8)	<0.01	11.7%	57.2 (13.2)	64.1 (12.6)	<0.01	12.1%
Cerebral fractional tissue oxygen extraction (cFTOE)	33.1 (10.9)	25.7 (11.4)	0.003	22.4%	33.3 (12.3)	22.8 (11.0)	0.002	31.5%	40.6 (10.3)	32.6 (11.5)	0.005	19.7%
Splanchnic tissue oxygenation index (sTOI) %	36.7 (19.3)	52.1 (20.8)	0.01	41.96%	44.6 (10.4)	57.6 (14.3)	0.01	29%	41.3 (10.4)	53.8 (16.5)	0.01	30.2%
Splanchnic fractional tissue oxygen extraction (sFTOE)%	64.7 (13.4)	44.4 (20.3)	0.004	31.4%	51.4 (11.5)	37.0 (14.9)	0.005	28%	55.6 (11.8)	42.7 (15.1)	0.0004	23.2%

† 3 infants, †† 1 infant and ††† 3 infants excluded from this analysis due to motion artefacts of NIRS measurement

[ID596] Table 1 Blood transfusion (BT) and cerebral and splanchnic NIRS parameters according to postnatal age groups

Descriptive analysis and t-tests were performed using SPSS 22.0. The study was approved by the regional Research Ethics Committee and written parental consent was obtained.

Results: A total of 59 preterm infants receiving transfusion were recruited to the three postnatal age groups: Group 1; n = 20, Group 2; n = 21 and Group 3; n = 18. The median (range) gestational age was 26 (23–27), 25 (23–30) and 26 (24–34) weeks and birth weight 763 (600–1180), 740 (600–1240) and 793 (520–1746) grams for the respective postnatal age groups. The cerebral TOI increased by 5, 11 and 12% following transfusion in Group 1, Group 2 and Group 3 infants respectively; whilst splanchnic TOI increased by 42, 29 and 30% in those postnatal age groups respectively. Both the cerebral and splanchnic FTOE decreased after blood transfusion but more so in the splanchnic tissue (Table 1).

Conclusions: The results indicate that the improvement of splanchnic tissue oxygenation following transfusion was more pronounced compared to cerebral oxygenation. We propose that this is likely due to an adaptive mechanism of splanchnic tissue in response to anaemia and sparing of brain perfusion.

Keywords: blood transfusion, anaemia, splanchnic oxygenation, brain perfusion

Disclosures: None declared

EPIDEMIOLOGY & NETWORKS

12. ASSOCIATION BETWEEN HOSPITAL VOLUME AND MORTALITY OF CONGENITAL DIAPHRAGMATIC HERNIA REPAIR SURGERY IN JAPAN

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Background: Congenital diaphragmatic hernia (CDH) is one of the most common major congenital anomalies, with an annual incidence of 1 in 2500 to 5000 live birth. Hospital surgical volume is one of the important hospital factors which often influenced quality improvements and several health policy initiatives, usually high-volume hospitals achieved better outcome. However, only a few studies have investigated the effect of the hospital surgical volume on the outcomes of CDH repair surgery. The aim of this study was to examine the relationship between the hospital surgical volume and in-hospital mortality of these patients.

Methods: Data pertaining to CDH infants (age in day <28) who underwent CDH repair surgery between April 2010 and March 2017 were retrieved from the Japanese national inpatient database and retrospectively analyzed. Hospitals were classified into 4 categories by the quartile of surgical volume of CDH. The risk for in-hospital mortality were estimated by the Cox regression. Each patient had the records of baseline characteristics, comorbidity at admission and all medical practices based on daily basis among the hospital stay, which were used as the covariates. Differences of characteristics among the hospitals were considered in the Cox regression by the clustering method based on generalized estimating equation, where correlations of each hospital are accounted by the robust sandwich estimator.

Results: The patients received CDH repair surgery and distribution of the case numbers were widely spread across 114 hospitals in Japan. Mean (sd) surgical volume of CDH in each hospital was 1.2 (1.6) cases per year and 8.7 (10.9) cases among 7 years in total. Overall mortality in this study was 9.5%. Very low volume hospitals had highest mortality (11.9%) among the four categories of hospitals. The Cox regression analysis in our study presented the surgical volume of CDH in middle-volume and high-volume hospitals were associated with decreasing in-hospital mortality. The hazard ratio were 0.82 (95% confidence interval [95% CI], 0.72–0.93, p = 0.003) in the second volume quartile, 0.65 (95% CI 0.58–0.72, p < 0.001) in the third volume quartile, and those of high-volume hospitals was 0.66 (95% CI 0.53–0.82, p < 0.001).

Conclusions: The present study indicated a volume-outcome relationship in CDH repair surgery cases, although there are several unmeasured confounding variables. Further centralization of surgeries should be considered to achieve better outcome.

Keywords: Congenital Diaphragmatic Hernia, volume effect, Administrative Database, DPC, Japan

Disclosures: none declear

13. INFLUENCE OF SEX IN MORBIDITY AND MORTALITY AMONG VERY-LOW-BIRTH-WEIGHT INFANTS LESS THAN 30 WEEKS GESTATIONAL AGE

Fermín García Muñoz Rodrigo[1], Jorge G Fabres[2], Carlos Zozaya Nieto[3], Laura Sanfeliciano[4], Josep Figueras Aloy[5], Miguel Saénz de Pipaón[6], Ivonne D D'Apremont[2], Amorina Pardo[7], Larissa Genes de Lovera[8], Aldo Bancalari[9], Jose L Tapia[2], Máximo Vento[10]

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[13] Table. 1. Risk for major neonatal morbidity and survival according to sex (females vs. males) in VLBW infants less than 31 weeks GA

Outcomes	Adjusted Odds Ratio	95% CI	p
RDS	0.742	0.678–0.763	<0.001
Pneumothorax	0.710	0.562–0.899	0.004
NEC	0.679	0.563–0.819	<0.001
IVH (All grades)	0.757	0.670–0.820	<0.001
Severe IVH (grade III or periventricular hemorrhagic infarction)	0.679	0.562–0.810	<0.001
Periventricular Leucomalacia	0.790	0.657–0.950	0.012
BPD (Oxygen by 28 d)	0.662	0.582–0.753	<0.001
Moderate or severe BPD (O2 at 36 weeks corrected age)	0.621	0.532–0.724	<0.001
Survival	1.656	1.403–1.955	<0.001
Survival without major morbidity	1.737	1.532–1.969	<0.001

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Background: Accumulated evidence has shown female advantage in clinical outcomes in Very-Low-Birth-Weight (VLBW) infants. Not all previous studies considered perinatal confounding factors. In addition, it has been suggested that recent progress in perinatal care might have benefited males relatively more than females and changed differences in morbidity and mortality. The aim of our study was to determine whether sex differences in morbidity, mortality, and survival without major morbidity among VLBW infants under 30 weeks gestational age (GA), adjusting for perinatal risk factors, still persist considering the improvement in perinatal care, in two large cohorts of premature infants.

Methods: Retrospective analysis of prospectively collected data of VLBW infants, born at 240 to 306 weeks GA between January 2013 and December 2016 in the collaborative centers of the Spanish Neonatology Society (SEN1500) and in the South American Collaborative Neonatal (NEOCOSUR) Networks. The following patients were excluded:173 infants (1.6%) who died in the delivery room, 467 (4.2%) with major congenital anomalies (74 of them died in delivery room), and six infants with ambiguous genitalia or whose sex was not properly recorded. Differences between sexes were compared by multivariate logistic regression analyses adjusting for confounding factors, and results are expressed as OR and 95% CI.

Results: During the study period, 11,140 VLBW inborn infants were recorded in the study centers, 6385 (57.3%) in the SEN1500 network and 4755 (42, 7%) in Neocosur. After exclusions, 10,568 patients were analyzed. Mean (SD) GA was 27.7 (1.8) weeks; birth weight 1023.1 (257.4) g; male sex: 53.2%; multiples: 28.1%. Table 1 summarizes morbidity and survival odds of female vs. males, after adjusting for confounders.

Conclusions: After adjusting for GA, BW, multiple gestation, antenatal steroids, chorioamnionitis, maternal hypertension, maternal antibiotics, premature rupture of membranes, Cesarean section, advanced neonatal resuscitation and Network of origin, female infants had a lower risk of respiratory morbidity, NEC, and brain damage, and a higher likelihood of survival and survival without major morbidity.

Keywords: Very-low-birth-weight infant; Sex; Morbidity; Mortality; Networks.

Disclosures: No conflicts of interest.

14. MORTALITY PREDICTION IN VERY LOW BIRTH WEIGHT NEONATES USING THREE NEW PREDICTIVE MODELS

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Background: Preterm birth is the main cause of perinatal mortality. Decisions regarding care and treatment of these infants are specially challenging for health care professionals and families. Several predictive models for preterm mortality have been developed. Some of them are widely used throughout the world (CRIB score, NICHD model), however very few have been validated in other populations. In Spain, SEN1500 database includes data from over 2500 very low birth weight preterm infants per year born in our country. The aim of this study was to develop and validate different mortality predictive models for preterm infants registered in the SEN1500 database.

Methods: Inclusion: Infants born alive with birth weight < 1500 g or gestational age < 30 weeks admitted to 65 Spanish Neonatal Units and registered in SEN1500 database. Exclusion: fetal or delivery room deaths, major congenital defects or chromosomal abnormalities. Periods: "Development" of predictive models (2009–12) and "Validation" (2013–15). Predictive mortality models: Model 1 (prenatal), model 2 (first 24 h of life), and model 3 (during hospital admission). Statistical analysis: dependent variable: hospital mortality. Significant independent variables were used in multivariable regression models. To establish the cut-off point between "death" and "no death", Kappa indexes were used. Specificity, sensitivity, accuracy and area under the curve (AUC) were calculated for the 3 models.

Results: 14953 newborns were included, 8734 in the development phase and 6219 in the validation phase. 2015 of the included infants died, 373 (18,5%) before 24 h of life, 1315 (65,3%) during the first month of life and 327 (16,2%) between 30 days of life and final discharge.

In the development phase, AUC to predict mortality was 0,833 (95% CI: 0,821–0,845) ($p < 0,001$) in model 1 and 0,872 (95% CI: 0,860–0,884) ($p < 0,001$) in model 2. In model 3, AUC to predict mortality was 0.999 (95% CI: 0.998–0.999) ($p < 0,001$) for the first month of life and 0.950 (95% CI: 0.930–0.961) ($p < 0,001$) after 30 days of life.

Cut off values for the different models, concordance (Kappa index) and prediction accuracy in the validation phase are shown in Table 1. Models 1 and 2 showed a "moderate" concordance, whilst in model 3 concordance was "very good".

Conclusions: A national cohort of preterm patients was used to develop and validate three new mortality predictive models to be used in the prenatal period, first day of life and during hospital admission. Use of dynamic models of changing probability to predict individual mortality can improve outcome accuracy.

Keywords:

Disclosures: None declared

15. PUBERTAL GROWTH OF CHILDREN BORN PRETERM

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Predictive model	Observations (n)	Cut-off point	Kappa index	Accuracy %	Concordance
Model 1 (prenatal)*	6131 cases (706 died)	0,30	0,426	87,7	*Moderate*
Model 2 (24 hours of life) *	5418 cases (612 died)	0,35	0,461	89,1	*Moderate*
Model 3 (During hospital admission)	5292 cases (544 died)	0,013 (<=30 d) 0,091 (> 30 d)	0,860	97,3	*Very good*

[14] Table 1 Kappa Index (Concordance): Poor (0-0.20), Weak (0.21-0.40) Moderate (0.41-0.60), gOOD (0.61-0.80), Very Good (0.81-1.00)

Helsinki and Helsinki University Hospital, Helsinki, Finland; [3]UCL Great Ormond Street Institute of Child Health, London, United Kingdom; [4]Oulu University Hospital and University of Oulu, Oulu, Finland; [5]University of Turku, Turku, Finland; [6]MRC–PHE Center for Environment & Health, School of Public Health, Imperial College London, United Kingdom; [7]Norwegian University of Science and Technology, Trondheim, Norway

Background: Preterm birth (<37 gestational weeks) is associated with elevated levels of cardiometabolic risk factors in adulthood. Prematurity also affects early growth and preterm born children appear to be shorter as adults than those born at term. In addition, earlier puberty is associated with higher risk of cardiovascular disease in term born adults. As compared to term born controls, earlier pubertal growth was indeed detected in preterm and very low birth weight (VLBW) adolescents. Whether preterm birth across the whole range of gestational ages would also predict earlier pubertal growth, remains to be studied.

Methods: Growth data for the ESTER Preterm Birth Study were obtained from school healthcare (where most Finnish children are measured) annually until age 16 years, with final height measured at >19.9 years. We included subjects with ≥3 height measurements available above 6/7 years in girls/boys, and 15 severely disabled subjects were excluded. The analysis included 131/92/52 men and 147/105/51 women born term (≥37) / late preterm (34 + 0 to 36 + 6) / early preterm (<34 gestational weeks) respectively. To study group differences in pubertal growth we used Super-Imposition by Translation And Rotation (SITAR), a mixed effects growth curve model that summarizes pubertal growth with a fitted mean curve and three subject-specific random effects: body size, tempo, and velocity. The models were unadjusted.

Results: Final height was similar in all men, mean 177.6 (SD 7.2)/178.0 (SD 6.8)/178.0 (SD 6.9) cm, and in all women, mean 163.7 (SD 5.9)/164.3 (SD 5.7)/163.8 (SD 5.6) cm born term/late preterm/early preterm. When comparing the pubertal growth of early and late preterm groups (separately for men and women) to those born at term, no differences appeared in body size, growth tempo, or velocity (Figure). Mean age at peak height velocity was similar in all gestational age groups: 13.5 (SD 1.0)/13.6 (SD 0.9)/13.6 (SD 0.9) years in men and 11.8 (SD 0.9)/11.8 (SD 0.7)/11.8 (SD 0.8) years in women (Figure). Mean peak height velocity was also similar in all groups: 9.7 (SD 1.0)/9.7 (SD 1.1)/9.8 (SD 0.9) cm/year in men and 7.6 (SD 0.8)/7.6 (SD 0.7)/7.6 (SD 0.8) cm/year in women (Figure).

Conclusions: Against our hypothesis and other findings with preterm and VLBW children, neither early nor late preterm born children as a group displayed advanced pubertal growth spurt or other differences in pubertal growth compared to those born at term. We are currently pursuing analyses in subgroups including those defined by narrower strata of gestational age and birth weight SD score.

Keywords: preterm birth, growth, puberty

Disclosures: None declared

17. MEASURING EXTRAUTERINE GROWTH RESTRICTION IN VERY PRETERM INFANTS: DOES CHOICE OF REFERENCE MATTER?

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Background: Extrauterine growth restriction (EUGR) among children born very preterm (VPT) is a risk factor for poor neurodevelopmental outcome. It is commonly defined as a weight for postmenstrual age (PMA) less than the 10th percentile of postnatal growth references. Fenton's postnatal references, derived by meta-analysis of national birthweight and child growth charts, are commonly used in clinical care and research. Recently, the Intergrowth (IG) 21st project proposed alternative curves derived from multinational healthy preterm infants based on the assumption that normal growth in very preterm populations differs from the in-utero development of term children. We used these two approaches to investigate EUGR prevalence in a multinational sample of European VPT infants.

Methods: Data come from the EPICE (Effective Perinatal Intensive Care in Europe) project, a prospective multinational population based observational study in 19 regions from 11 European countries covering 850 000 annual. We included 6351 infants discharged home or to domiciliary care before 50 weeks PMA. Neonates with missing PMA, discharged place and weight at discharge were excluded from the analysis. EUGR was defined as weight at discharge for PMA and sex < 10th percentile using Fenton and IG references. We compared the prevalence of EUGR by selected neonatal characteristics and country of birth, using X2 tests. We used generalized linear regression models with a Poisson distribution and robust standard errors to estimate adjusted risk ratios (aRR).

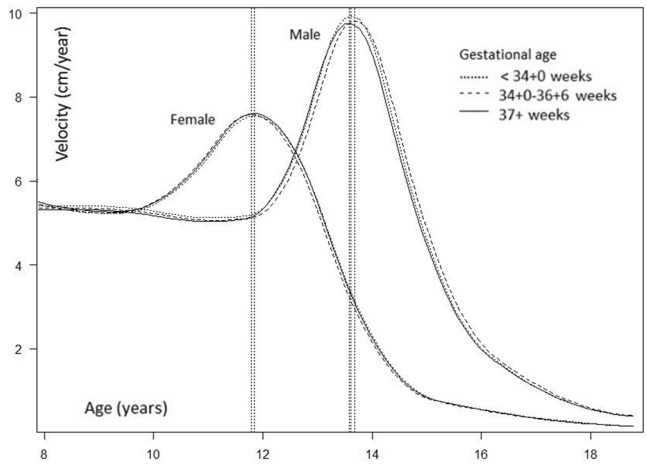
Results: Mothers were on average 30 years old among which 57% were nulliparous and 68% had singleton deliveries. The prevalence of EUGR using Fenton's references was 44.67% for boys and 46.14% for girls (NS) compared to 33.6% for boys and 25.5% for girls for IG ($p < .01$). Prevalence of EUGR by country ranged from 24.7% in Sweden to 60.5% in Portugal for Fenton and from 13.6% in Sweden to 42.7% in Portugal for IG as shown on the graph. Lower gestational age at birth, being SGA at birth and having a severe neonatal morbidity were risk factors for being EUGR, regardless of the reference. Boys were more growth restricted than girls when using IG, but not Fenton. Adjusting for case-mix did not reduce variability between regions: the aRR

for EUGR for Portuguese compared to Swedish VPT infants was 2.5 (95% confidence interval (CI): 2.0–3.1) for Fenton and 3.3 (95% CI: 2.6–4.6) for IG.

Conclusions: Accurately identifying infants with sub-optimal growth is important for clinical care and for research on the etiology and consequences of EUGR. The difference in EUGR prevalence linked to choice of reference as well as the large variations between countries suggest that references should be validated in their target populations before adoption.

Keywords: very preterm births, extrauterine growth restriction, neonatal growth curves,

Disclosures: None declared



[16] Figure 1 Velocity of growth in term (≥37), late preterm (34 + 0 to 36 + 6), and early preterm (<34 gestational weeks) groups of men and women. The curves were obtained from the SuperImposition by Translation And Rotation (SITAR) analysis. No differences in pubertal growth were seen between the groups either in men or women. Mean age at peak height velocity in men born at term was 13.5 (SD 1.0) years, late preterm 13.6 (SD 0.9) years (difference to term-born men +0.11 years, 95% CI: −0.15, 0.37), and early preterm 13.6 (SD 0.9) years (difference to term-born men +0.04 years, 95% CI: −0.27, 0.36). Mean age at peak height velocity in women born at term was 11.8 (SD 0.9) years, late preterm 11.8 (SD 0.7) (difference to term-born women −0.05 years, 95% CI: −0.26, 0.16), and early preterm 11.8 (SD 0.8) years (difference to term-born women +0.01 years (95% CI: −0.26, 0.28). Mean peak height velocity in men born at term was 9.7 (SD 1.0) cm/year, late preterm 9.7 (SD 1.1) cm/year (relative difference to term-born men +0.6%, 95% CI: −3%, 4%), and early preterm 9.8 (SD 0.9) cm/year (relative difference to term-born men +2%, 95% CI: −2%, 5%). Mean peak height velocity in women born at term was 7.6 (SD 0.8) cm/year, late preterm 7.6 (SD 0.7) cm/year (relative difference to term-born women −0.5%, 95% CI: −3%, 2%), and early preterm 7.6 (SD 0.8) cm/year (relative difference to term-born women −0.9%, 95% CI: −4%, 2%).

18. INCREASING USE OF THERAPEUTIC HYPOTHERMIA FOR HIE OUTSIDE OF THE CURRENT EVIDENCE-BASE: A NATIONAL POPULATION STUDY 2011–2016

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Background: Hypoxic-ischaemic encephalopathy (HIE) remains a leading cause of mortality and neurodisability in newborns. Therapeutic Hypothermia (TH) has been shown to be a safe and effective treatment in infants ≥36 weeks gestation with moderate/severe (M/S) HIE, as evidenced by TOBY study and NICE guidance. However, there are increasing concerns clinicians are extending TH management to late preterm (LP) infants and those with mild HIE without proven benefits or safety.

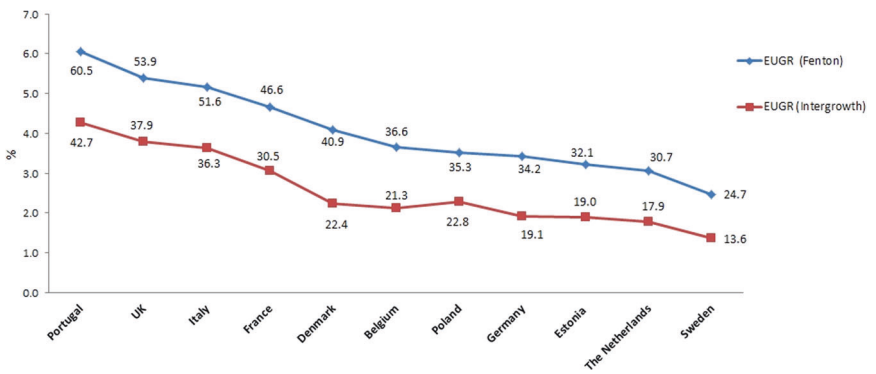
We aimed to quantify the national prevalence of HIE, associated mortality and the use of TH in both LP infants and those with mild HIE.

Methods: National cohort study using data held in the National Neonatal Research Database from prospectively completed electronic hospital records from infants 34 to 42 weeks gestational age (GA) admitted to neonatal units in England and Wales between 2011 and 2016. Data were collected on infants who were coded as having HIE (Mild or M/S). Office for National Statistics birth data were used to calculate GA prevalence rates per 1000 live births. Data were sub-grouped by GA into two groups, LP (34 to 35 weeks) and ≥36 weeks. Two epochs (2011 to 2013 and 2014 to 2016) were compared to evaluate any temporal changes in practice. Data were analysed using Stata with significance set as $p < 0.05$.

Results: 407,462 neonates from 34 to 42 weeks (70,781 LP infants) were admitted to neonatal units during the study period. The rate of HIE in LPs was 6.25/1000 compared to 2.88/1000 in infants ≥36 weeks. Of infants ≥36 weeks GA with HIE (n = 11,587), 29% (n = 3421) were diagnosed with mild HIE and 30% (n = 1027) of these infants underwent TH, increasing significantly from Epoch 1 and 2 (24.7 vs 35.4%, $p < 0.001$).

33% (n = 210) of LP infants with HIE underwent TH, again a significant increase between Epoch 1 and 2 (26 vs 39.4%, $p < 0.001$). Overall, LP infants with HIE were significantly more likely to die than those ≥36 weeks (13.1 vs 6.6%, odds ratio 2.11, 95% CI 1.66–2.69, $p < 0.001$) and TH did not reduce their risk of death (odds ratio 0.95, 95% CI 0.88–1.03, $p = 0.25$).

Conclusions: In England and Wales, the use of TH in mild HIE and LP infants is increasing with more than 1 in 3 infants now being treated. This risks exposing infants to non-evidence based treatment with potential adverse effects and increasing healthcare costs. The high prevalence of mild HIE overall and the high mortality in LP infants highlights the urgent need for prospective



[17] Image 1 Prevalence of EUGR using Fenton & Intergrowth references by country

well-designed studies to evaluate safety and efficacy in these populations.

Keywords: Hypoxic-ischaemic encephalopathy; Therapeutic Hypothermia; late preterm

Disclosures: None declared

19. CLINICAL OUTCOMES FOR CHILDREN WITH PRE/PERINATALLY AQUIRED CEREBRAL PALSY DIFFER BY PRESENCE OF CONGENITAL ANOMALIES

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Background: The reported prevalence of congenital anomalies (birth defects) in children with cerebral palsy (CP) ranges from 11–40%. The variation in range is likely accounted for by the different methods and definitions of included anomalies used in studies. Children with CP and congenital anomalies are described as having more severe clinical outcomes than their peers with CP without anomalies, however studies have been further limited by small samples. The aim of this study was to describe clinical outcomes for children with CP with and without congenital anomalies, stratified by type of congenital anomaly present.

Methods: This international study (The Comprehensive CA-CP Study) pooled linked data from CP and congenital anomaly registers in 6 regions of Europe and 3 regions of Australia. Data on children with pre/perinatally acquired CP, born 1991–2009 was included. EUROCAT definitions of major anomalies were applied to all registries. Cases with anomalies were coded with a CP adaptation of the EUROCAT aetiological classification system and allocated to: chromosomal or genetic syndromes (regardless of anatomy of anomalies), anomalies associated with a teratogenic syndrome, cerebral anomalies (with or without other non-cerebral anomalies) or non-cerebral anomalies only. Descriptive analyses of clinical outcomes for children with and without anomalies, stratified by case classification, were conducted.

Results: 23% of 8201 children with CP had a congenital anomaly with 14% syndromes, 3% teratogenic syndromes, 54% cerebral anomalies and 30% non-cerebral anomalies. Term births were more common in the syndrome, teratogenic syndrome and cerebral anomaly groups (73, 79, 69%), than the no anomalies and non-cerebral groups (56, 50%). Children with anomalies had more severe outcomes (non-ambulation and severe associated impairments) than those without anomalies (all $p < 0.01$). Severe outcomes were common in children with cerebral anomalies: GMFCS IV-V 46%, severe impairments of intellect 52%, vision 17%, hearing 6%, speech 44% and epilepsy 56%, as well as in the genetic syndrome and teratogenic syndrome groups. While severe impairments were less common in children with non-cerebral anomalies, the proportion of intellectual impairment was higher than in children without anomalies (32 v 25%) ($p < 0.01$).

Conclusions: Nearly one in four children with pre/perinatally acquired CP had a major congenital anomaly in this study, the largest international data linkage study of its kind. Severe clinical outcomes are common in these children, particularly in those with cerebral anomalies and/or underlying syndromes. Future research from the Comprehensive CA-CP Study dataset will include investigation of pathways to CP via specific anomalies.

Keywords: cerebral palsy, congenital anomalies, clinical outcomes

Disclosures: None declared

20. ISSUES IN QUALITY OF LIFE OF ADULTS BORN VERY PRETERM OR VERY LOW BIRTH WEIGHT COMPARED TO ADULTS BORN FULL-TERM: A SYSTEMATIC REVIEW

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Background: Several longitudinal cohort studies that follow participants who were born very preterm (VPT) or with a very low birth weight (VLBW) have now gathered outcome data at adult age.

The current systematic review aimed to explore whether Health-related Quality of Life (HRQoL) of adults born VPT or VLBW differs from HRQoL of adults born full-term.

Methods: A systematic review was preregistered under PROSPERO-ID CRD42018084005. Studies were eligible for inclusion when: authors claimed that they had measured HRQoL of adults born preterm (<32 weeks of gestational age) or very low birth weight (<1500 grams birth weight), who were 18 years of age or older; the article was written in English; and a comparison to a control group or valid control norms was reported. We searched Pubmed, Scopus, Psycinfo, Web of Science, Embase, and publication lists from experts in this field. Bias was assessed of how clear hypotheses were stated, if attrition happened at random and if other bias-related problems occurred.

Results: A total of 18 studies of 15 unique cohorts from 11 different countries were included in this review. Most of these studies showed that a VPT or VLBW birth does not affect adult HRQoL, especially when handicapped participants were excluded. Differences were mainly found on objective HRQoL, subscales such as physical functioning, for those most handicapped (born small for gestational age or with neurosensory impairments) and for males or females separately.

Conclusions: There is no clear-cut evidence that HRQoL differs between adults born VPT or VLBW and controls born full-term, although some groups, especially subjects with one or more handicaps, seem at risk for lower HRQoL. A future meta-analysis should focus on the determinants of HRQoL and the associations between preterm birth, handicaps and HRQoL. Heterogeneity in HRQoL measurements and the definition of handicaps impairs the comparability of studies.

Keywords: quality of life; adult outcome; very preterm; very low birth weight

Disclosures: This systematic review was done for EU-project RECAP (www.recap-preterm.eu), funded by the European Commission; Horizon 2020; Grant Number: 733280. The authors declare no conflict of interest.

21. UNPLANNED OUT-OF-HOSPITAL DELIVERIES IN FINLAND 1996–2013

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Background: Finland has a total area of 338,145 km^2 and a population of 5,5 million. Annual amount of births has decreased to less than 50 000 during the last years. During the years 1996–2013 14 delivery units were closed in Finland, equaling one third of the units. There has been a concern whether these closures may raise the amount of unplanned out-of-hospital deliveries (UOHD). The aim of the study was to evaluate incidence, characteristics, risk factors and outcome of UOHDs in Finland.

Methods: We conducted a national register study using data on births, causes-of-death and congenital anomalies including all live and stillbirths in 1996–2013. The study group included a total of 1420 infants. The collected data included maternal and delivery characteristics and obstetric procedures, characteristics of infants and admissions to neonatal care unit, diagnoses, congenital anomalies and causes of death.

Results: The annual rate of UOHDs increased from 46 to 260 per 100,000 births (Figure 1). Risk factors of UOHD were low socioeconomic status (OR: 1.39, 95% CI 1.19–1.62), duration of labor <7 h (OR: 12.0, 95% CI 9.8–14.7), ≥3 previous births (OR: 2.73, 95% CI 2.41–3.09), prematurity (OR 1.50, 95% CI 1.24–1.81), distance to the delivery unit ≥ 35 km (OR: 2.77, 95% CI 2.50–3.08) and less prenatal visits (OR 2.37, 95% CI 2.11–2.66). UOHD infants had seven times higher perinatal mortality compared to in hospital births. 24 of these infants died before the age of seven days and 25 infants before the birth. Very preterm birth (OR: 32.2, 95% CI 3.34–310), fewer prenatal visits (OR: 1.88, 95% CI 1.15–3.07), SGA (OR: 4.25, 95% CI 1.28–14.1) and maternal smoking (OR: 1.86, 95% CI 1.12–3.10) were risk factors of perinatal morbidity and mortality.

Conclusions: Increase in incidence of UOHDs may be due to several factors, such as closure of smaller delivery units and poorer antenatal care due to social problems. UOHDs are potentially high-risk events for infants. Perinatal mortality rate is significantly higher especially among preterm infants and if no antenatal care was recorded.

Keywords: unplanned home delivery, perinatal mortality, perinatal morbidity

Disclosures: None declared

FOLLOW UP

23. GENDER AND VICTIMISATION, NOT PREMATURITY, PREDICTS SELF-ESTEEM TRAJECTORIES INTO ADULTHOOD

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Background: Self-esteem is an important predictor for mental well-being. Some studies have reported lower self-esteem in those born very preterm. However, it is unknown whether trajectories of self-esteem from childhood into adulthood are explained by premature birth or other individual or environmental risk factors.

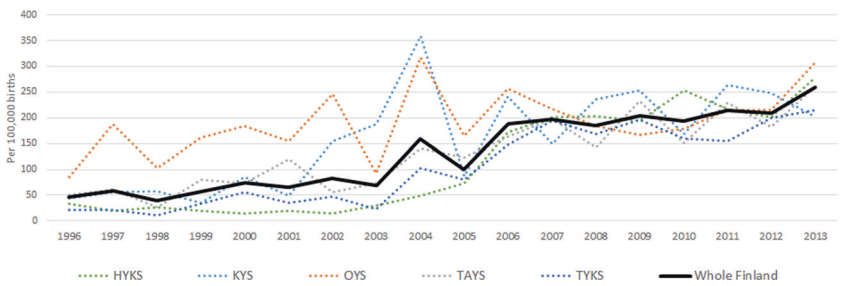
Methods: The Bavarian Longitudinal Study (BLS; N = 460) is a population-based very preterm (VP; <32 weeks gestation) or very low birth weight (VLBW; <1500 g) birth cohort with term born controls. Self-esteem at 6, 8, 13 and 26 years were measured for three domains: body, peers and cognition. Latent class growth analyses were used to identify trajectories of self-esteem, and regression models were used to examine the effects of prematurity, as well as individual, social and parental factors.

Results: Three classes were identified for body related self-esteem: a high group (class 1), medium-low group (class 2), and extremely low group with some catch-up (class 3). Two classes were identified for peer related self-esteem, an increasing group (class 1) and decreasing group (class 2). Two classes were also identified for cognition related self-esteem although differences were small. Being born VP/VLBW did not explain differences in self-esteem trajectories once the models were adjusted for individual differences, peer relationships and parenting. Being female was a significant predictor for worse body (OR = 3.04, 95% CI: 1.18–7.81) and peers (OR = 2.68, 95%CI: 1.50–4.79) but slightly better cognition (OR = 2.57, 95%CI: 1.32–5.03) self-esteem, and being bullied was a significant predictor for worse body (OR = 9.78, 95% CI: 2.31–41.47) and peers (OR = 3.71, 95%CI: 1.65–8.35) self-esteem.

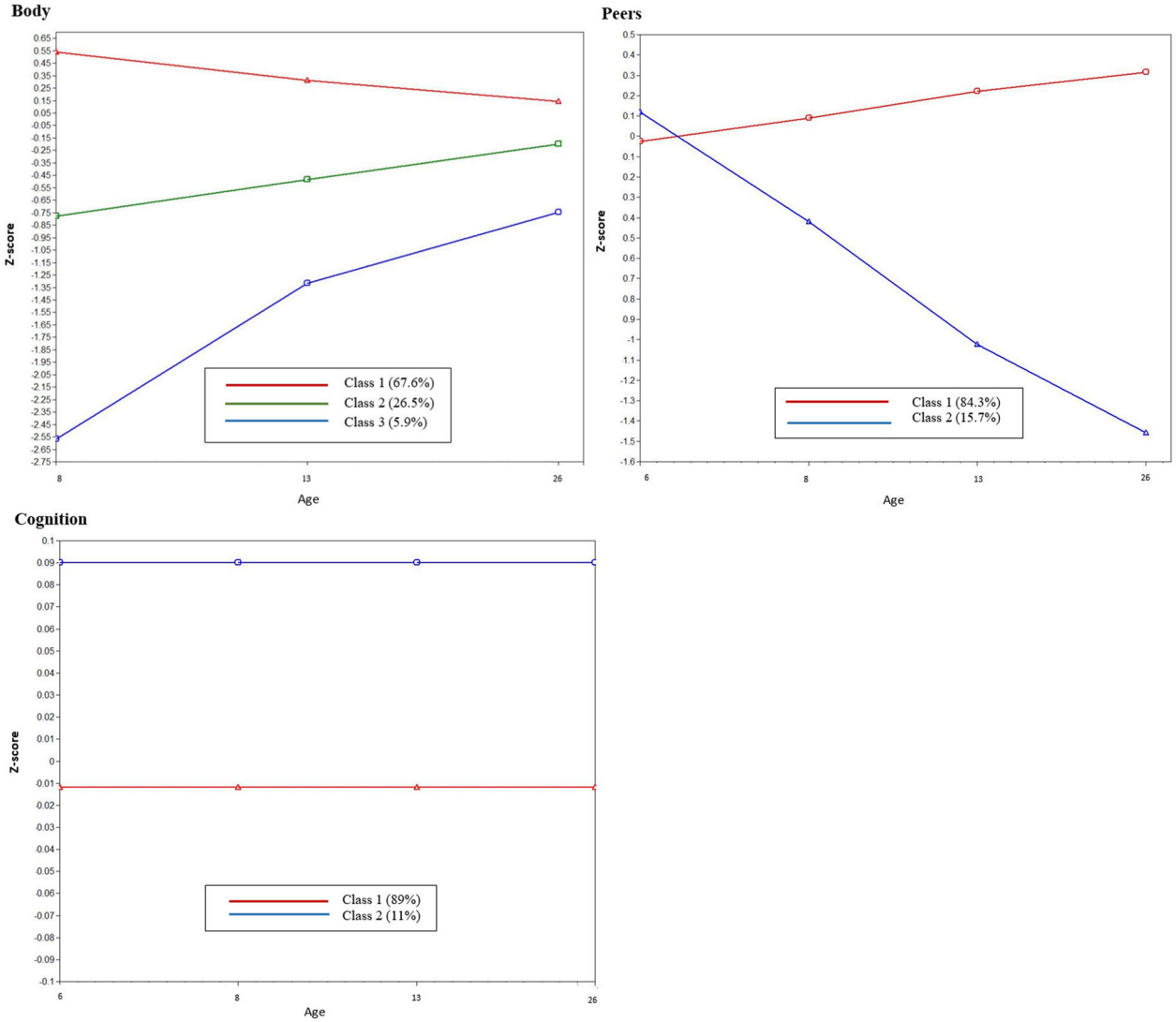
Conclusions: Children born VP/VLBW are not at more risk of having worse self-esteem once other individual, social and family factors are taken into account. Interventions should focus on enhancing self-esteem for females and in reducing bullying behaviours in schools with a focus on VP/VLBW children who are at increased risk of being bullied.

Keywords: preterm, self-esteem, bullying, gender

Disclosures: None declared.



[22] Figure 1 Unplanned home births 1996–2013 in Finland



[23] Figure 1 Trajectories of self-esteem in body from 8 to 26 years, and in peers and cognition from 6 to 26 years.

24. ASSOCIATION OF PRETERM BIRTH/LOW BIRTH WEIGHT WITH ROMANTIC PARTNERSHIP, SEXUAL INTERCOURSE AND PARENTHOOD IN ADULTHOOD: A META-ANALYSIS

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Background: Social relationships are important determinants of wellbeing, health and quality of life. There are conflicting findings regarding the association between preterm birth/low birth weight (PT/LBW) and experiences of social relationships in adulthood such as romantic partnership, sexual intercourse and parenthood. Furthermore, the quality of relationships with romantic partners or friends after being born PT/LBW has rarely been addressed. In this study we aimed to systematically investigate the association between PT/LBW birth and social outcomes in adulthood

Methods: In this systematic review and meta-analysis, we searched PubMed, PsycINFO, Web of Science, and Embase for observational studies reporting on social outcomes in PT/LBW adults—i.e., ever being in a romantic partnership, ever having experienced sexual intercourse, parenthood, quality of romantic relationship and peer social support - compared to full-term born controls. Pooled analyses were based on odds ratios (95% CIs) and Hedges' g, which were meta-analysed using random-effects models.

Results: Of the 1829 articles screened, 21 were selected for meta-analysis. Summary data describing a maximum of 4,423,798 adult participants (PT/LBW = 179,724) were analyzed. PT/LBW born-adults were less likely to have ever experienced a romantic partnership (OR = 0.74 [95% CI = 0.66–0.83]; I2 = 94.4%), to have had sexual intercourse (OR = 0.43 [95% CI = 0.31–0.61]; I2 = 76.3%), or to had become parents (OR = 0.78; [95% CI = 0.67–0.90]: I2 = 98.2%), than full terms. A dose-response relationship according to degree of prematurity was found for romantic partnership and parenthood. Overall, effect sizes did not differ with age and gender. When PT/LBW born-adults were in a romantic partnership or had friends, the quality of relationships was not poorer compared to adults born full-term.

Conclusions: Our findings suggest that preterm/low birth weight born-adults are less likely to experience a romantic partnership, sexual intercourse, or to become parents, however preterm birth/low birth weight does not seem impair the quality of relationships with partners and friends. A lack of sexual or

partner relationships might increase the risk of lower well-being, and poorer physical and mental health.

Keywords: preterm birth, low birth weight, social relationships, adulthood, meta-analysis

Disclosures: None declared

25. SPECTRAL POWER, FUNCTIONAL CONNECTIVITY AND NETWORK ANALYSIS IN SCHOOL-AGED PRETERM BORN CHILDREN: AN EEG STUDY

Charlotte van't Westende[1], CachanPeeters-Scholte[2], Lisette Jansen[2], Janneke van Egmond-van Dam[2], Martijn Tannemaat[2], Sica Wiggers-de Bruine[2], Annette van den Berg-Huysmans[2], Victor Geraedts[1,2], Alida Gouw[1], Sylke Steggerda [2]; Cornelis Stam[1]; Laura van de Pol [1]

[1]VU University Medical Center, Amsterdam, The Netherlands; [2]Leiden University Medical Center, Leiden, The Netherlands

Background: In the past decades, survival rates of prematurely born children have increased significantly due to improved neonatal care. Extremely (EP) and very prematurely (VP) born children have an increased risk of long-term adverse motor and cognitive outcomes. In contrast to structural changes, little is known about how differences in functional brain activity in preterm born children at school age relate to neonatal variables and cognitive and motor outcome. The aim was to study quantitative EEG (analysed at the level of oscillatory activity, functional connectivity and brain network variables) and its relationship with cognitive and motor outcome in EP and VP born children at 9–10 years of age.

Methods: Participants were involved in a prospective longitudinal cohort of 113 preterm infants (GA < 32 weeks) born between May 2006 and October 2007. At 9–10 years of age these children were invited for neurodevelopmental follow-up at the outpatient department of the LUMC as part of clinical care. Sixty-six prematurely born children were analysed for brain activity (EEG), motor development (MABC) and cognitive outcome (WISC-III). The oscillatory activity of the brain was analysed with the power spectrum of the recorded EEG signal, functional connectivity was quantified with the Phase Lag Index (PLI) and functional networks were constructed using the Minimum Spanning Tree (MST) method.

Results: Relative power and functional connectivity were significantly higher in VP compared to EP children in the upper alpha frequency band ($U = 478.5$, $p = 0.016$ and $U = 492.5$, $p = 0.008$, respectively). Based on the significant results in relative power and functional connectivity in the A2 frequency band, differences in MST networks in the upper alpha frequency band between the EP and VP group were explored. VP children had more integrated networks than EP children (Degree: $U = 491.5$, $p = 0.008$; Leaf fraction: $U = 473.0$, $p = 0.020$). In the total group, a strong positive correlation was found between relative upper alpha power and motor outcome at 9–10 years of age ($\rho = 0.560$, $p < 0.001$).

Conclusions: These results suggest that 9–10 years after birth, the effects of prematurity can be observed in terms of alterations in functional brain activity. Functional brain activity in VP children seem to have more alpha power and higher functional connectivity, and functional networks seem to be more integrated than networks in EP children. In addition, motor deficits are related to alterations in alpha activity.

Keywords: Electroencephalography, power spectrum, functional connectivity, network analysis, prematurity, children

Disclosures: This study was sponsored by Chiesi Pharmaceuticals B.V. Schiphol

26. THE EPICURE STUDY: DISABILITY AT 11 YEARS OF FOLLOWING EXTREMELY PRETERM BIRTH IN 1995 AND 2006

Emmi Suonpera[1], Marialivia Bernardi[1], Amanda Fahy[1], Samantha Johnson[2], Yanyan Ni[1], Rebecca Lancaster[2], Jayne Trickett[2], Dieter Wolke[3], Neil Marlow[1]

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Background: Developing neonatal care has led to consistently rising survival at extremely low gestations. In national data from 2006 increasing survival without disability and improved developmental scores at 30 months were seen compared to births in 1995, but there was no reduction in the proportion with severe or moderate impairment. We report a study to evaluate whether early advantages have translated into improved outcomes in early adolescence.

Methods: We compared published outcomes for the 1995 EPICure cohort at 11 years with the outcome for a sample of the 2006 EPICure2 cohort. For the latter we evaluated outcomes for 200 extremely preterm children born in two geographic regions of England. Outcome definitions and measures were chosen to match those used in the original study.

Results: The EPICure2 sample was representative of the whole cohort over a range of clinical characteristics and the index of multiple deprivation decile. The 2006 sample was comparable to the 11 year EPICure sample over the same measures but showed higher deprivation (IMD 1995 mean IMD 5.3; 2006 mean IMD 4.9).

Outcome for 176 children <26 weeks of gestation born in England in 1995 was compared to that of 112 children born in 2006. Moderate or severe disability was present in 43% of those born in 2006 compared to 51% in 1995 (OR 0.64 (95% CI: 0.36, 1.11)). Motor disability was present in similar proportions in each cohort (20 v 19% respectively; OR 0.92 (95% CI: 0.46, 1.83)). Mean IQ scores were 81.4 (sd 19.2) in 2006 and 82.7 (sd 18.4) in 1995 (difference in means adjusted for confounders −0.2 (−0.6 to 0.2).

Conclusions: Despite evidence of increasing survival at <26 weeks of gestation, early signals of improving outcomes are not reflected in the 11 year outcomes in the sample evaluated.

Keywords: extremely preterm birth, disability, long term outcomes, epidemiology

Disclosures: None declared

27. SELF-ESTEEM AND WELL-BEING IN PRETERM BORN ADOLESCENTS: AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

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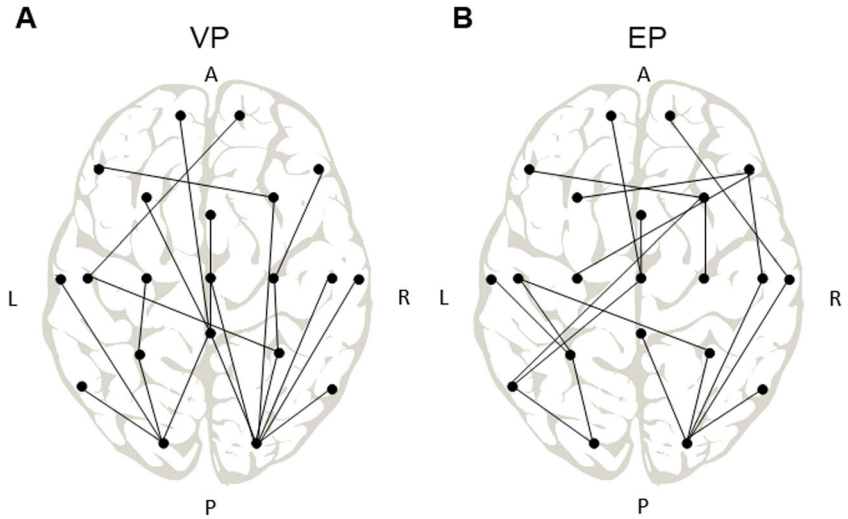
[1]University of Warwick, Coventry, United Kingdom; [2]Psychologische Hochschule Berlin, Germany

Background: Although several studies investigated the longitudinal association between preterm birth and mental health problems, few studies have focused on the association between preterm birth and subjective well-being and global self-esteem in adolescence. Furthermore, existing studies revealed mixed findings regarding the influence of preterm birth on adolescents' well-being and self-esteem. The main objective of the current study is to investigate whether self-esteem and well-being of adolescents born preterm are different than those born full-term in an individual participant data (IPD) meta-analysis.



[25] Figure 1 Group-averaged MST networks are projected on the scalp for the VP group (n = 36) (A) and the EP group (n = 19) (B). MST = Minimum Spanning Tree, EP = extreme prematurely born, VP = very prematurely born

Methods: We obtained individual participant data from four population-based cohorts of individuals born preterm: The Avon Longitudinal Study of Parents and Children (ALSPAC; United Kingdom); the Millennium Cohort Study (MCS; United Kingdom); the Basel Study of Preterm Children (BSPC; Switzerland); and the Bavarian Longitudinal Study (BLS; Germany). Well-being was self-reported in all cohorts, and global self-esteem was self-reported in three cohorts (ALSPAC, MCS, BSPC) between 13 and 18 years of age. Well-being measure included 5 sub-scales: family relations, peer relations, school environment, physical appearance and general well-being. Preterm and full-term adolescents were compared using two-stage random effects individual participant data (IPD) meta-analyses.

Results: Adolescents who were born preterm and full-term did not significantly differ from each other in terms of well-being (−.01; −.02 to .01, z = −.76, p = .45) and global self-esteem (−.00; −.02 to .02, z = −.03, p = .98). In addition to the overall well-being score, there were no significant differences between preterm and full-term born adolescents in any of the sub-scales of well-being. Furthermore, the findings remained non-significant for moderate to late and very preterm subgroups. There was no significant heterogeneity between studies for both well-being (Q = 1.47, I2 = .000, p = .69) and self-esteem (Q = 2.20, I2 = 8.99, p = .33).

Conclusions: Adolescents born preterm and full-term reported similar levels of well-being and self-esteem. Our findings support the view that preterm birth adolescents without long-standing health conditions perceive their well-being and self-esteem to be as good as that of their term born peers.

Keywords: preterm birth, self-esteem, well-being, adolescence, meta-analysis

Disclosures: None declared.

28. FOLLOW-UP OF CHILDREN BORN VERY PRETERM UNTIL 5 YEARS OF AGE IN EUROPE

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Background: Infants born very preterm are at risk of developing multiple health and developmental problems. Because the prognosis of each individual child is unknown at discharge, follow-up programs are essential for identifying health needs early and enabling timely intervention. Despite their recognized importance, little is known about whether children are being followed up, for how long, and how perinatal risk and social factors are related to the use of these follow-up services. We aimed to describe use of follow-up services in a European cohort of very preterm births.

Methods: We used data from the Screening to improve Health In very Preterm infantS (SHIPS) study, which followed up the area-based EPICE cohort of births before 32 weeks' gestation in 2011/12 in regions from 11 European countries. Perinatal data were abstracted from medical records. Socioeconomic and child health data were collected with parent-report questionnaires at 2 and 5 years, where parents were also asked whether their child was receiving follow-up for their prematurity (never had follow-up, had follow-up before 5 years, or continued follow-up at 5). We assessed differences in follow-up by country, sociodemographic characteristics and child characteristics using logistic regression models and estimated adjusted follow-up rates for key sub-groups.

Results: Parents of 3095 children participated in the study at 2 and 5 years. A majority (94%) had received preterm-related follow-up since discharge. The percentage of children who were still in follow-up at 5 years varied by country from 11 to 62%: <15% in regions in Germany, UK, Italy, Estonia and Poland; 27 to 33% in France, Denmark and Sweden; and ›40% in Portugal, the Netherlands and Belgium. The probability of still having follow-up at 5 was inversely related to gestational age but was not related to maternal age, educational level or migration status. In contrast, the latter two factors were related to never having follow-up, in addition to higher gestational age. Adjusting for maternal and child characteristics had little impact on the differences between countries in follow-up (range from 11 to

61% for children still followed and from 0 to 15% for children who had no follow-up).

Conclusions: Large disparities by country in the percentages of children still receiving follow-up at 5 years of age raise questions about the optimal follow-up duration after very preterm birth. Social factors were not related to follow-up at 5, but affected the probability of receiving no follow-up, suggesting that social barriers may be most important for initial contacts with follow-up services.

Keywords: Follow-up, very preterm birth

Disclosures: None declared

29. MAKING THE MIRACLES HAPPEN: EXPERIENCES OF PARENTS OF EXTREMELY PRETERM BORN YOUNG ADOLESCENTS

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Background: Parenting has become a widely discussed concept, saturated with expert knowledge. Extremely preterm (EP) birth has a significant initial impact on parenting experiences. No previous studies have explored parents' experiences and parenting stress at the time their EP born child transitions to secondary school.

Methods: Parents of EP (≤26 weeks of gestation) born young adolescents (YAs) with or without severe/moderate (S/M) morbidities (defined impairments in vision, hearing, mobility and/or cognition), and parents of term-born YA, who participated in a study of long-term outcomes of EP birth, were interviewed about their parenting experiences. These participants were selected purposefully to gain a maximum variation sample of parents from varying socio-economic and ethnic backgrounds. The interviewees also completed the Parenting Stress Index-Short Form (PSI-SF). Interview transcripts were analysed using narrative and thematic methods. The mean Total Stress scores were explored among both groups of parents. Scores ≥85th percentile were considered of high stress.

Results: Twenty-two parents of EP YAs and 14 parents of control YAs were interviewed. Ten (45%) EP YAs had S/M morbidities, with none in controls. The mean Total Stress score for the EP and control parents was 91.1 and 57.9 respectively; 5 EP and none of the control parents reported high stress. Parents of 3 YAs with morbidities had high stress. Interviewees constructed their identities as parents in relation to how their children were to parent, and what they perceived to be socially expected of them as parents. They sought to present coherent accounts of themselves as parents, where the end goal of parenting was to raise a 'functioning, independent and happy' adult. As EP YAs less often met the expected 'steps' of transition to adolescence, such as forming new friendships and gaining independence, parents of EP YAs had to more often account for challenges in fulfilling the 'goal of parenting'.

Conclusions: All interviewees constructed their identities as parents against a shared social understanding of parenting. Parents of EP born YAs found it more challenging to experience fulfilment in their parenting roles. Support services for these families should consider parents' personal experiences.

Keywords: extremely preterm birth; parenting stress; adolescence

Disclosures: None declared

30. POST-DISCHARGE PROTEIN SUPPLEMENTATION IN 137 VERY PRETERM BORN BREASTFED INFANTS DID NOT IMPROVE COGNITIVE OR NEUROPSYCHOLOGICAL DEVELOPMENT AT SIX YEARS OF AGE

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Background: Very preterm infants are at increased risk of cognitive deficits, motor impairments and behavioral problems. Insufficient growth has been linked to increased risk of adverse neurodevelopmental outcome in this group of children. Several studies have evaluated the importance of post-discharge preterm formula (PF) to this group of infants but breastfeeding continues to be the recommended nutrition if possible. Human breast milk contains fewer proteins than preterm formula, but demonstrates other advantages. However little is known about the need for protein supplementation in breastfed very premature infants and the effect on cognitive and neuropsychological development in childhood.

Methods: A follow-up study on cognitive and neuropsychological development at 6 years corrected age (CA) (mean 6.5 ± 0.4 years) in 137 very preterm born infants (gestational age (GA) $24 + 3$ to $32 + 0$ weeks; median $30 + 0$ weeks) randomized to either mothers milk (66 children/33 boys) or fortified mothers milk (71 children/31 boys) from shortly before discharge to 4 months CA. The intervention group received human milk fortified with 1.375 grams of protein/day. Only infants without serious congenital or chromosomal anomalies, or major neonatal morbidities were eligible for the study. Infant growth was closely monitored during the first year of life. At six years of age the children were tested using Wechsler Intelligence Scale for Children IV and parents completed the Five to Fifteen questionnaire.

Results: Total IQ was unaffected by protein supplementation, mean score 103.4 ± 11.1 points in the intervention group and 105.7 ± 10.1 points in the control group, both groups were within the normal range of the test. Children in the lowest social groups had a total of 7.0 IQ points (95% CI: 3.6–10.4) less than children from the highest group ($p < 0.001$) and multiple births had 6.8 (95% CI: 2.8–10.7) IQ points lower than their singleton peers ($p = 0.001$). GA, sex and birth weight did not affect the total IQ score. The results of the Five to Fifteen questionnaire was unaffected by the intervention. In all subdomains boys reported significantly more difficulties than girls. The same effect was seen in children from the lowest social group compared to children in the highest social group in the subdomains; executive functions, perception, memory, language and social skills but not in motor skills.

Conclusions: Post-discharge protein supplementation in very preterm breastfed infants without severe neonatal morbidity did not affect cognitive or neuropsychological development at six years of age. The study revealed mean total IQ scores in the normal range for both groups. Healthy very preterm infants in this study did not benefit from supplementary protein in addition to breastfeeding but the amount of protein supplementation might have been too small.

Keywords: Very preterm infants, protein supplementation, cognitive development, breastfeeding, post-discharge nutrition, five to fifteen questionnaire, Wechsler Intelligence Scale for Children IV, follow up.

Disclosures: None declared.

31. SOCIAL ADJUSTMENT IN ADOLESCENTS BORN VERY PRETERM: UNDERLYING MECHANISMS OF IMPAIRMENT

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Background: Accumulating evidence shows neurodevelopmental impairments in adolescents and young adults born very preterm (VP). Less attention has been devoted to social functioning after VP birth, especially during adolescence. This is surprising since achieving adult levels of social competence is a fundamental maturational task during adolescence and poor social competence in adolescence is associated with increased psychiatric morbidity. The aim of our study was to increase the understanding of social adjustment and autism spectrum disorder (ASD) symptoms in adolescents born VP by studying the role of emotion recognition and cognitive control in the relation between VP birth and social adjustment.

Methods: A Dutch cohort of 61 VP and 61 full-term adolescents aged 13 years participated. Social adjustment was rated by parents, teachers, and adolescents and ASD symptoms by parents. Emotion recognition was assessed with a computerized task including pictures of child faces expressing anger, fear, sadness, and happiness with varying intensity. Cognitive control was assessed using a visuospatial span, antisaccade, and sustained attention to response task. Performance measures derived from these tasks served as indicators of a latent cognitive control construct, which was tested using confirmatory factor analysis. Mediation analyses were conducted with emotion recognition and cognitive control as mediators of the relation between VP birth and social problems.

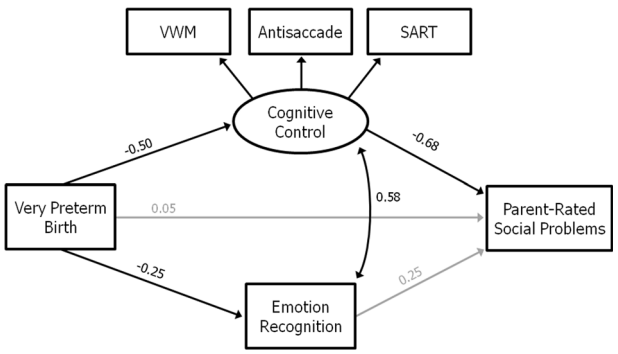
Results: VP adolescents showed more parent- and teacher-rated social problems and increased ASD symptomatology than controls. No difference in self-reported social problems was observed. Moreover, VP adolescents showed deficits in emotion recognition and cognitive control compared to full-term adolescents. The relation between VP birth and parent-rated social problems was significantly mediated by cognitive control but not by emotion recognition (see Figure 1). VP birth was associated with a 0.67-SD increase in parent-rated social problems through its negative effect on cognitive control. The model accounted for 35% of the variance in parent-rated social problems, while 11% of the variance was explained by VP birth alone.

Conclusions: The findings provide strong evidence for a central role of impaired cognitive control in the social problems of VP adolescents. Social problems are associated with psychiatric morbidity and should receive more attention in follow-up after VP birth. Since follow up in clinical practice mostly ends far before puberty onset, the focus on social development of VP children should be increased to detect and act on social impairments early in life.

Keywords: very preterm birth, adolescence, social, cognitive control, emotion recognition

Disclosures: Prof. dr. Ruurd van Elburg is an employee at Danone Nutricia Research, Utrecht, the Netherlands. The other authors have no conflicts of interest to disclose.

SART = sustained attention to response task; VWM = visuospatial working memory.



[31] Figure 1 Path model of the effect of very preterm birth on parent-rated social problems mediated by cognitive control and emotion recognition. Standardized regression coefficients are related to the association between very preterm birth and the mediator (path a), the mediator and parent-rated social problems (path b), and the direct effect of very preterm birth on parent-rated social problems controlling for the mediators (path c'). Significant paths ($p < .05$) are depicted in black and non-significant paths in gray

NEONATAL FETAL NUTRITION AND METABOLISM

32. OPTIMISING NURTITION DURING THERAPEUTIC HYPOTHERMIA: AN OBSERVATIONAL STUDY USING PROPENSITY SCORE MATCHING

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Background: There is limited evidence to inform provision of nutrition during therapeutic hypothermia in infants with hypoxic ischemic encephalopathy (HIE) [1]. Clinical practice is inconsistent. Enteral feeding is often withheld due to concerns for risk of necrotising enterocolitis (NEC) but evidence suggests that enteral feeding could be a beneficial adjunct to hypothermia [2]. Parenteral nutrition may increase the risk of infection.

The aim of this study was to use propensity score methods to investigate the associations between the provision of both enteral nutrition (EN) and parenteral nutrition (PN) and rates of NEC, late infection, and survival in infants who underwent therapeutic hypothermia for HIE.

Methods: Retrospective cohort study of data held in the UK National Neonatal Research Database. Infants were included if born at ≥36 weeks gestational age (GA), between 01 Jan 2010 to 31 Dec 2017 and either received therapeutic hypothermia for 72 h or died during treatment.

Propensity models were built for EN and PN analyses separately using a stepwise approach. Variables including birth weight, GA, sex, severity of hypoxia, severity of illness, and organisational factors were a priori selected for the propensity model3. 1:1 matching was implemented where rates of NEC4, late infection and survival were compared between (i) those who received EN in the first 3 days and those who did not, and (ii) those who received PN in the first 3 days and those who only received standard intravenous fluids.

Results: From 2010 to 2017, 6031 infants received therapeutic hypothermia for HIE, mean (SD) gestational age was 39.4 (1.6) weeks and mean birth weight 3370 (627) grams; 55.2% were

Outcomes	(i) Enteral Feeding Analysis				(ii) Parenteral Feeding Analysis			
	No EN Rate, %	EN Rate, %	OR [95% CI]	P	No PN Rate, %	PN Rate, %	OR [95% CI]	P
N	1,613	1,613			1,571	1,571		
Severe NEC	0.2	0.4	1.8 [0.0, 15.5]	0.324	0.3	0.3	1.0 [0.0, 3.2]	0.928
NEC (non-UK NC)	0.9	0.6	0.7 [0.2, 1.6]	0.350	0.9	1.1	1.2 [0.6, 2.2]	0.550
Late infection-NNAP	0.4	0.2	0.6 [0.0, 2.9]	0.458	0.2	1.0	5.6 [2.3, 16.5]	0.002
Late infection	17.6	12.3	0.7 [0.5, 0.8]	<0.001	18.4	19.8	1.1 [0.9, 1.3]	0.312
Survival	91.9	96.1	2.1 [1.6, 3.0]	<0.001	89.6	93.0	1.5 [1.2, 2.0]	<0.001
BF at discharge	47.5	54.6	1.3 [1.2, 1.5]	<0.001	46.0	45.5	1.0 [0.9, 1.1]	0.771

Abbreviations: TA: therapeutic hypothermia; CI: confidence interval; OR: odds ratio; P: p-value; NEC: necrotising enterocolitis; NNAP: National Neonatal Audit programme; BF: breast feeding.

[32] Table 1 Results from the 1:1 matching analyses investigating association between (i) enteral feeding and (ii) parenteral feeding on outcomes including NEC, infection and survival

males and 45.5% were delivered by caesarean section. 3405 infants (56.5%) received EN in the first 3 days and 2740 infants (45.4%) received PN in the first 3 days.

Matching reduced the total sample size to 3226 for the EN analysis and 3142 for the PN analysis. Table 1 presents the results from these analyses. There was no evidence of an association between EN and NEC, although NEC was rare. Provision of both EN and PN were associated with moderately higher rates of survival at discharge, however PN was also associated with a slightly higher rate of late infection.

Conclusions: EN during therapeutic hypothermia was associated with higher survival rates and other benefits. PN was associated with higher rates of infection but a greater survival. Following hypoxic insult, hypothermia and EN may have a protective effect on the gut. Use of EN during therapeutic hypothermia appears safe. Although several clinical variables were used for matching, residual confounding cannot be excluded as an explanation for these results.

Keywords: Hypoxic ischaemic encephalopathy, Nutrition, Infants, newborn, NEC, Late onset sepsis

Disclosures: None declared

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33. FAT LOSS IN CONTINUOUS TUBE FEEDING

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Background: Extrauterine growth restriction is common among preterm and extremely low birth weight infants and poor postnatal growth is associated with impaired neurodevelopment. Hence, to optimize neonatal nutrition is crucial. Continuous tube feeding has shown to lead to better growth and faster full enteral feeding. However, it is well known that continuous tube feeding results in lipid loss. We hypothesized that by placing the pump lower than the infant it would be possible to reduce lipid loss. Our objective is to investigate the effect of enteral syringe pump placement on fat loss during continuous and bolus tube feeding of breast milk to preterm infants.

Methods: An experimental study where 81 feeding simulations were performed; with nine continuous infusions in each of six modalities: Horizontal Higher, Horizontal Matched, Horizontal Lower, Tilted Higher, Tilted Matched and Tilted Lower, and 27 bolus feedings: nine flushed with air, nine with water and nine that were not flushed (Fig. 1). Each simulation utilized 16 mL of breast milk given over four hours. Continuous infusions were given with a flow rate of 4 mL/h. Bolus was given as 8 mL over the course of 15–20 min every other hour. Analysis for fat, crude and true protein, carbohydrate, total solids and energy, was performed before and after each simulation using Miris Human Milk Analyzer, Miris HMA™ Uppsala, Sweden. The percent of macronutrient loss was compared between all simulations.

Results: An average fat loss of 40% occurred when using the continuous feeding method and the fat loss was not reduced by tilting the pump or by placing the pump higher or lower than the infant. Meanwhile, the bolus feeding method only resulted in an average fat loss of 11% (Table 4). Further, an average energy loss of 14% occurred during continuous feedings compared to 5% during bolus feedings (Table 4). For the results of all the feeding simulations see Table 1.

Conclusions: Considerable fat loss is seen during continuous tube feeding. Neither height in relation to the infant or tilting of the pump can reduce fat loss. The best way to reduce fat loss is to use the bolus feeding method.

Keywords: Breast Milk, Continuous Tube Feeding, Fat Loss, Preterm

Disclosures: Mattias Paulsson has received honoraria for teaching assignments from the following pharmaceutical companies: Fresenius Kabi, B Braun and Baxter Medical. No other authors have conflicts of interest to disclose.

34. ADVERSE EFFECTS OF COW'S MILK-BASED FORTIFIER (CMDF) OCCUR DESPITE USE OF A 100% HUMAN MILK BASE DIET: A META-ANALYSIS

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Background: Cow's milk (CM) based nutritional products may have diverse adverse effects in very low birthweight (VLBW) preterm infants. Hence a current recommendation, when mother's own milk (MOM) supply is insufficient, is to use donor breast milk (DBM) rather than preterm formula to provide 100% HM base diet, which is then fortified, most commonly using CM derived fortifier (CMDF). Despite the increasing and widespread prevalence of this practice, the safety of using a CMDF in this circumstance has received very little scientific attention. Therefore, we tested for any major morbidities associated with this use of CMDF, versus a comparison group fed HM derived fortifier (HMDF).

Methods: Only one randomised trial (RCT) has compared CMDF with HMDF in VLBW infants fed 100% HM base diet (OptiMoM, 2018). We identified two further studies where the same comparison was possible after reanalysis of raw data: (1) the original RCT of Sullivan et al. (2010) compared HM plus CM based products (fortifier and preterm formula) vs HM + HM based products. A subgroup analysis of 114 babies with 100% MOM base diet allowed comparison of CMDF and HMDF; (2) 2 of 4 groups in the quasi-experimental study of Assad (2014) were reanalysed ($n = 214$) to compare CMDF pre-2012 and HMDF post-2012; all fed 100% HM base diet. These 3 studies were analysed individually for major morbidities associated with fortifier type and then the data were combined using meta-analyses with a fixed effect model.

Results: OptiMoM RCT was only powered to examine feed tolerance yet our own analysis showed higher total morbidity events/case in the CMDF v HMDF group based on necrotizing enterocolitis (NEC); retinopathy of prematurity (ROP), broncho-pulmonary dysplasia (BPD), sepsis, and death (0.74 v 0.48 adverse events/case; $P = 0.03$). Relative risk (RR) of severe ROP alone was 6.4 in the CMDF v HMDF group ($P = 0.04$). The Sullivan RCT subgroup reanalysis had well matched groups for baseline demographic factors; the CMDF group had higher risk of NEC (Bell's stage II+) ($RR = 4.2$; $P = 0.04$); and NEC surgery or death ($RR = 5.1$; $P = 0.01$; number needed to harm = 7). The Assad reanalysis showed significant adverse effects of CM versus HM derived fortifier for NEC (RR 7.5; $P = 0.02$), ROP (RR 2.5; $P = 0.001$), PDA (RR 2.7; $P = 0.007$) and feeds withheld >24h (RR 5.9; $P = 0.001$). Results of meta-analyses are summarised in the table.

Conclusions: Even with 100% base diet of MOM and/or DBM, use of a CMDF was associated with major morbidities versus a comparison group fed a HMDF. These morbidities include NEC, NEC surgery or death, severe ROP, PDA, feed intolerance and total adverse events (NEC, ROP, sepsis, BPD and death). Such safety data are now needed for newer hydrolysed CM derived fortifiers. Our findings have significant implications for neonatal nutrition.

Keywords: preterm nutrition, cow's milk derived fortifier, human milk derived fortifier, necrotising enterocolitis, retinopathy of prematurity, patent ductus arteriosus, broncho-pulmonary dysplasia, sepsis, death, feed tolerance

Disclosures: Dr. Lucas is a scientific advisor for Prolacta, Inc. Dr. Abrams is a member of the scientific advisory board of MilkPep, the education program of the Milk Processor Education Program.

35. MID-UPPER ARM CIRCUMFERENCE AND MID-THIGH CIRCUMFERENCE GROWTH OF PRETERM INFANTS IS CORRELATED WITH PROTEIN-ENERGY RATIO OF NUTRITIONAL INTAKE

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Background: Sufficient protein intake is necessary for lean mass accretion. Early growth of preterm infants is profoundly influenced by protein intake and by the protein-energy ratio. Robust monitoring of lean mass accretion would aid researchers and clinicians looking to optimize nutrition in preterm infants, but current methods (such as stable isotope dilution or bioimpedance measures) are cumbersome or of questionable reliability. Limb circumference measures predict whole body muscle mass in adults and have been suggested as a simple cotside test to monitor lean mass accretion. This study assessed whether such measurements correlated with protein intake and protein-energy ratio.

Methods: Infants born prior to 30 weeks post-menstrual age were recruited from a single neonatal unit. Mid-upper arm circumference (MUAC), mid-thigh circumference (MTC), weight, length and head circumference (OFC) were measured at recruitment and weekly until discharge. Baseline characteristics were recorded. Detailed nutritional intake information was recorded for each day of each infant's admission and daily nutrient intakes calculated. Mixed effects linear modelling was used to assess the influence of total energy intake, protein intake and protein-energy ratio on changes in each of the measurements (standardised by SD score). Optimized models were compared to elicit which anthropometric measurements responded most sensitively to variation in protein intake and protein-energy ratio.

Results: 212 infants were recruited with a mean gestational age (GA) at birth of 27 weeks and birthweight (BW) of 930g. Modelling (see Table 1) of baseline characteristics demonstrated that BW and corrected GA significantly influenced all growth parameters ($p < 0.01$ for all). Weight, length and OFC changes were influenced by total energy intake, protein intake and protein-energy ratio, though the model using total energy intake was superior, with a lower Akaike and Bayesian information criteria (AIC/BIC). MTC was significantly influenced by total energy intake but not protein intake, though replacement of total energy intake with protein-

Outcome	No. studies pooled	Relative risk (RR) greater risk in CMDF v HMDF	P value
NEC	3	3.3	0.008
ROP	3	2.4	0.001
PDA	2	1.6	0.009
BPD	3	1.3	0.1
Death	2	2.2	0.1
Secondary outcome: feeds withheld >24 hours (FW24)			
FW24	2	3.4	0.0001

[34] Table 1 Meta-analyses for outcomes in relation to fortifier type

	Measurement									
	Weight		OFC		Length		Right MUAC		Right MTC	
Parameters Included in Model	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Corrected Gestational Age (CGA)	558	581	221	243	512	533	1103	1125	966	988
CGA + birthweight (BW)	490	517	50.0	74.7	332	359	1056	1083	897	924
CGA + BW + Total Energy Intake	412	445	-25.5	6.55	308	340	NS		885	917
CGA + BW + Protein Intake	451	485	21.3	53.3	318	350	NS		NS	
CGA + BW + Protein-Energy Ratio	464	497	17.0	49.1	330	362	1047	1080	883	915

[35] Table 1 Information criteria scores for models to predict growth of anthropometric measurements

energy ratio improved the model, with a lower AIC and BIC. MUAC was not influenced by total energy intake or by protein intake when taken in isolation. However, the model was improved by using protein-energy intake as an independent variable.

Conclusions: MUAC and MTC growth varies in response to the protein-energy ratio of nutritional intake in preterm infants. Their patterns of response to energy and protein intake are distinct from those of conventional anthropometric measurements and are perhaps more reflective of lean tissue accretion. Further work using gold standard body composition techniques is required to establish whether MUAC/MTC growth reflects lean mass accretion in preterm infants.

Keywords: Preterm, Neonatal, Nutrition, Protein, Anthropometry, Growth

Disclosures: None declared

AIC - Akaike Information Criterion; BIC—Bayesian Information Criterion; MUAC—Mid-Upper Arm Circumference; MTC Mid-Thigh Circumference; NS—p-value for the introduced variable >0.05. All models where new parameters had a significant influence ($p < 0.05$) have the AIC and BIC provided, with the best model for each measurement highlighted in grey.

36. EXPOSURE TO HUMAN MILK-OLIGOSACCHARIDES IN THE FETAL PERIOD BY AMNIOTIC FLUID

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Background: Amniotic fluid (AF) is the first fluid to enter the gastrointestinal tract. Human milk oligosaccharides (HMOs) are complex carbohydrates that are found abundantly in human milk. Accumulating more evidence demonstrates that HMOs are both human milk prebiotics to help beneficial microbes as metabolic substrates and are also antimicrobials with direct bacteriostatic or bactericidal properties or antiadhesives which block the attachment of potentially pathogenic microbes. Although HMOs in breast milk have been adequately studied, there has been any data on the presence of lactose and HMOs in the amniotic fluid. The aim of our study was to evaluate if the amniotic fluid contains lactose and HMOs.

Methods: Amniotic fluid samples from 50 mothers (median (IQR) gestational age, 38.1 weeks (36.4–38.9)) were collected during delivery via caesarean section. The samples were analyzed in the laboratory of Jennewein Biotechnologie GmbH (Rheinbreitbach, Germany) using high performance anion exchange chromatography with pulsed amperometric detection (HPAEC-PAD) or liquid chromatography coupled with mass spectrometry (LC/MSMS) for lactose and 7 HMOs (N-acetylneuraminic acid (Neu5Ac), 3-sialyl lactose (3′-SL), 6′- Sialyllactose (6′-SL), N-acetylglucosamine (GlcNAc), 2′-fucosyllactose (2′-FL), 3-fucosyl lactose (3′-FL), and lacto-N-tetraose (LNT)).

Results: In all amniotic fluid samples, we were able to identify Neu5Ac and 3′-SL concentrations: The median (IQR) concentration of Neu5Ac: 0.334 µg/ml (0.275–0.365) (min-max: 0.199–0.489 µg/ml) and 3′-SL: 2.177 µg/ml (1.845–2.574) (min-max: 0.929–4.082 µg/ml). The other HMOs, 6′-SL, GlcNAc and LNT, were identified in none of the amniotic fluid samples. Although 2′-FL and 3′-FL were identified in four samples, we have not yet evaluated these results because of the small number of samples. The median (IQR) concentration of lactose was 5185 µg/ml (4.259–7.990) (min-max: 1.659–30.108). There was a statistically significant positive correlation between the concentration of Neu5Ac and 3′-SL in the amniotic fluid (correlation coefficient according to Pearson, $r = 0.769$, $p < 0.001$). The concentration of lactose was not correlated with the concentration of Neu5Ac or 3′-SL.

Conclusions: We were able to show that the amniotic fluid, as well as breastmilk, contains lactose and at least two HMOs N-acetylneuraminic acid and 3′-sialyl lactose. These new findings provide clear evidence that a fetus is already exposed to at least some HMOs during the fetal period. Further experimental studies must be performed to understand the physiological significance of HMOs in amniotic fluid.

Keywords: Amniotic fluid, Fetus, Human milk oligosaccharides, Lactose, 3-sialyl lactose, N-acetylneuraminic acid,

Disclosures: No

37. ARE LOW MATERNAL SERUM VITAMIN D LEVELS ASSOCIATED WITH POOR OUTCOME IN THE NEONATAL AND CHILDHOOD PERIOD?

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Background: Vitamin D is an important steroid hormone with a crucial role in calcium homeostasis, immunity, and glucose metabolism. It is sourced from ultraviolet B light and diet. Vitamin D deficiency is a global health problem and leads to considerable morbidity. An increasing area of concern surrounds the role during pregnancy. There is growing evidence that maternal vitamin D deficiency may influence neonatal outcomes such as gestation, birthweight and infant anthropometric measurements. There is also a smaller body of research suggesting impact in later life. This study aims to evaluate the effect of maternal serum vitamin D levels on neonatal and infant outcome, within a diverse ethnic population.

Methods: A retrospective, observational study of 1453 women originally recruited to the Born in Bradford project (BiB). Mother-offspring pairs were prospectively recruited between March 2007-

December 2010 in Bradford, West Yorkshire. Antenatal serum vitamin D levels were taken at 26–28 weeks gestation and analysed using liquid chromatography. A baseline questionnaire of maternal demographics was performed. Follow up explored health indicators and development over time. Women were excluded in the case of stillbirth or missing co-variable data. Multiple regression was used to address the relationship with neonatal variables, while general linear modelling (GLM) explored interaction with childhood outcome. Ethical approval was obtained from the Born in Bradford Scientific Steering and Executive Group.

Results: 1285 women were eligible for inclusion. 46.1% were Pakistani, 39.6% White British and 18.3% of other ethnic origin. The mean vitamin D level was 31.73 nmol/L. Only 5.9% Pakistani women had sufficient vitamin D levels. Deficient antenatal serum vitamin D was associated with reduced birthweight on adjusted analyses ($p < 0.05$). Low maternal vitamin D level was associated with reduced head circumference in Pakistani infants ($p < 0.01$). Pakistani children were more likely to present to medical services and had reduced scores on the Early Years Foundation Stage Profile (EYFSP). Higher maternal vitamin D levels in White British mothers were associated with improved overall communication score in the EYFSP on multiple regression analyses ($p < 0.05$). This study did not identify any significant findings between maternal vitamin D level and skinfold thickness or behaviour at school entry level.

Conclusions: This study provides improved knowledge of the potential roles of vitamin D deficiency during pregnancy in an ethnically diverse population. Antenatal serum vitamin D deficiency is associated with adverse effects both immediately after birth and extending into early childhood. Findings support existing research. Large-scale trials are advocated to explore relationships further, particularly in relation to neurocognitive development.

Keywords: Vitamin D

Disclosures: None declared

38. IMPACT OF MATERNAL STRESS ON MACRO-NUTRIENT CONTENTS OF MATERNAL BREAST MILK EXPRESSED FOR PRETERM INFANTS

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Background: Breast milk is the recommended nutrition for all infants within first 6 months, as per WHO (World Health Organisation). It is a dynamic substrate and is quite variable in its composition. It shows inter-personal, inter-day and intra-day variability in nutrients and energy makeup. Various maternal socioeconomic and dietary factors have been implicated as potential modulators of maternal expressed breast milk (MEBM) composition. Reduction of psychological stress and anxiety has been linked with improved lactation, however, effect of maternal stress on macro-nutrient composition of MEBM is not yet established.

Methods: To study the impact of various levels of stress on macro-nutrient content of breast milk expressed for preterm infants. This was a prospective cohort study of mothers and their infants born <32 weeks and/or <1500 g, recruited two to three weeks postpartum. Maternal and infant baseline data including socio-economic and psychological factors were recorded via questionnaires. Stress was assessed via 1–5 severity rating question and perceived stress score (PSS) scale. 24-hour pooled expressed breast milk sample was analysed weekly, using a Milk Analyser. Statistical analysis was performed using IBM SPSS-25 software. Linear regression on each macronutrient and multivariate analysis on maternal stress adjusted for maternal BMI and daily hours of sleep was performed.

Results: Total no of mothers participated were 50, but 39 had paired data available for analysis. Mean age of mothers was 35 (SD±4.9) years and BMI was >25kg/m^2 in 46%. Mothers with high stress levels had marginally decreased protein in MEBM, in the first few weeks after delivery (1.16 vs 1g/dl), fat appeared slightly lower throughout however calories and carbohydrates were shown to be higher (Table 1) on protein showed significant negative correlation to stress score ($p < 0.05$). Multivariate analysis. of maternal stress scores adjusted for maternal BMI and current duration of sleep per day (hours), did not show any effect on any other macro-nutrients and caloric composition of MEBM

Conclusions: MEBM protein is decreased in mothers who experience high levels of psychological stress. This may have implication in postnatal infant growth. However, caloric contents of MEBM seems to be unrelated to stress. Observed variability in carbohydrates is potentially a reflection stress related hormonal effect in mothers. Our study suggests that maternal milk composition can be improved by intervening to reduce maternal stress

Keywords: Maternal expressed breast milk, macro-nutrients, psychological stress, relationship, prenmature infants

Disclosures: none declared

NEONATAL GI PHYSIOLOGY & NEC

40. NECROTIZING ENTEROCOLITIS, THE BRAIN-GUT AXIS AND PAIN IN ADOLESCENCE

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Background: Necrotizing enterocolitis (NEC) is a severe gastrointestinal condition associated with prolonged, extreme visceral pain and recurrent procedural pain. Pain management in infants with NEC remains challenging. Pain symptoms range from being absent to not responding to analgesics. Cumulative neonatal pain is also associated with long term adverse effects beyond school age. A growing body of evidence suggests a complex interplay between gut innervation, gut microbiota and neurodevelopment through the Brain-Gut Axis. Our objective was to develop a hypothesis linking disruption of gut microbiota in early life to long term effects of neonatal pain in NEC survivors.

Methods: We analyzed data from own research and recent literature. Own data included analysis from The Project on Preterm and Small for Gestational Age Infants in the Netherlands (POPS). POPS is a large population based cohort of newborns with a gestational age of less than 32 weeks and/or birth weight below 1500 g. At the age of 19 years, survivors participated in an extensive follow-up program, comprising a Cold Pressor Task and a validated Pain Coping Questionnaire that assessed pain coping

postnatal weeks	EBM	mean values n=39 (SD)	total n=39 high stress levels (scores >26) n=15	moderate stress levels (scores 13-26) n=24
3-5	F	4.1(0.7)	4 (0.8)	4 (0.9)
	P	1.13 (0.1)	1.0 (0.1)	1.16 (0.2)
	C	7.382 (0.2)	7.4 (0.35)	7.35 (1.1)
	E	73.5(7.4)	73 (7.9)	73.1(12.9)
6-8	F	4 (0.5)	3.8	4.1(1.2)
	P	1.00 (0.1)	0.9 (0.1)	0.9 (0.2)
	C	7.5(0.2)	7.6 (0.2)	7.41 (1.8)
	E	73.2 (5.2)	74.5 (4)	71.6(17.3)
9-11	F	3.9 (0.4)	3.77	4 (1.2)
	P	0.85 (0.1)	0.8 (0.02)	0.8(0.2)
	C	7.32(0.3)	7.6 (0.2)	7.2 (2.4)
	E	70.6 (4.4)	69 (5)	70.8(22)

[39] Table 1 Difference in EBM composition between mothers with and without high stress levels (values expressed per 100 ml of EBM) - stress scores on PSS scale

styles. Furthermore, participants completed a standardized intelligence quotient (IQ) test (MCT-IL). Recent reviews on associations between changes in gut microbiota, the Brain-Gut Axis and NEC were studied.

Results: Our data showed that NEC was significantly associated with lower pain threshold and pain tolerance in adolescence. In contrast, NEC was not associated with altered pain coping styles.

Changes in microbiota are associated with the onset of NEC, and antibiotics during the disease may further disrupt normal gut microbiota. Microbiota composition is thought to affect neurodevelopment by immunomodulation, and by production of neurotransmitters and short chain fatty acids (SCFA). In an animal model, associations between microbiota producing SCFA, inflammation and pain have been found. Although we did not find studies on the innervation of the gut in conditions of NEC and preterm birth, evidence suggests that gut microbiota modulates visceral sensory pathways in early life.

Conclusions: NEC, a condition accompanied by severe and prolonged visceral pain, was associated with lower pain tolerance and pain threshold. The association may indicate clinically relevant long term effects of severe neonatal pain in ex preterm infants, up to the age of 19 years. We hypothesize that changes in gut microbiota, influencing the bioactivity of SCFA may contribute to this effect through the Brain-Gut Axis.

Keywords: Neonatal Pain; Necrotizing enterocolitis; Adolescents

Disclosures: None declared

41. LOW SPLANCHNIC OXYGENATION MEASURED WITH NEAR INFRARED SPECTROSCOPY IS ASSOCIATED WITH INCREASED RISK FOR NECROTIZING ENTEROCOLITIS IN EXTREMELY PRETERM NEWBORNS

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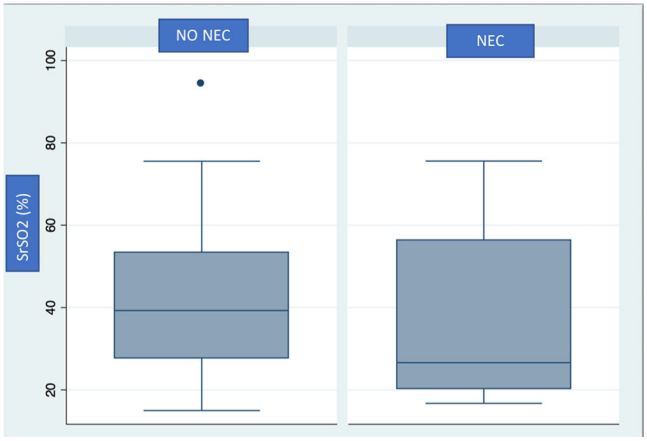
Background: Necrotizing enterocolitis (NEC) has a multifactorial etiology and affects mainly preterm newborns. Current understanding is that necrosis of the intestinal mucosa is the final endpoint of different triggers, which results in different clinical presentation of NEC. One important factor is impaired immature intestinal microcirculation and splanchnic hypoperfusion. Near Infrared Spectroscopy (NIRS) can non-invasively and continuously monitor organ perfusion. Our aim was to investigate if there is an association between splanchnic regional oxygenation (srSO2) in the first week of life and the risk of developing NEC in extremely preterm newborns.

Methods: In this prospective observational cohort study we included extremely preterm newborns born at Karolinska University Hospital between September 2014-December 2016. At enrolment each patient underwent an abdominal ultrasound, then NIRS optods were placed in the first week of life under enteral nutrition. We used INVOS 5100C equipped with neonatal sensors to measure both cerebral and splanchnic oxygenation. Each patient was monitored for at least 20 min, baseline time excluded. We reviewed clinical data from case notes including: demographic and nutritional data, blood tests and brain scans. We follow up the clinical course to observe if they developed NEC. Primary outcome was risk of developing NEC (Bell´s stage >II). Secondary outcome was association with age at full enteral nutrition.

Results: 49 patients were enrolled. One patient was too unstable to undergo abdominal ultrasound and NIRS monitoring and was excluded. Median gestational age was 25.5 weeks (range 23.0–27.9 weeks) and median birth weight 624 g (range 485–1353 g). 9 patients developed NEC, median postnatal age at NEC onset was 14 days (range 6–35 days). 3 patients' recordings were lost due to technical problems. We evaluated NIRS measurements from 45 patients. None of the patients had or was treated for hypotension during monitoring. Infants with splanchnic oxygenation (srSO2) < 30% had a higher risk of developing NEC compared those with srSO2 > 30% (RR 4, (95%CI 1,15–13.95). There was a significant difference in the variability of



[42] Figure 1 Splanchnic oxygenation (srSO2) in the first week of life in patients who later developed NEC (NEC) vs patients who did not develop NEC (NO NEC)

the srSO2, represented by the standard deviation, between the 2 groups (NEC 6,23% vs NO NEC 10,8%, p = 0,02). We found no association between srSO2 and age at full enteral nutrition.

Conclusions: Low splanchnic oxygenation (srSO2 < 30%) and low variability of srSO2 during the first week of life seems to be associated with an increased risk of developing NEC in extremely preterm newborns. The presence of artefacts due to movements, intraluminal air in the intestine or meconium can interfere with the interpretation of NIRS and should be carefully taken into account.

Keywords: Near Infrared Spectroscopy, Necrotising Enterocolitis

Disclosures: None declared

43. EARLY ANTIBIOTICS TREATMENT IS ASSOCIATED WITH LESS NECROTIZING ENTEROCOLITIS IN PRETERM, VERY LOW BIRTH WEIGHT INFANTS AROUND THE WORLD: NEOMUNE-NEONUTRINET COHORT STUDY

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	Mean for Infants without NEC	Mean for Infants with NEC	Mean difference	LCI	UCI	P value
sTOI	42.8	34.6	-8.15	-15.3	-0.96	0.026
sTOE	0.54	0.63	0.09	0.01	0.17	0.023
Ln(SCOR)	4.34	3.97	-0.37	-0.74	0.00	0.051

[ID246] Table 1 Splanchnic NIRS measurements in those infants with NEC compared with infants without NEC (excluding those infants who developed Haemorrhagic Parenchymal Infarcts)

Background: Antibiotic treatment is used frequently in very low birth weight (VLBW, ≤ 1500 g) preterm infants in neonatal intensive care units (NICUs). Previous studies have reported higher risk of necrotizing enterocolitis (NEC) after prolonged antibiotics (AB) use during the first weeks of life. Little is known how AB initiated soon after birth affect NEC incidence. We investigated the association between early AB treatment (AB initiated within first three days after birth) and later development of NEC, using the NEOMUNE-NeoNutriNet cohort of VLBW preterm infants from 13 NICUs in five continents (n = 2829).

Methods: Data were collected from birth until postmenstrual age (PMA) 37 weeks, or less in case of early discharge or death. NEC incidence was compared between infants who received AB within the first three days and those who did not, without or with statistical adjustments for NICU, gestational age (GA), birth weight, gender, delivery mode, antenatal steroids, Apgar score, type and time of enteral nutrition, and use of probiotics. In explorative analyses, PMA at NEC onset was compared between the two groups and NEC incidence was correlated with the duration of early AB treatment.

Results: The large majority (2562/2829) of infants received AB within three days of birth (Early-AB) and 3.9% of these developed NEC. For the remaining 267 infants, not receiving AB or AB after three days or more (No early-AB), NEC incidence was 9.0%. After statistical adjustment for NICU, NEC incidence was still lower in the Early-AB group (OR 0.56; 95% CI, 0.34–0.93, P < 0.05). The significance level increased further after adjustment for covariates (P < 0.0001). The exploratory analyses showed no association between early AB use and PMA at NEC onset, but prolonged AB use tended to associate with increased risk of NEC (P = 0.094) after adjustment for GA and other potential confounders.

Conclusions: Early initiation of AB in VLBW infants was associated with less NEC compared with a minority who did not get early AB. Non-infective factors leading to preterm birth in the No-early-AB group, such as preeclampsia or fetal growth failure, may have a negative impact on gut health but possibly, early AB postpones gut bacterial colonization and thereby reduces NEC-related gut inflammatory responses.

Keywords: Very low birth weight infants; Early antibiotics treatment; Necrotizing enterocolitis

Disclosures: Prof van Goudoever is the director of the Dutch Human Milk Bank and is a member of the National Health Council. Ms. Cormack serves on scientific advisory boards for Nestlé Nutrition Institute and Danone/Nutricia. Prof Simmer is the Director of the Human M

44. NEAR INFRARED SPECTROSCOPY AND GUT BIOMARKERS IN PRETERM INFANTS—CAN THEY PREDICT NEC?

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Background: We previously established normal ranges of regional tissue oxygenation in preterm infants using Near Infrared Spectroscopy (NIRS). Survival of very preterm infants has improved but the incidence of NEC has not changed. Progress in the prevention of Necrotising Enterocolitis (NEC) has been limited by difficulties in clearly defining high risk groups of preterm infants and because there are no routinely used effective gut biomarkers. There is an unmet need to identify prospective biomarkers to create a window of opportunity for prevention.

We aimed to establish if gut biomarkers of tissue injury and splanchnic NIRS measurements differed in infants with NEC compared to those without NEC.

Methods: We examined 48 infants <30w gestation admitted to our tertiary level NICU (after ethical approval and informed consent) from Oct 2016 to May 2018. Exclusion criteria: birthweight ≤2nd centile, abnormal antenatal dopplers, major congenital anomalies or Twin to Twin Transfusion Syndrome. For 60 min each week splanchnic (sTOI) and cerebral (cTOI) Tissue Oxygenation Index was measured simultaneously using NIRO-300 (Hamamatsu KK, Japan).Subsequently splanchnic Fractional Tissue Oxygen Extraction (sFTOE) and Splanchnic Cerebral Oxygenation Ratio (SCOR) were calculated. Weekly urinary intestinal and liver fatty acid binding proteins (I- FABP, L-FABP), Trefoil Factor 3 (TTF3) and stool Calprotectin were measured by ELISA and weekly clinical status recorded. NEC was defined as ≥ Bells stage 2.

Results: Median birthweight was 884 g (460–1600), median gestational age 26 + 3 weeks (23 + 0–29 + 6) and 52% female. 7 infants developed NEC.

Over the first 7 weeks of life none of the biomarkers were affected by presence of PDA, enteric feed volumes or haemoglobin level. There were no statistically significant differences in I-FABP, L-FABP, TFF3 and Calprotectin levels between those infants with and without NEC.

sTOI was significantly lower and sFTOE was significantly higher in those infants who developed NEC compared to those without NEC. The SCOR was lower in infants who developed NEC (Table 1). sTOI, and sFTOE were significantly associated with NEC even after adjusting for confounding factors such as gender, PDA, enteral feed, ethnicity and haemoglobin.

Conclusions: Infants who developed NEC had significantly lower splanchnic oxygenation. If preterm infants at the highest risk of NEC had continuous NIRS measurements and individual trends examined, then a reduction in sTOI and corresponding increase in sFTOE could herald the onset of NEC. This novel finding could help clinicians diagnose NEC sooner. In the future an algorithm could provide more sophisticated information than a single biomarker alone.

Keywords: Preterm; Necrotising Enterocolitis (NEC); gut biomarkers; I-FABP; L-FABP; TFF; Calprotectin; Near Infrared Spectroscopy (NIRS)

Disclosures: None declared

45. RISK OF NECROTIZING ENTEROCOLITIS ASSOCIATED WITH THE SINGLE NUCLEOTIDE POLYMORPHISMS VEGF C-2578A, IL-18 C-607A, AND IL-4 RECEPTOR A-CHAIN A-1902G: A VALIDATION STUDY IN A PROSPECTIVE MULTICENTER COHORT

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Background: The etiology of necrotizing enterocolitis (NEC) is multifactorial and an underlying genetic predisposition to NEC is increasingly being recognized. A growing number of studies identified single nucleotide polymorphisms (SNPs) of selected genes with potential biological relevance in the development of NEC. However, few of these genetic studies have been replicated in validation cohorts.

Methods: We aimed to confirm in a cohort of 358 preterm newborns (gestational age < 30 weeks, 26 cases of NEC ≥ Bell stage 2) the association with NEC of three candidate SNPs: the vascular endothelium growth factor (VEGF) C-2578A polymorphism (rs699947), the interleukin (IL)-18 C-607A polymorphism (rs1946518), and the IL-4 receptor α-chain (IL-4Rα) A-1902G polymorphism (rs1801275).

Keywords: VEGF, IL-18, IL-4 receptor α-chain, polymorphisms, necrotizing enterocolitis, preterm

Disclosures: None declared

46. FECAL MICROBIOTA TRANSPLANTATION PROTECTS AGAINST NECROTIZING ENTEROCOLITIS IN A DONOR SPECIFIC MANNER

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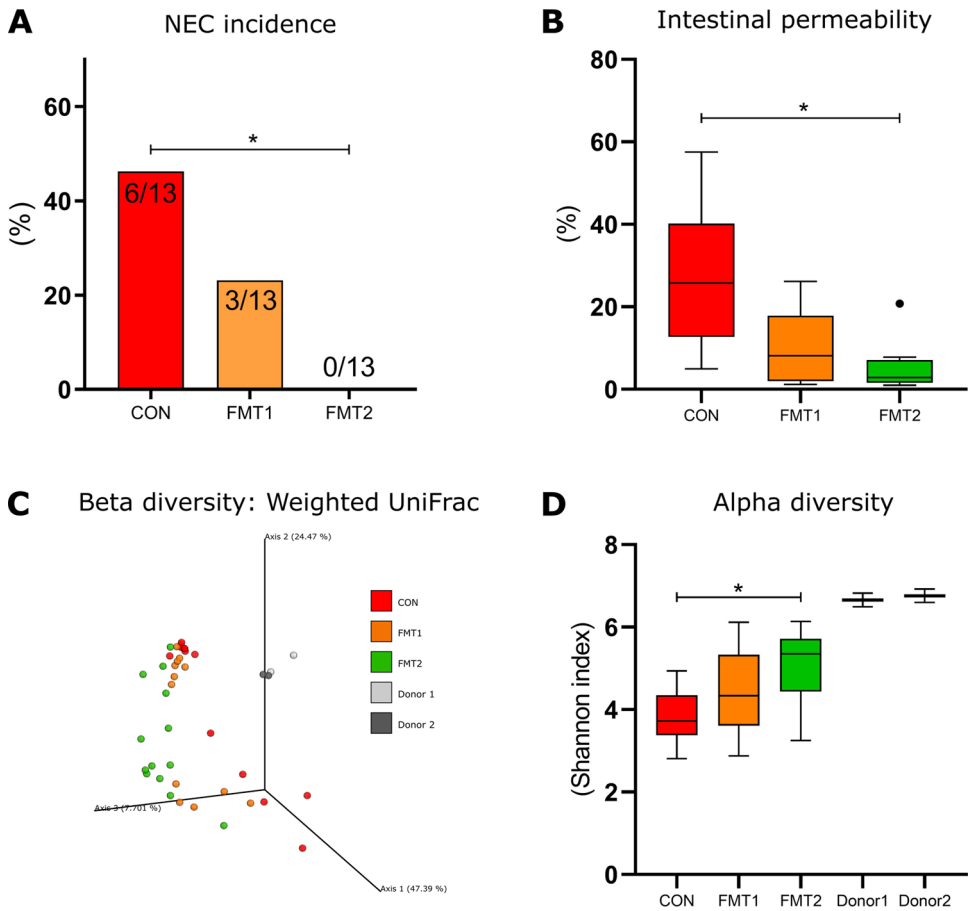
Background: Prevention of necrotizing enterocolitis (NEC), a life-threatening gastrointestinal morbidity of preterm infants, remains a challenge. We recently showed promising effects of fecal microbiota transplantation (FMT) from healthy suckling donors to newborn preterm pigs as a NEC-preventive strategy. Besides ensuring clinical improvements, FMT changed the recipient gut microbiota towards anaerobicity, reducing facultative anaerobic dysbiosis and increasing bacterial diversity. It remains unclear if any eubiotic donor feces will provide similar benefits. Hence, we hypothesized that FMT, using feces from two phenotypically similar donors would result in similar recipient response.

Methods: In a randomized, controlled experiment, using cesarean-delivered, formula-fed preterm pigs (n = 13–14 per group) as models for NEC-susceptible preterm infants, we compared FMT from two donor pig herds (FMT1 and FMT2). Donor material consisted of mixed, homogenized colon content from 5–8 term born, sow-reared, 12 ± 2-days-old piglets from each herd. Pooled donor bacterial compositions were comparable at order level of taxonomic classification (e.g. 65–69% Clostridiales and 18–22% Lactobacillales). A total amount of 0.1 g donor feces suspended in sterile saline was administered by rectal route twice daily the first two days after birth. On day 5, animals were



[46] Figure 1 Gut clinical and microbiological responses to FMT by two separate but comparable donors. A. Incidence of necrotizing enterocolitis. B. Urinary lactuse-mannitol ratio as a functional measure of intestinal permeability. C. PCoA plot of bacterial beta diversity using weighted UniFrac distance metrics. D. Bacterial alpha diversity using Shannon index

euthanized and necropsied, and colon content collected for gut microbiota analysis.

Results: FMT2 resulted in complete NEC protection (0 vs. 23 and 46% in FMT1 and controls respectively, $p < 0.05$ vs. CON, Figure 1A). An in vivo test of gut barrier function showed reduced intestinal permeability only in FMT2 ($p < 0.05$, Figure 1B). Besides, diarrhea was reduced and growth rate increased in FMT2 but not FMT1 recipients relative to controls (both $p < 0.05$). Bacterial 16S rRNA gene amplicon sequencing showed changes in beta-diversity after FMT2 but not FMT1 (weighted UniFrac, $p < 0.05$ vs. CON by PERMANOVA, Figure 1C). Similarly, only FMT2 increased alpha diversity relative to controls (Shannon-index, $p < 0.05$ by Kruskal-Wallis test, Figure 1D). Whereas few donor-derived obligate anaerobes colonized the recipients, FMT2 recipients had increased Lactobacillus (25 vs. 0.5 and 7%) and decreased Enterococcus (25 vs. 57 and 56%) relative abundances compared with controls and FMT1 recipients.

Conclusions: We compared the effect of FMT, using two similar donor pools and found clear differences in recipient clinical and microbiological responses. The results indicate that the ability of FMT to protect against NEC may be mediated by a limited number of bacteria. Identification and isolation of these bacteria could lead to the development of a safe and well-defined NEC prevention therapy.

Keywords: preterm, fecal microbiota transplantation, necrotizing enterocolitis, gut microbiota, lactobacillus, gut permeability

Disclosures: None declared

47. ANTAGONISTIC RELATIONSHIP BETWEEN ANTIBIOTICS AND FECAL MICROBIOTA TRANSPLANTATION PREDISPOSES TO NECROTIZING ENTEROCOLITIS IN PRETERM PIGS

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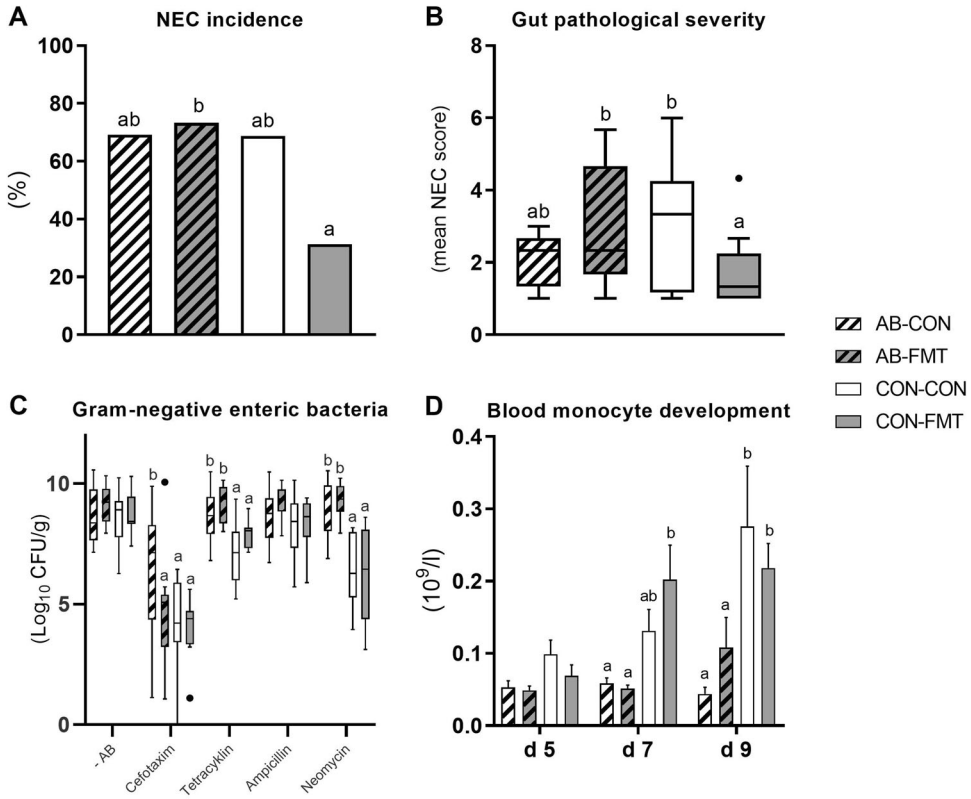
Background: A significant morbidity of preterm infants is necrotizing enterocolitis (NEC), an inflammatory bowel condition involving gut barrier disruption and mucosa bacterial invasion. Antibiotics (AB) are indispensable for treating bloodstream infections in preterm infants but come at a price. Prolonged parenteral AB appears to increase the risk of NEC, whereas prophylactic enteral AB may reduce it. However, any AB treatment causes gut dysbiosis and AB resistance. Fecal microbiota transplantation (FMT) is capable of preventing NEC and may reduce AB resistance. We hypothesized that sequential enteral antibiotics and FMT would effectively prevent NEC with negligible increase in antibiotics resistance.

Methods: In a controlled 2x2 factorial experiment ($n = 13–16$ per group), cesarean-delivered preterm pigs used as model organisms were administered enteral broad-spectrum antibiotics or saline for the first four days of life, and subsequently given



[48] Figure 1 Clinical, microbiological and immunological responses to sequential enteral antibiotics treatment and rectal fecal microbiota transplantation. A. Incidence of necrotizing enterocolitis. B. Gut pathological severity index. C. Antibiotics resistance of Gram negative bacteria from colon content, expressed as number of colony-forming units on MacConkey selective agar with or without antibiotics compounds. D. Blood monocyte levels in blood collected 5, 7 and 9 days after birth. Columns with different letters denote statistically significant differences at $p < 0.05$

rectal FMT (with documented NEC-reducing potential from healthy suckling donor piglets) or control saline. The AB cocktail consisted of 50/12.5 mg/kg/d Amoxycillin/Clavulanic acid and 50 mg/kg/d Neomycin, administered twice daily. The FMT (0.1 g feces per animal) was administered 2–3 cm into the rectum twice daily using a soft catheter. Animals were fed increasing volumes of infant formula and necropsied at nine days of age, after continuous clinical monitoring, and microbiological and immunological evaluations on days 5, 7 and 9.

Results: Only animals receiving no AB followed by FMT treatment (CON-FMT) had reduced NEC incidence (31 vs 69% in CON-CON, $p < 0.05$, Figure 1A). Gut pathological severity was reduced in both single treatments (AB-CON and CON-FMT, Figure 1B) compared with control (CON-CON), whereas to our surprise, the combination treatment (AB-FMT) was not. AB improved growth rate and reduced diarrhea the first 4 days of life (both $p < 0.05$), but the effects disappeared after AB discontinuation. However, both at AB discontinuation and five days later, AB-treated animals had increased AB resistance of the gut microbiota to both the administered and unrelated AB compounds. Notably, FMT treatment after AB discontinuation reduced AB-induced Cefotaxim resistance to control levels ($p < 0.05$, Figure 1C). Finally, AB treatment suppressed blood myeloid cell development, which was not affected by FMT (Figure 1D).

Conclusions: The results offer insights into the principal role of the gut microbiota after preterm birth. Importantly, FMT succeeding initial AB treatment in early life has the capacity to eliminate antibiotics resistance but may be clinically detrimental and requires further refinement. Additionally, we suggest cautious use of early enteral antibiotic treatment in preterm newborns, due to disturbance of immune system development.

Keywords: preterm; necrotizing enterocolitis; antibiotics; fecal microbiota transplantation; antibiotics resistance; cefotaxim; innate immunity; monocytes

Disclosures: None declared

49. DEVELOPMENT OF THE GUT MICROBIOTA IN EXTREMELY PRETERM INFANTS: THE EFFECT OF PERINATAL FACTORS AND LINKS WITH NECROTISING ENTEROCOLITIS

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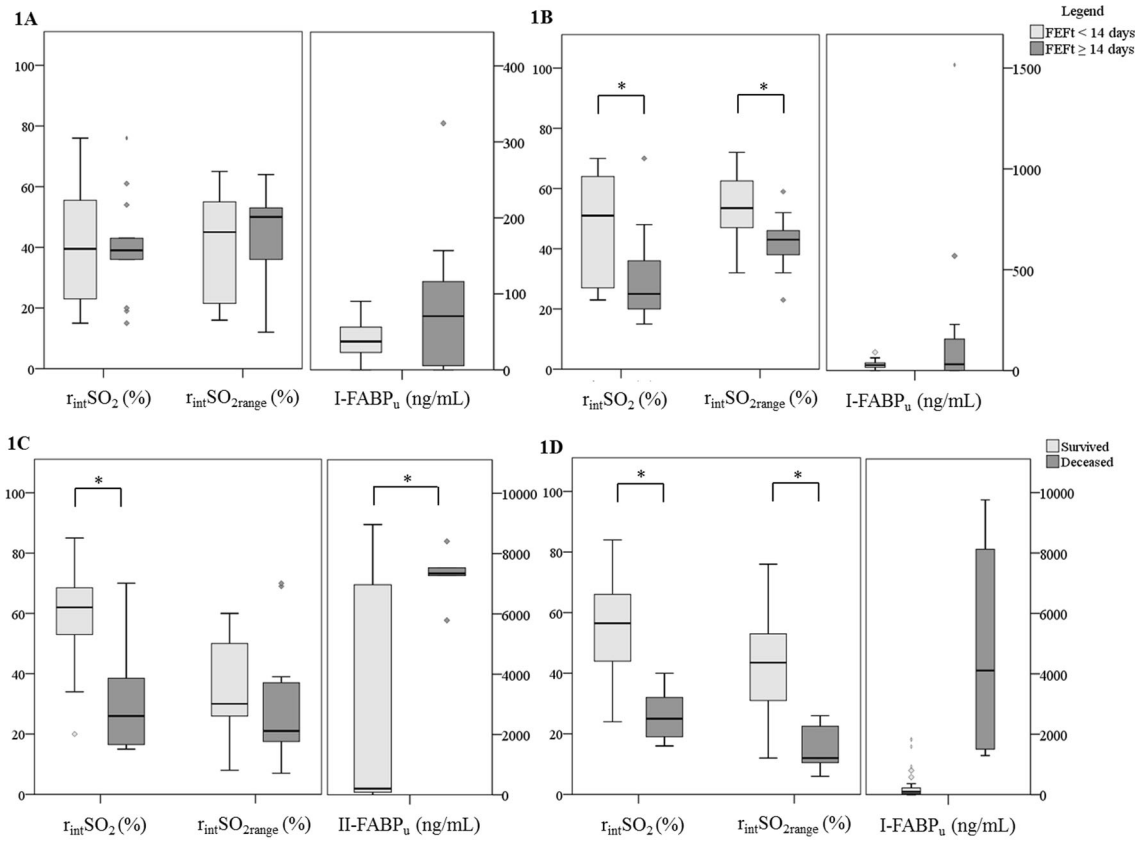
Background: Extremely preterm infants develop in a highly unusual environment, with routine antibiotic administration and the NICU environment contributing to altered bacterial colonization of the gut. However, the influence of other perinatal factors on the gut microbiota remains poorly understood, as does the consequent impact on clinical outcomes. We aimed to characterize the development of the gut microbiota in extremely preterm infants, and to describe the influence of a range of perinatal factors on microbial colonization. We also investigated links between the gut microbiota and later development of necrotizing enterocolitis.

Methods: We carried out a prospective longitudinal study following 89 extremely preterm infants (gestational age <28 weeks) admitted to the NICU at Queen Silvia's Children's



The boxes represent the individual $r_{int}SO_2$, $r_{int}SO_{2range}$, and I-FABP$_u$ values between the 25th and 75th centiles (interquartile range); Last measurement before the first re-feed (1A) and first measurement after first re-feed (1B) between infants with a rapid (< median FEFt of 14 days) and infants with a long intestinal recovery (≥ median FEFt of 14 days); Measurements 24 hours (1C) and 48 hours (1D) after NEC onset between infants who survived and died; the whiskers represent the range of the values with the exception of outliers. Outliers are represented by the circles and diamonds, defined as values between 1.5 interquartile range and 3 interquartile ranges from the end of a box. Significant differences are marked with asterisks: * < .05.

[ID421] Figure 1 Biomarkers predicting time to reach full enteral feeding and survival in preterm infants with NEC

Hospital in Gothenburg, Sweden. Data was collected on a wide range of perinatal factors, including gestational age, birth weight, delivery mode, Apgar scores, chorioamnionitis, maternal and infant antibiotic treatment, prenatal steroids and necrotizing enterocolitis. DNA was extracted from stool samples taken at regular intervals from birth to six weeks of age and the V3–5 region of the 16S rRNA gene was sequenced using the MiSeq platform. We described the development of the gut microbiota and used Orthogonal Partial Least Squares to explore associations with a range of perinatal factors.

Results: The gut microbiota of extremely preterm infants showed low diversity throughout the first six weeks of life and was dominated by facultative anaerobes belonging to the genera Staphylococcus and Enterococcus and the class Gammaproteobacteria. Obligate anaerobic commensals from the genera Bifidobacterium and Bacteroides, which are abundant in the gut of healthy term infants, were only found at low levels in a minority of infants, while obligate anaerobes from the phylum Firmicutes were slow to establish. Lower gestational age at birth and chorioamnionitis were both linked with enrichment in various Proteobacteria and delayed colonization by bifidobacteria, while babies born by caesarian section had increased prevalence of Streptococcus. High levels of Klebsiella (>88%) were noted in a third of infants (2/6) in the days prior to development of necrotizing enterocolitis.

Conclusions: Increased abundance of potential pathogens, along with low levels of commensals providing colonization and translocation resistance, may help explain poor clinical outcomes in extremely preterm infants. In particular, necrotizing enterocolitis was often preceded by high levels of Klebsiella. Bacterial colonization patterns were influenced by a range of factors, including gestational age at birth, birth mode and chorioamnionitis.

Keywords: Gut microbiota, necrotising enterocolitis, extremely preterm, perinatal factors

Disclosures: None declared

50. PREDICTING INTESTINAL RECOVERY AND SURVIVAL AFTER NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS

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Background: Preterm infants who develop necrotizing enterocolitis (NEC) are managed with a nil per mouth (NPO) regimen. The duration of NPO is currently determined by consensus based guidelines. As enteral feeding is essential for gut function and growth, it is desirable to minimize the duration of NPO. Re-feeding before full intestinal recovery, however, has been associated with the development of recurrent NEC. So far, little is known about the individual intestinal recovery in preterm infants suffering from NEC. We evaluated if several biomarkers are able to predict intestinal recovery and survival in preterm infants with NEC.

Methods: We included preterm infants (gestational age <37 weeks) who developed NEC Bell's stage ≥2 between January 2015 and May 2017. After NEC onset, we continuously measured intestinal tissue oxygen saturation (rintSO2) for two hours daily and calculated mean and range. We collected urinary intestinal fatty binding protein (I-FABPu) levels once daily. To predict survival, we used data collected 24 and 48 h after NEC and performed logistic regression analysis. As a measure for intestinal recovery, we determined the group's median time to reach full enteral feeding (FEFt) and designed two groups; < or ≥ median FEFt. We repeated the logistic regression analyses and added data collected around the first re-feed. We determined cut-off points with ROC-curves and designed one prediction model.

Results: We included 40 preterm infants with NEC with a median gestational age of 27.1 [IQR 25.9–29.3] weeks and a birth weight of 1033 [IQR 796–1306] grams. Thirteen infants (33%) died. Median FEFt was 14 [IQR 12–23] days. A higher rintSO2 and a larger rintSO2range after the first re-feed significantly predicted FEFt < 14 days (Figure 1). For every 10% increase in rintSO2 and rintSO2range, the OR to reach FEFt < 14 days was 1.8 (95% CI 1.1–3.0) and 3.0 (95% CI 1.1–8.1) in the entire group and 2.7 (95% CI 1.1–6.6) and 13.5 (95% CI 1.2–157.8) in conservatively treated infants. A rintSO2 cut-off of 53% combined with a rintSO2range cut-off of 50% predicted FEFt < 14 days with an OR of 16.7 (95% CI 2.3–122.2). I-FABPu did not predict FEFt. In addition, we found that the rintSO2 and I-FABPu at 24 h, and the rintSO2 and rintSO2range 48 h after NEC onset, significantly predicted survival (Figure 1).

Conclusions: A higher rintSO2 and a larger rintSO2range measured after the first enteral feed after NEC may help to predict a rapid intestinal recovery. In addition, a higher rintSO2, a larger rintSO2range, and a lower I-FABPu concentration measured during the first 48 h after NEC onset predict survival in preterm infants with NEC.

Keywords: Necrotizing enterocolitis, biomarkers, intestinal oxygen saturation, intestinal-fatty acid binding protein, intestinal recovery, time to reach full enteral feeding, survival

Disclosures: None declared

NEONATAL HEMATOLOGY AND BILIRUBIN

51. PRETERM NEONATES BENEFIT FROM LOW PROPHYLACTIC PLATELET TRANSFUSION THRESHOLD DESPITE VARYING RISK OF BLEEDING OR DEATH

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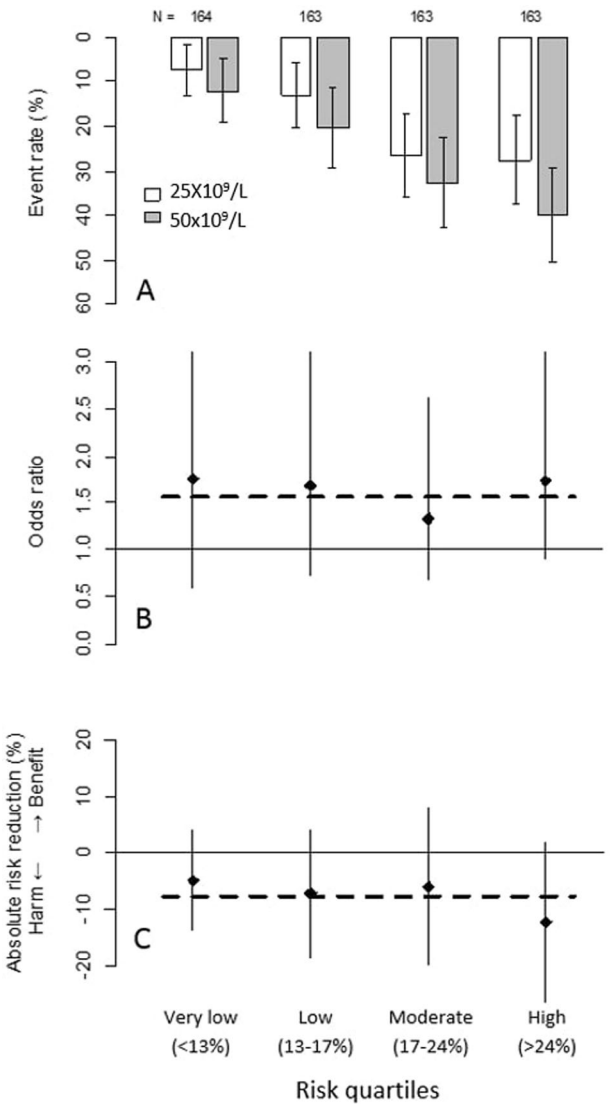

[51] Image 1 Image title: Absolute risk difference (ARD) between a high (50x10^9/L) and low (25x10^9/L) threshold for prophylactic platelet transfusion thresholds in preterm neonates with respect to major bleeding and/or mortality within 28 days after randomization. Event rates (panel A), odds ratios (panel B) and absolute risk differences (panel C) are presented for all four risk categories, vertical lines represent 95% confidence intervals, horizontal lines represent overall trial results. A negative absolute risk reduction represents the risk decrease for a low prophylactic platelet transfusion threshold as compared to a high threshold

Background: The Platelets for Neonatal Thrombocytopenia (PlaNeT-2) trial reported an overall unexpected benefit of a prophylactic platelet transfusion threshold of 25x10^9/L compared to 50x10^9/L for major bleeding and/or mortality in preterm neonates (7% absolute risk reduction). However, some neonates in the trial may have experienced little benefit or even harm from the 25x10^9/L threshold. We aimed to assess this heterogeneity of treatment effect in the PlaNet-2 trial, in order to investigate whether all preterm neonates benefit from the low threshold.

Methods: We developed a multivariable logistic regression model in the PlaNet-2 data to predict baseline risk of major bleeding and/or mortality for all 653 neonates. We then ranked the neonates based on their predicted baseline risk and categorized them into four risk quartiles. Within these quartiles we assessed the absolute risk difference between the 50x10^9/L and 25x10^9/L threshold group.

Results: A total of 146 neonates died or developed major bleeding. The internally validated C-statistic was 0·63 (95% confidence interval 0.58–0.68). The 25x10^9/L threshold was associated with absolute risk reduction in all risk groups, varying from 4.9% in the lowest to 12.3% in the highest risk group.

Conclusions: These results suggest that a 25x10^9/L prophylactic platelet count threshold can be adopted in all preterm neonates, irrespective of predicted baseline outcome risk. Future studies are needed to improve the predictive accuracy of the baseline risk model.

Keywords: Neonatal hematology, platelet transfusions, major bleeding, PlaNeT-2 trial.

Disclosures: None declared.

NEONATAL INFECTIOS DISEASES / IMMUNOLOGY

52. CHORIOAMNIONITIS IS A RISK FACTOR FOR EARLY AND LATE ONSET SEPSIS IN PRETERM INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Chorioamnionitis (CA) is considered a key risk factor for (very) preterm delivery and for adverse neonatal outcome. Sepsis is one of the major causes of morbidity and mortality in the newborn and is classically divided into early onset sepsis (EOS; 72 h of life; acquired after delivery and often nosocomial). Association between CA and EOS appears to be self-evident, but several studies suggest that CA might be protective against LOS. We aimed to conduct a systematic review of studies reporting on CA as risk factor for neonatal sepsis.

Methods: PubMed/MEDLINE and EMBASE databases were searched. Studies were included if they examined preterm infants and reported primary data that could be used to measure the association between exposure to CA and the presence of neonatal sepsis. A random-effects model was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Sources of heterogeneity were determined by subgroup and meta-regression analyses. The following categories of sepsis were analyzed: EOS, LOS, undefined onset sepsis (UOS), culture-proven, and clinical sepsis. CA was subdivided into clinical and histological.

Results: 3768 potentially relevant studies, 113 meeting inclusion criteria (387,899 infants; 44,832 cases of CA) were analyzed. Meta-analysis showed a significant association between any CA and any EOS (OR 4.34, CI 3.68 to 5.11), any LOS (OR 1.27, CI 1.10 to 1.47), and any UOS (OR 1,59, CI 1,34 to 1,89). CA was significantly associated with culture-proven EOS (OR 4.57, CI 3.83 to 5.44), clinical EOS (OR 3.74, CI 1.84 to 7.62), and culture-proven LOS (OR 1,31, CI 1,12 to 1,53), but not with clinical LOS (OR 1.48, CI 0.75 to 2.90) in subgroup analysis. CA-exposed infants had significantly lower gestational age (−1,11 weeks, CI −1,34 to −0,89), lower birth weight (−48,30g, CI −70,25 to −26,35), and higher mortality than the infants not exposed to CA in meta-analyses. Lower GA in the CA-exposed group was significantly associated with a higher risk of LOS, but not with EOS, in meta-regression.

Conclusions: We observed a strong positive association between CA and EOS and a moderate, but still significant, association between CA and either LOS and UOS. Meta-analysis confirmed that preterm infants exposed to CA are younger and sicker than those without exposure. This fact appears to confound the association between CA and nosocomial LOS, since CA-exposed preterm infants would require longer hospitalization and more days of invasive therapies.

Disclosures: None

53. MOLECULAR PROFILING OF NEONATAL DRIED BLOOD SPOTS REVEALS CHANGES IN INNATE AND ADAPTIVE IMMUNITY FOLLOWING FETAL INFLAMMATORY RESPONSE

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Background: The fetal inflammatory response (FIR) increases the risk of perinatal brain injury, particularly in extremely low gestational age newborns (ELGANs, < 28 weeks of gestation). One of the mechanisms contributing to such a risk is a postnatal intermittent or sustained systemic inflammation (ISSI) following FIR. The link between prenatal and postnatal systemic inflammation is supported by the presence of well-established inflammatory biomarkers in the umbilical cord and peripheral blood. However, the extent of molecular changes contributing to this association is unknown.

Methods: Using RNA sequencing and mass spectrometry proteomics, we have profiled the transcriptome and proteome of archived neonatal dried blood spot (DBS) specimens from 21 ELGANs (8 females and 13 males). Histological acute chorioamnionitis was diagnosed in 15 cases, where 10 of them were affected by FIR. Total RNA sequencing of the 21 archived DBSs produced more than 500 million paired-end reads, which we transformed into a table of 25,221 gene-level summarized count expression profiles. Nearly half of these genes (11,279) showed reliable levels of expression in at least 6 of the 21 samples. Mass-spectrometry proteomics on DBSs produced 650 quantified protein expression profiles, from which we selected 245 as being reliably expressed in at least 6 of the 21 samples.

Results: Sample-level gene and protein expression changes, projected in two dimensions, show a clear separation between infants with and without FIR. Comparing FIR-affected and unaffected ELGANs, we identified 783 gene and 27 protein expression changes of at least 50% magnitude with an experiment-wide significance level below 5% false discovery rate. Our data show in detail the postnatal activation of the innate immune system, including NLRC4-inflammasome dependent mechanisms, and support the expansion of myeloid-derived suppressor cells, in FIR-affected ELGANs. We also observed in FIR-affected ELGANs that downregulated genes support the inhibition of adaptive immune responses, consistently with lower levels of T-cell receptor excision circles and of lymphocyte percentage over leukocytes during the first postnatal week.

Conclusions: We have generated the largest catalog to date of postnatal transcriptomic and proteomic changes associated with FIR in archived DBS, which confirm the postnatal activation of the innate immune system and reveal an impairment of the adaptive immunity in FIR-affected ELGANs. The altered pathways provide novel insights into the possible mechanisms that trigger a systemic inflammation after FIR and the onset of perinatal brain injury.

Disclosures: "None declared"

NEONATAL PULMONOLOGY, NEONATAL RESPIRATORY SUPPORT, RESUSCITATION

54. NEBULIZED PORACTANT ALFA REDUCES THE RISK OF RESPIRATORY FAILURE AND REINTUBATION AT 72 h IN SPONTANEOUSLY-BREATHING SURFACTANT-DEFICIENT NEWBORN PIGLETS

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Background: The short-term efficacy of nebulized poractant alfa has been studied in animal models showing an acute pulmonary improvement at 3 h. However, the primary efficacy outcome in clinical trials aimed at investigating non-invasive surfactant administration techniques is the rate of failure as measured by the need for intubation and surfactant instillation in the first 72 h of life. We have set up a long term (72 h) respiratory distress syndrome (RDS) model in spontaneously-breathing surfactant-deficient newborn piglets to investigate the rate of respiratory failure of nebulized poractant alfa compared to standard InSurE (Intubation Surfactant Extubation) technique and nasal CPAP only.

Methods: Eighteen spontaneously breathing newborn piglets (n = 6/group), were submitted to bronchoalveolar lavages to induce surfactant-deficient RDS, and then were randomized to three nasal CPAP (nCPAP)-ventilated groups: 1) nebulized poractant alfa (400 mg/kg; dose chosen from previous 3-hour study for exemplary purpose only, not predictive yet of the most suitable dose for clinical use) via a customized eFlow Neos vibrating-membrane nebulizer system, 2) bolus administration using InSurE technique (200 mg/kg) or 3) nCPAP only. Pulmonary (gas exchange, lung mechanics) and hemodynamic (arterial blood pressure, heart rate) parameters were evaluated at 6-hour intervals for 72 h. Lung and brain histological analyses were also performed.

Results: After bronchoalveolar lavages, newborn piglets developed RDS. During the 72 h observation, both surfactant treatment groups significantly improved pulmonary outcomes compared to nCPAP only, without hemodynamic alteration. Moreover, differently from nCPAP group, in both surfactant treatment groups there were no cases of respiratory failure.

Conclusions: In newborn piglets with RDS, the nebulization of 400 mg/kg of poractant alfa by means of a customized eFlow Neos nebulizer system showed to be safe and effective in reducing the risk of respiratory failure in the first 72 h after treatment. This finding needs to be verified in a randomized control trial in spontaneously-breathing newborn infants.

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Disclosures: This study was supported by: Chiesi-Farmaceutici S.p.A.

55. TWO-YEAR OUTCOMES OF PREMATURE INFANTS ENROLLED IN THE FIRST-IN-HUMAN STUDY OF AMNION CELLS FOR BRONCHOPULMONARY DYSPLASIA

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Background: We have previously reported on the immediate safety and neonatal outcomes of six premature infants with severe bronchopulmonary dysplasia (BPD) who were administered human amnion epithelial cells (hAECs)[1]. One infant died in the neonatal period due to unrelated causes. In this study, we aimed to assess the follow-up outcomes of the five surviving infants till 2-year corrected age (CA). The focus of the study was to assess long-term safety of low dose hAEC administration in neonates.

Methods: Study follow-up consisted of assessment of any serious adverse events, growth, respiratory, cardiac and neurodevelopmental outcomes at four time points (6, 12, 18 and 24 months corrected age). Study follow-up investigations included chest x-rays, cranial, abdominal ultrasounds, and echocardiograms at regular intervals and an MRI brain at 2-years CA.

Results: All five infants were alive at 2 years CA. Median time to wean off home oxygen was 24 (10–36) months. Two infants had associated pulmonary hypertension, which resolved by 2 years of age. Three infants were re-hospitalised briefly for viral infections during the follow-up period. There were no cranial or abdominal ultrasound abnormalities noted. MRI brain findings included normal (n = 2), and mild-moderate white matter loss (n = 2). Neurodisabilites diagnosed included hemiplegic cerebral palsy (n = 1), global developmental delay (n = 2), and severe hearing loss (n = 3). All infants were ambulant. No evidence of tumour formation was noted on serial physical examinations or on any imaging.

Conclusions: There were no long-term adverse events observed in the study infants that could be attributed to hAEC administration. We observed long-term effects of extreme prematurity, and severe BPD in the cohort. A dose escalation study to establish the optimum dose of hAECs in infants at risk of BPD is currently underway [2].

Keywords: stem cells, amnion, placental cells, BPD, safety

Disclosures: None declared

References:

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56. NON-INVASIVE RESPIRATORY SUPPORT FAILURE IN PRETERM INFANTS: THE INFLUENCE OF INSPIRATORY TIME ON THE EFFICIENCY OF BI-LEVEL CPAP. RANDOMISED PROSPECTIVE TRIAL

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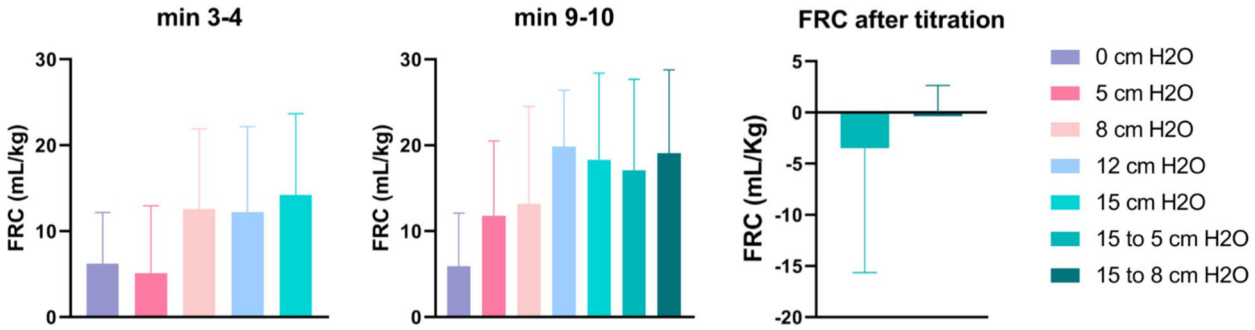
Background: It remains unclear whether non-invasive ventilation in Bi-level CPAP mode is more effective than nasal CPAP in premature infants. Short inspiratory time can lead to ineffectiveness of non-invasive ventilation when device with open exhalation circuit such as Infant Flow SiPAP is used in BiPhasic mode (Bi-level CPAP). Optimal inspiratory time could compensate circuit leakage and improve the efficiency of non-invasive ventilation. The aim of



[57] Figure 1 Functional residual capacity

present study is to compare three modes of non-invasive respiratory support of Infant Flow SiPAP to define whether inspiratory time influences on the efficiency of non-invasive ventilation in preterm infants compared to nasal CPAP.

Methods: 298 premature babies born at 28–35 weeks were included. After initial stabilization on CPAP in delivery room, they were randomized immediately after admission to NICU and divided into 3 groups. 97 newborns formed 1st group where BiPhasic mode with insp.time1.0 s and frequency 30 per minute. 86 newborns formed 2nd group BiPhasic mode with insp. time 0.5 s and frequency 60 per minute. Group 3 included 115 premature babies on CPAP mode. Estimated mean airway pressure was similar on BiPhasic groups (1st and 2nd). Incidents of non-invasive support failure in groups was evaluated. The failure criteria were the increase of FiO2 > 0.4 (FiO2 >0.3 for <1000 g) and/or Silverman score = 4 or higher.

Results: In 1st group, where the respiratory therapy was provided by BiPhasic mode with inspiratory time of 1.0 s the failure was in two times less than in 2nd group and 3rd group: 33% vs 65% vs 62% ($p = 0.00003$). Respiratory support failures in 2nd and 3rd group were similar. RR of failure BiPhasic Tin1.0/Fr30 vs CPAP: 0,53 [0,39; 0,72], RR of failure BiPhasic Tin1.0/Fr30 vs BiPhasic Tin0.5/Fr60: 0,50 [0,36; 0,70]; RR of failure BiPhasic Tin0,5/Fr60 vs CPAP: 1,05 [0,85; 1,28].

At the sametime the time of respiratory support failure incidents was similar in three groups: Me (min-max) (hours age of life) 2,0 (1–26); 1,75(1–27); 2(1–23) in group 1,2 and three.

Conclusions: Infant Flow SiPAP on BiPhasic mode (Bi-Level CPAP) has advantage over CPAP when inspiratory time is 1.0 s to compensate the leakage and create an optimal peak inspiratory pressure. BiPhasic mode with inspiratory time 0.5 s has the same efficiency as CPAP mode and has no advantages over CPAP

The time of incidents of non-invasive support failure does not depend on respiratory support mode.

Disclosures: None declared

57. HIGH-CPAP INCREASES THE DEGREE OF LUNG AERATION IN PRETERM RABBITS AT BIRTH

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Background: Preterm infants require continuous positive airway pressure (CPAP) at birth to adequately aerate their lungs. CPAP of 5–8 cmH2O is recommended, yet the optimal strategy is unknown. Higher CPAP levels may initially increase surface area which is essential for gas exchange but may cause overdistension after lung aeration. The role of CPAP then changes into preventing alveolar collapse and re-entry of lung liquid for which a lower CPAP level may be adequate. A dynamic strategy based on the transitional phases of lung may be more beneficial in aerating the lungs and support breathing. The aim was to investigate the effect of CPAP strategies on respiratory function and lung aeration at birth.

Methods: Preterm rabbit pups (29 days gestation; term ~32 days) were delivered via caesarean section and received 0 ($n = 7$), 5 ($n = 6$), 8 ($n = 7$), 12 ($n = 8$), 15 ($n = 5$) cmH2O CPAP continuously. Two additional groups started at 15 cmH2O which was titrated to 5 ($n = 6$) or 8 ($n = 6$) cmH2O CPAP after stabilization. Functional residual capacity (FRC; lung aeration) was measured using phase contrast X-ray imaging. The study was conducted in the experimental hutch 3 of beamline 20B2 in the Biomedical Imaging Centre at the Spring-8 synchrotron. The study period ended after 10 min after starting CPAP or when intermittent positive pressure ventilation (iPPV) was initiated.

Results: High-CPAP strategies (>8 cmH2O) led to a higher FRC at 3–4 and 9–10 min after birth when compared to standard-CPAP strategies (5–8 cmH2O). (Figure 1) In the dynamic CPAP groups, CPAP was titrated after 4.15 ± 1.39 min. Titration to 5 or 8 cmH2O CPAP led to a change in FRC of −3.5 ± 12.1 versus 0.0 ± 2.6 mL/kg ($p = 0.589$). (Figure 1) Breathing rate was higher in the high-CPAP group at 3–4 min but was similar between groups at 9–10 min. Pups receiving standard-CPAP strategies needed non-significantly more and sooner PPV ($p = 0.697$). In the dynamic groups iPPV was started after titration. During the experiment, only one pup needed iPPV while being supported on 15 cmH2O CPAP. Values were excluded after iPPV was started, reducing the differences between groups regarding FRC and breathing rate at minute 9–10. After iPPV pups ($n = 8$) gained 16.9 ± 3.3 mL/kg FRC.

Conclusions: Preterm rabbits supported with high-CPAP strategies established better lung aeration. Titration to 8 cmH2O CPAP maintained the degree of lung aeration. Pups receiving standard-CPAP strategies needed non-significantly more and sooner iPPV. Pups gained FRC after iPPV.

Keywords: Preterm, CPAP, spontaneous breathing, lung aeration

Disclosures: None declared

58. CEREBRAL OXYGENATION AND HEMODYNAMIC PARAMETERS DURING PRESSURE-CONTROLLED VS VOLUME-TARGETED VENTILATION IN EXTREMELY PREMATURE INFANTS

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Background: Despite the advances in the non-invasive respiratory support conventional mechanical ventilation (CMV) remains an important therapy in the management of newborns with severe respiratory failure. It has been reported that volume-targeted CMV may be superior to pressure-controlled CMV in the neonate resulting in reduced risk of death or bronchopulmonary dysplasia, however it is not a standard of care in all neonatal units yet and its physiological effects are not fully understood. Hence, this study was aimed at determining the effects of volume-targeted mechanical ventilation on cerebral oxygenation and hemodynamic parameters of extremely premature infants.

Methods: A prospective crossover study was conducted at the Department of Neonatology, Poznań University of Medical Sciences in 2017–2018. 20 infants born before 28 weeks of gestation requiring mechanical ventilation were enrolled. Each newborn was ventilated for 3 h with pressure controlled-assist/control (PC-A/C) ventilation, followed by 3-hours of PC-A/C volume guarantee (VG) ventilation. During both periods cerebral oxygenation (StO2) was assessed using near-infrared spectroscopy (NIRS) and hemodynamic parameters: cardiac output (CO), stroke volume (SV), cardiac index (CI), stroke volume variation (SVV), index of contractility (ICON) were measured using electrical velocimetry (EV).

Results: The average birth weight in the study group was 848 g and the average gestational age was 25.7 weeks. During PC-A/C VG ventilation minute expiratory volume (MVE) was more stable (SD 0.02 vs 0.05 $p < 0.001$) and mean airway pressure (MAP) was lower (8.4 vs 8.7 cmH20, $p < 0.01$), than during pressure-controlled mode. There was no statistically significant difference between mean values of StO2 (80 vs 81%, ns), but the variability of StO2 assessed by comparison of its standard deviation was statistically significantly lower during PC-A/C VG ventilation (SD 1.4 vs 1.9, $p < 0.01$). No statistically significant differences were found for hemodynamic parameters (eg. CO 0.25 vs 0.24 L/min, ns; SV 1.6 vs 1.7 ml, ns; SVV 15 vs 14.5%, ns), but there was a trend towards less variable values of heart rate during the PC-A/C VG ventilation (SD 1.8 vs 2.3, $p < 0.09$).

Conclusions: It has been shown that hemodynamic parameters are stable and cerebral oxygenation is less variable during PC-A/C VG ventilation as compared to the pressure-controlled mode. This may be due to less fluctuations in carbon dioxide levels in the blood and more stable cerebral blood flow. Obtained results confirm beneficial cardiorespiratory and cerebral effects of volume-VOLUMEtargeted ventilation in extremely premature infants.

Keywords: volume-targeted ventilation, near-infrared spectroscopy, electrical velocimetry, cerebral oxygenation

Disclosures: None declared

59. A COMPARISON OF THE EFFECT OF TWO INTERFACES FOR RESPIRATORY SUPPORT ON BREATHING IN PRETERM INFANTS AT BIRTH: A MATCHED-PAIRS ANALYSIS

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Background: Applying a face mask for respiratory support affects breathing in preterm infants at birth by provoking the trigeminocardiac reflex. We compared the effect of bi-nasal prongs on breathing and heart rate with a face mask in preterm infants at birth.

Methods: In a retrospective matched-pairs study of infants < 32 weeks of gestation receiving respiratory support via bi-nasal prongs or face mask were compared at the Leiden University Medical Centre and the General University Hospital in Prague. Infants who were initially breathing at birth and an interface was applied at birth were matched with a 1:1 ratio for gestational age (+/−4 days), birth weight (+/−300 gram), general anaesthesia and gender. Breathing, heart rate and other parameters were collected before and after interface application and in the first 5 min thereafter.

Results: In total, 130 infants were included (65 infants with bi-nasal prongs were matched to 65 infant with face mask) with a median (IQR) gestational age of 27 + 2 (25 + 3–28 + 4) vs 26 + 6 (25 + 3–28 + 5). The percentages of infants who stopped breathing after the interface was applied were not different between the groups (bi-nasal prongs 43/65 (66%) vs face mask 46/65 (71%), p = NS). However positive pressure ventilation was significantly more often given when bi-nasal prongs were used (55/65 (85%) vs 40/65 (62%), $p < 0.001$). Heart rate (101 (75–145) vs 110 (68–149) bpm, p = NS) and oxygen saturation (59% (48–87) vs 56% (35–84), p = NS) were similar in the first 5 min after an interface was applied in the infants who stopped breathing.

Conclusions: The trigeminocardiac reflex occurred often and was similar when using bi-nasal prongs or face mask.

Keywords: preterm infants, breathing, face mask, bi-nasal prongs, trigeminocardiac reflex, respiratory support.

Disclosures: None declared

60. SHIFT OF THE SPO2/PIO2 CURVE ASSESSED EARLY IN LIFE ENABLES PREDICTION OF BRONCHOPULMONARY DYSPLASIA IN EXTREMELY PRETERM INFANTS

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Background: Rightward shift of the peripheral arterial oxygen saturation (SpO2)/and inspired oxygen pressure (PIO2) curve is a sensitive marker of pulmonary gas exchange in preterm infants. We hypothesised that rightward shift of the SpO2/PIO2 curve in the first weeks of life is a predictor of bronchopulmonary dysplasia (BPD) at 36 weeks (w) postmenstrual age (PMA).

Methods: This was a prospective observational study. Infants born at <28 w gestation at the King Edward Memorial Hospital in Western Australia between 21st August 2017–1st April 2018 were eligible for inclusion. Rightward shift was assessed weekly from birth until 36 w PMA by recording SpO2 and PIO2 at hourly intervals for 24 h. Right shift was calculated from the paired SpO2/PIO2 values using a validated prediction table.

Results: 32 extremely preterm infants with a median (range) gestational age of 26.4 (23.9–28.0) w were studied. Infants with BPD were born at a lower gestation: Median (IQR) gestation was 25.7 (25.1–26.6) w for the BPD group compared to 27.3 (26.6–27.4) w for infants without BPD ($p < 0.001$). Shift values in infants with BPD were significantly higher compared to infants without BPD throughout week one to eight of life (all $p <= 0.001$, Mann-Whitney U tests). Receiver operating characteristic curve analysis showed a shift value of 11.4 kPa at one week of age predicts BPD with 89.5% sensitivity and 91.7% specificity (AUC:0.91, $p < 0.001$).

In Kruskal-Wallis test, no significant difference was seen in the four groups of different BPD severity. After adjusted for GA and BW by logistic regression, the levels of IL-17 became significantly lower in all three BPD groups; the levels of IFN-α2 became significantly lower in the moderate and severe BPD groups, comparing to the control group. (IQR: interquartile range, OR: odds ratio, CI: confidence interval.) *Comparing to the control group, significance was defined by $p < 0.05$.

Cytokines on Day 7	Group	Kruskal-Wallis			Logistic regression (GA, BW)			
		Median	IQR	p	OR	95% CI		p
						Lower	Upper	
IL-17 (pg/ml)	Control	22.40	32.45					
	Mild	24.70	25.94	0.909	0.974	0.951	0.998	0.036*
	Moderate	24.10	41.29		0.973	0.950	0.997	0.027*
	Severe	24.48	54.98		0.973	0.951	0.997	0.025*
IFN-α2 (pg/ml)	Control	257.60	207.14					
	Mild	163.83	220.68	0.411	0.998	0.995	1.000	0.088*
	Moderate	224.30	295.5		0.996	0.992	1.000	0.036*
	Severe	165.90	145.69		0.995	0.990	0.999	0.023*

[ID373] Table 1 The association between BPD severity and D7 salivary IL-17/IFN-α2 levels in premature neonates before and after regression

A shift value of 16.1 kPa at one week of life predicts moderate and severe BPD at 36w PMA with 77.8% sensitivity and 86.4% specificity (AUC:0.84, $p = 0.004$). Shift at two weeks of life was significantly correlated with shift at 36w PMA ($R2 = 0.71$, $p < 0.001$).

Conclusions: Shift assessed at one week of age enables prediction of BPD at 36 weeks PMA. Prediction of moderate and severe BPD should be treated with caution for the limited number of infants included in the study. Nevertheless, infants with high shift values at two weeks of age are at risk of moderate to severe BPD. Early detection of preterm infants at risk for the development of BPD might benefit from targeted early interventions.

Keywords: Shift, Oxyhaemoglobin dissociation curve, Bronchopulmonary dysplasia, Extremely preterm infants

Disclosures: None declared.

61. SALIVARY CYTOKINE — A NON-INVASIVE PREDICTOR FOR THE DEVELOPMENT OF BRONCHOPULMONARY DYSPLASIA IN PREMATURE NEONATES

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Background: Bronchopulmonary dysplasia (BPD) is one of the most common respiratory morbidity in premature neonates and causes several complications in their future life. Researchers revealed strong correlation of cytokines with the development of BPD. Nevertheless, in most of the previous studies, cytokines were obtained from serum, plasma, tracheal aspirates, or bronchoalveolar lavage, which were invasive and might result in iatrogenic anemia to these tiny premature neonates. In this study, we aimed to provide a less invasive method of cytokine detection by analyzing the neonates' salivary cytokine.

Methods: Premature neonates younger than 34 weeks of gestational age born from August 2012 to May 2017 were enrolled in our study. Neonates of mother with sepsis or clinical chorioamnionitis, and those with perinatal infection within 7 days of life were excluded. Salivary samples were collected from each neonate on their first (D1) and seventh (D7) day of life. Salivary cytokine levels were detected by Human Cytokine/Chemokine Magnetic Bead Panel. Other laboratory and clinical data were collected from their medical records. Kruskal-Wallis test, chi square test, and logistic regression test were used to analyze the salivary cytokine levels and the clinical characteristics among the four groups: the control group, the mild BPD group, the moderate BPD group, and the severe BPD group.

Results: 125 survived neonates met the criteria and were enrolled in this study — 33 in the control group, 26 in the mild group, 25 in the moderate group, and 41 in the severe group. In Kruskal-Wallis test, their gestational age (GA) and birth weight (BW) was strongly and negatively associated with the BPD severity. The levels of D1 salivary Interleukin (IL)-6, IL-8, IL-10, IL-17, Interferon (IFN)-γ1, and D7 salivary IL-6 were significantly higher in the BPD groups than that in the control group ($p = 0.001$, 0.001, 0.000, 0.043, 0.037 and 0.001, respectively). After adjusted for GA and BW by logistic regression, D7 salivary IL-17 and IFN-α2 levels were significantly lower in the moderate and severe BPD groups compared to the control group ($p = 0.027$ and 0.025 in IL-17; $p = 0.036$ and 0.023 in IFN-α2.)

Conclusions: Our research revealed that early-life salivary cytokine levels, especially lower IL-17 and IFN-α2 levels, were

associated with future development of BPD in premature neonates. These results add a new view of salivary cytokine expression to the pathogenesis of BPD, helping us predict and prevent this critical pulmonary morbidity early.

Keywords: Salivary cytokine, bronchopulmonary dysplasia, prematurity

Disclosures: None declared

62. BIOLOGICAL INTERACTIONS BETWEEN A NEW SYNTHETIC SURFACTANT (CHF5633) AND SECRETORY PHOSPHOLIPASE A2 SYSTEM

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Background: Secretory phospholipase A2 is the enzyme responsible for the hydrolysis of phospholipids at the sn-2 position and the first step of the inflammatory cascade. sPLA2 activity has been directly correlated to mortality and other major outcomes in ARDS (both in adults and children).(1,2) sPLA2 is also directly correlated to oxygenation, need for ventilatory support and lung compliance in preterm babies with RDS and in those with pneumonia or sepsis. (3) Inflammatory acute lung injury models have demonstrated the importance of sPLA2 in their pathogenesis and the possible interest of a strategy involving a sPLA2-resistant surfactant or surfactant protection against sPLA2.(4)

Methods: We aimed to explore the biological interactions between sPLA2 and CHF5633 synthetic surfactant and to verify that CHF5633 is at least as effective as poractant-alfa in sPLA2 inhibition. Jurkat cells were differentiated in macrophage-like cells and stimulated with azacitidine, INF-gamma and LPS. sPLA2-IIA (lung subtype of the enzyme) mRNA expression and protein concentration were measured with RQ-PCR and ELISA, respectively. Enzyme activity was assayed as previously published.(5) CHF5633 and poractant-alfa inhibition of sPLA2-IIA was tested at 0-75-150-300-1500 µg/ml for 24h. Single phospholipids, DOPG and POPG (poractant-alfa and CHF5633 components, respectively) and DPPC at 20, 20 and 320 µg/ml, respectively, were also tested. TNFalpha, IL-1Beta, GM-CSF, IL-6, and IL-8 were also assayed.

Results: Both poractant-alfa and CHF5633 significantly reduced sPLA2-IIA content in a dose-dependent manner in cultured Jurkat cells (Figure 1). CHF5633 and poractant-alfa did not significantly affect any cytokine amount at any dose. POPG seems slightly weaker than DOPG in inhibiting the TNFalpha-induced expression of sPLA2-IIA. In fact, POPG (at 20 µg/ml) significantly reduced TNF-alfa expression (DPPC as control 1.6 ± 0.1 vs. POPG 0.5 ± 0.2, rel. exp.; $p = 0.03$) but with no visible effect on sPLA2-IIA at gene and enzyme-amount levels. No phospholipid significantly affected any cytokine amount.

Conclusions: Both poractant-alfa and CHF5633 reduced sPLA2-IIA in a dose-dependent manner. Cytokine amounts were not affected by neither surfactants. These data cannot exclude a stronger effect of surfactants in other human cells or in complex in vivo systems, through a paracrine effect.

Disclosures: N. Pelizzi and F. Salomone are Chiesi Farmaceutici employees. Chiesi Farmaceutici supplied its own products (poractant alfa and CHF5633) without limitations to the study. Apart of this, the authors declare no other conflict of interests.

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63. CLINICAL OUTCOMES OF AUTOMATED OXYGEN CONTROL IN PRETERM INFANTS: A RETROSPECTIVE COHORT STUDY

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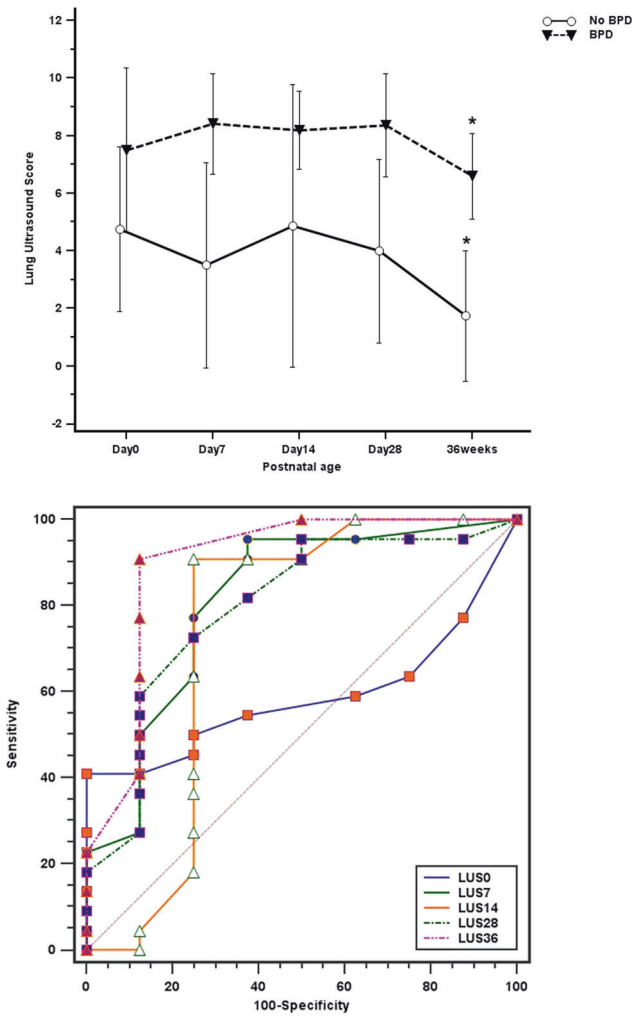

[64] Figure 1 LUS score in patients with bronchopulmonary dysplasia (BPD) and without bronchopulmonary dysplasia (No BPD), at differents end points: 1-7-14-28 day of postnatal age and at 36 weeks of GA

Background: Adhering to the therapeutic range for supplemental oxygen in preterm infants is a difficult but important task to prevent damage associated with hypoxaemia and hyperoxaemia. Several trials demonstrated that time spent within target range increases when automated oxygen control (AOC) is used, however none of these trials assessed clinically relevant outcomes. In mid-2015 AOC was implemented as standard of care in the NICU of Leiden University Medical Center. This study aimed to compare clinical outcomes of preterm infants born before and after implementation of AOC.

Methods: Using a retrospective cohort design, preterm infants born under 30 weeks of gestation were compared using two cohorts: after implementation of AOC as standard of care in mid-2015 (August 2015–December 2018) and prior to implementation (May 2012–August 2015). Patient demographics (gestational age, sex etc.), mortality, occurrence and treatment of retinopathy of prematurity (using ETROP criteria), bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC), intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL), duration of NICU stay and number of ventilation days were scored for all preterm infants. Effect estimates were adjusted for confounders.

Results: In total, 612 preterm infants were included (306 pre-cohort vs 306 in the post-implementation cohort) with a median (IQR) gestational age of 28¬+1 (26 + 4 – 29). There were no statistically significant differences between cohorts regarding gestational age, sex, parity, antenatal corticosteroid administration, birth weight, 5-min Apgar score and mode of delivery. The proportion of preterm infants that died within 1 month of corrected term age or developed ROP, BPD, NEC, IVH or PVL did not differ between cohorts (pre: 163/306 vs post: 160/306, p = NS; Table 1). Duration of stay on the NICU was slightly higher in the post-implementation group (pre: 32.9 SD 26.1 vs post: 35.4 SD 27) but not significantly different. A decrease in ventilation days from 6.4 ± 10.1 in the pre- group to 4.7 ± 8.3 days in the post-implementation group was not statistically significant after multivariate analysis.

Conclusions: Implementation of AOC did not lead to a decrease or increase in short term morbidity or mortality in very preterm infants.

Keywords:

Disclosures: None declared

64. SEMI-QUANTITATIVE LUNG ULTRASOUND EVALUATION OF DEVELOPING BPD IN EXTREMELY PRETERM NEONATES: PRELIMINARY RESULTS OF A MULTICENTER PROSPECTIVE COHORT STUDY

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Background: Lung ultrasound (LUS) is a non-invasive, radiation-free, point-of-care technique used to diagnose acute neonatal respiratory disorders, and to guide respiratory care using semi-quantitative LUS aeration scores. LUS findings of bronchopulmonary dysplasia (BPD) have not yet been formally characterized, and the role of LUS in developing BPD remains to be defined. The objective was to describe semi-quantitative LUS findings in extremely preterm infants with developing BPD and investigate the reliability of a LUS score to predict BPD.

Methods: Preterm neonates (30 weeks' gestation or less) were eligible and underwent serial LUS examination (d0, d7, d14, d28 and at 36w of postconceptional age): LUS score was calculated as previously described. Blood gases were measured by arterialized capillary samples, or adequately calibrated transcutaneous devices, within 1h from LUS. Basic clinical data were also registered. BPD was diagnosed according to NICHD criteria at 36 weeks post-gestational age.

Results: We enrolled 38 neonates (GA 26.9 (1.9);BW 904 (291);5′ Apgar 7 (2.8);CRIB2 11.4 (3.9) Males 17(44.7%), of whom 27(71%) were diagnosed with BPD. LUS score correlates with oxygenation index at any time point (min p = 0.35) and remains stable over time (p = 0.196 RM-ANOVA within patient analysis). LUS values are significantly different betweenpatients who develop BPD and those who don't (RM-ANOVA between patients' analysis p = 0.002; post-hoc p < 0.0001 at 36 weeks' post-conception; Fig. 1). LUS calculated in the first day of life is not predictive of BPD (AUC: 0.58; p = 0.467), but LUS calculated at 1 week of life can reliably predict BPD (AUC: 0.813 (0.63–0.93); p = 0.01; best cut-off: 5, sensitivity 90%; specificity 63%; Fig. 2).

Conclusions: Conclusions. LUS findings described by a semi-quantitative score do not change over time but the LUS score is significantly higher in babies with BPD as compared to those who do not developBPD. LUS at 7d of life may reliably predict the diagnosis of BPD at 36 weeks post-conceptional age.

Keywords: lung ultrasound, BPD, preterm

Disclosures: None declared

Figure 2. ROC curves for BPD prediction. ROC curve plots sensibility and 1-specificity for LUS score at 1 (LUS0)-7(LUS 7)-14 (LUS 14)-28 (LUS 28) days of life and 36 weeks of gestational age (LUS 36).

65. DOES THE USE OF DEFERRED CONSENT AFFECT RECRUITMENT, PARTICIPANT CHARACTERISTICS, AND OUTCOMES WITHIN A NEONATAL RESUSCITATION TRIAL?

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Background: Neonatal trials that rely on antenatal consent risk selection bias by excluding those in whom it was not possible to obtain antenatal consent. Waiver of prospective consent, followed by deferred (retrospective) consent, is controversial in neonatal trials, but has been found to increase the proportion of eligible infants recruited, and to enrol infants with different risk factors from those recruited using prospective, antenatal consent. We evaluated the effects of the addition of deferred consent in a large delivery room randomised trial comparing two resuscitation techniques on the proportion of infants recruited, their baseline characteristics, and the outcomes between groups.

Methods: A secondary analysis of the 426 infants born at 23–26 weeks' gestation who were enrolled in the Sustained Aeration of Infant Lungs (SAIL) Trial. SAIL compared the use of sustained inflations at birth, with standard resuscitation. In SAIL,

6/21 recruiting centres used deferred consent (DEF) in addition to (n-4), or in place of (n = 2) prospective antenatal consent (PRO). We compared infant data from centres where DEF was available, versus those where it was not. Using Chi squared, Fisher's exact, or Mann-Whitney U-tests as appropriate, we compared proportions of eligible infants recruited, baseline characteristics, and SAIL outcomes (primary outcome of death or bronchopulmonary dysplasia (BPD) at 36 weeks, these two individual components, and secondary outcomes prior to hospital discharge).

Results: Fifteen centres used PRO consent only: 197 of 473 eligible infants were randomised; 42%. Six centres used/included DEF consent; 286 of 315 were eligible and randomised (84%), 229 of 315 consented (73%); absolute difference: 31%, 95% confidence interval (CI): 24.4%, 37.7%; $p < 0.001$. In centres using DEF, mothers were older, more likely to be Caucasian, less likely to have chorioamnionitis, less likely to have had a full course of antenatal corticosteroids (73 vs. 84%, $p = 0.005$), and more likely to have a vaginal birth (45 vs. 27%, $p < 0.001$). Infants enrolled at centres using DEF were more likely to be male, were heavier, less likely to be growth restricted, and less likely to be intubated at birth. There was an 8% difference in death/BPD between groups; DEF 65% vs. PRO 57%; risk difference 7.7, CI −1.6%, 17.0%; $p = 0.10$. Primary components and secondary outcomes are shown in the table.

Conclusions: A higher proportion of eligible infants was recruited when deferred consent was available. Baseline differences included less exposure to antenatal corticosteroids; outcome differences included higher risk of NEC and any IVH, and less risk of any ROP, in the deferred consent group. These data suggest that a study sample recruited using only antenatal consent may select a population not representative of those to whom the results will be applied.

Keywords: randomised trial, consent, outcome

Disclosures: none declared

66. PERINATAL HYPOXIC PRECONDITIONING INDUCES SURFACTANT SYNTHESIS AND PREVENTS LUNG DAMAGE AFTER AN HYPEROXIC INSULT IN A MICE MODEL OF THE FNT

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Background: PaO2 increases significantly with the initiation of air breathing immediately after birth causing physiological OS. Preterm newborns have immature antioxidant defenses and often need oxygen supplementation to achieve postnatal stabilization. The use of 100% O2 for resuscitation increases OS and specific morbidities. Hyperoxia causes structural and functional alterations of surfactant and reduces pneumocytes II ability to synthesize it while it causes OS in lung tissue. We hypothesize that hypoxic preconditioning during fetal-to-neonatal transition would preserve existing lung surfactant, pneumocytes II ability to synthesize surfactant and attenuate OS in lung submitted to hyperoxic insult.

Methods: Pregnant mice randomly delivered in an FiO2 = 0.14 (HYP) or 0.21 (NORM) and their offspring were kept for 8H in the assigned FiO2. FiO2 was increased then to 1.0 for 1H and thereafter switched to 0.21 in both groups. Offspring were sacrificed at P1 or P7. Controls were kept all the time in 0.21. We analyzed transsulfuration pathway metabolites, biomarkers of OS damage to proteins and to lipid components using validated HPLC-MS/MS approach. In addition, we determined peroxides and analyzed different signaling pathways such as synthesis surfactant pulmonary or HIF1a targets by qPCR and WB. Lung morphology was studied using violet cresyl and apoptosis with caspase-3 immunostaining. Finally, using EM we focused on pulmonary surfactant and structural disorganization of lung cell membranes.

Results: In the HYP group, reducing metabolites such as GSH, cystathionine and Cys were significantly increased as compared to the NORM group due to increased transsulfuration pathway metabolic activity secondary to overexpression of CBS. Moreover, the NORM group exhibited increased levels of biomarkers of oxidative damage to proteins, lipid peroxidation and peroxides as compared to the HYP. WB of SP-B, and pSTAT3 were reduced in the NORM group. Analysis of the pSTAT3 revealed high levels of IL-6 gene expression in the HYP group and decreased levels of sosc3 and HSP2 in the HYP group as compared to NORM and control groups at. Lung histology revealed increased caspase-3 positive cells in club cells in the NORM group. Finally, EM at P1 and P7 in type II pneumocytes showed in the NORM group a clear reduction of surfactant content compared with the control group while being preserved in the HYP group

Conclusions: Keeping mice offspring in a hypoxic atmosphere after birth favors the maintenance of a lung cell reducing environment that confers protection from a hyperoxic insult. Hence, the ability to store and synthesize surfactant is preserved and levels of biomarkers of oxidative stress are reduced. These results underscore the relevance of a strict control of oxygen supplementation in preterm infants after birth and may have translational applicability.

Keywords: lung, oxidative stress, surfactant

Disclosures: None declared

67. LAMELLAR BODY COUNTS ON GASTRIC ASPIRATE AND RESPIRATORY MECHANICS BY THE FORCED OSCILLATION TECHNIQUE FOR PREDICTING SURFACTANT NEED IN PRETERM INFANTS

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Background: Lamellar Body Counts (LBC) on gastric aspirate (GA) has been suggested as a possible method for the early identification of preterm infants requiring pulmonary surfactant (Verder 2013). Early assessment of respiratory system mechanical properties by the Forced Oscillation Technique (FOT) may also provide useful information for guiding surfactant therapy (Veneroni 2019).

to evaluate the role of LBC on GA and non-invasive lung mechanics assessed by FOT after birth in non-intubated preterm infants for an early prediction of surfactant need.

Methods: Inclusion criteria: preterm infants between 28 + 0 and 34 + 6 week gestation. Exclusion criteria: intubation for cardiopulmonary resuscitation, major congenital malformations, perinatal asphyxia. The LBC on GA was determined at birth as described in da Silva Daniel (2010). Respiratory system reactance (Xrs) was assessed by FOT within 2h of life: a small amplitude oscillatory pressure at 10 Hz was superimposed on CPAP at 5cmH2O by a modified ventilator (FabianHFO, Acutronic) and a face-mask, held in place by the attending physician. Xrs was calculated off-line from flow and pressure tracing over five artefact-free breaths. FiO2 was titrated to target 89–94% and surfactant was given as in Sweet (2016).

Results: Among the 53 infants enrolled to date, both LBC and Xrs were significantly lower in patients receiving surfactant (SURF, n 15) than those not receiving surfactant (no-SURF, n 38): LBC (median [IQR]) 18.0 [6.7;55.9] vs 81.0 [36.0 ;138.0] * 103/µL; Xrs (median [IQR] −25.6 [−41.3;−15.0] vs −52.0 [−57.7;−36.3] cmH2O*s/l (Mann-Whitney Rank Sum Test, $p < 0.05$).

Due to the high variability of the no-SURF, we divided it into two subgroups: spontaneously breathing patients not requiring respiratory support (SB) and patients requiring nasal CPAP but not surfactant (CPAP). Figure 1 represents Xrs (A) and LBC (B) (median[IQR]) among the 3 groups: Xrs was significantly lower in SURF than in SB and CPAP (Kruskal-Wallis 1-way ANOVA, $p < 0.05$), whereas LBC did not show significant differences among the 3 groups ($p > 0.05$).

Conclusions: Both LBC on GA and early assessment of lung mechanics by FOT were feasible and suitable for the clinical setting. Preliminary data suggest FOT showed a better predicting value than LBC for targeting surfactant therapy. This might be related to FOT's capability of measuring the overall mechanical properties of the lung rather than considering a single sampling of GA.

Keywords: surfactant, lung mechanics, CPAP, lamellar body counts

Disclosures: none declared

68. PULMONARY OUTCOME OF VLBW FOLLOWING PPROM—OBSERVATIONAL DATA OF COMBINED SURFACTANT-BUDESONIDE TREATMENT AND THE GNN

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Background: Topical lung-steroid treatment e.g. by surfactant/budesonide has become a therapeutic option for prevention of bronchopulmonary dysplasia (BPD). Infants with history of preterm premature rupture of the membranes (PPROM) are at high risk for BPD due to additional prenatal risk factors like anhydramnios, ascending materno-fetal infections, respiratory distress and need for increased respiratory support. Since 2008, the German neonatal network (GNN) is prospectively collecting clinical data of ~15.000 very low birth weight infants (<36 weeks of gestation and <1500 g birth weight).

Methods: In the GNN database, the groups with and without PPROM >5 days were compared. The clinical characteristics, ventilation support (duration of invasive and total ventilation), pneumothorax, duration of hospital stay and outcome parameters with respect to BPD at 36 weeks of gestational age (GA) and IVH were described (mean, SD or %) and statistically analyzed by Chi-square test. Subsequently in the subgroup developing BPD or death, a logistic regression analysis was conducted determining the effect of PPROM, GA or antenatal steroids.

Retrospectively, the clinical course of all premature infants born in the period 2016–2018 with PPROM at two level 1 neonatal intensive care units, treated on day one of life due to clinical severe respiratory distress with surfactant/budesonide was summarized.

Results: In Table 1 clinical characteristics of the surfactant/budesonide cohort with PPROM > 3 days ($n = 20$) is shown in comparison to the GNN groups with and without PPROM > 5 d. Ventilation strategies included continuous positive airway pressure (CPAP), high flow nasal cannula, conventional mechanical ventilation, high frequency oscillation (HFO), CPAP-HFO and nasal intermitted positive pressure ventilation (nIPPV). All analyzed parameters in GNN gave significant differences. Logistic regression analysis gave a risk reduction for development of BPD/death of 0.61 (95% CI: 0.59–0.63) for each completed gestational week, whereas PPROM increased the risk by 1.6 (95% CI: 1.3–2.1) and antenatal steroids showed no effects. The surfactant/budesonide cohort consisted of smaller, more premature infants with longer duration of PPROM and more invasive ventilation support.

Conclusions: Premature birth following PPROM > 5 days increases risk for mortality and long term respiratory morbidity. New treatment strategies like early surfactant/budesonide, CPAP-HFO- or nIPPV-ventilation are in use. Surfactant/budesonide was used in premature infants with high morbidity. It is unclear whether this treatment strategy improves outcome. Thus, efforts for randomized controlled clinical trials are needed.

	surfactant/budesonide cohort					GNN + PPROM>5d			GNN w/o PPROM>5d			
	M/ %	SD	N	Min	Max	M/ %	SD	N	M/ %	SD	N	
GA (wks)	26,5	3,5	19	22,3	32,9	27,8	2,7	482	28,8	2,8	9024	*
PPROM (wks)	4,2	2,8	19	0,5	10	2,4	2,1	74	0,9	1,9	350	*
PPROM GA (wks)	22,3	4	19	16,3	30,5	-	-	-	-	-	-	-
Multiple birth (%)	32	-	6	-	-	26,1	-	482	36,6	-	9030	*
Birth weight (g)	951	541	19	280	2450	1007	309	482	1066	307	9031	*
Antenatal steroids (%)	95	-	18	-	-	96,7	-		90,2	-		*
HFO (%)	53	-	10	-	-	31,9	-		13,7	-		*
Ventilation (d)	78	45	15	3	155	46	40	465	33	33	8938	*
Invasive ventilation (d)	6,7	6,4	15	0	18	10	18	476	6	14	8938	*
Need suppl. O_2 (d)	52	99	19	0	450	44	46	406	30	38	6815	*
BPD@36 wks (%)	16	-	3	-	-	29,2	-		16,3			*
Death (%)	16	-	3	-	-	5,8	-		3,2			*
BPD or death (%)	32	-	6	-	-	33,9	-		18,9			*
Pneumothorax (%)	26	-	5	-	-	8,2	-		4,6			*
IVH (°I-°II) (%)	26	-	5	-	-	13,7	-		11,7			*
IVH (°III-°IV) (%)	5	-	1	-	-	8,7	-		5,6			
Discharge (GA)	40,9	3,4	15	33,7	46	38,7	5,9	481	38,2	5,9	9028	*

[ID759] Table 1 On the left side clinical characteristics of the cohort treated with surfactant/budesonide is displayed. On the right side the german neonatal netwotk (GNN) groups with preterm premature rupture of the membranes (PPROM) longer than 5 days (GNN+PPROM>5d) or without this property (GNN w/o PPROM>5d). Either mean (M), SD and the number or the ratio (%) are shown. The GNN data were statistically compared using the Chi-square test. *: $p < 0.05$

Keywords: mixtures surfactant budesonide, preterm premature rupture of the membranes; pulmonary outcome; duration of ventilation

Disclosures: GS, WG and EH received speakers honoraria and research grants by Chiesi.

GA: gestational age, HFO: high frequency oscillation; Ventilation = invasive and non-invasive ventilation; IVH: intraventricular haemorrhage.

ORAL PRESENTATIONS—NEONATAL PULMONOLOGY, NEONATAL RESPIRATORY SUPPORT, RESUSCITATION

69. GESTATIONAL HYPERTENSIVE DISORDERS AND INTRAUTERINE GROWTH RESTRICTION AS RISK FACTORS FOR BRONCHOPULMONARY DYSPLASIA: A META-ANALYSIS AND META-REGRESSION

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Background: Gestational hypertensive disorders (GHD), including gestational hypertension and preeclampsia, are major risk factors for preterm birth and intrauterine growth restriction (IUGR). The adverse intrauterine environment associated with GHD and/or IUGR is considered to play a pathogenic role in some complications of very preterm birth, including bronchopulmonary dysplasia (BPD). We aimed to conduct a systematic review of studies reporting on GHD and IUGR/small for gestational age (SGA) as risk factors for BPD.

Methods: PubMed/MEDLINE and EMBASE databases were searched. A random-effect model was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Sources of heterogeneity were determined by subgroup and meta-regression analyses. BPD was defined as supplemental oxygen requirement on postnatal day 28 (BPD28), or at the postmenstrual age of 36 weeks (BPD36). K = number of studies.

Results: We found 148 studies meeting the inclusion criteria. Meta-analysis could not detect an association between GHD and BPD28 (k = 24, OR 1.04, CI 0.79–1.37) or BPD36 (k = 48, OR 1.04, CI 0.90–1.20). Gestational age (GA) was significantly higher in the GHD group and meta-regression revealed that the higher GA in this group was significantly associated with a lower odds of BPD. Analysis restricted to the studies without significant differences in GA, revealed a positive association between GHD and BPD36 (OR 1.51, CI 1.24–1.83). Regarding IUGR/SGA, meta-analysis showed a significant association with BPD36 (k = 73, OR 1.44, CI 1.24–1.68) but not BPD28 (k = 16, OR 1.06, CI 0.70–1.70). GA was significantly higher in the IUGR/SGA group, and meta-regression showed that the higher GA in this group was significantly associated with a lower risk of BPD.

Conclusions: Our data suggest that IUGR/SGA and GHD are risk factors for developing BPD but the association is significantly confounded by the lower GA of the "control" group.

Keywords: Bronchopulmonary Dysplasia; Gestational Hypertensive Disorders; Intrauterine Growth Retardation; Small for Gestational Age

Disclosures: None declared

70. PREVENTIVE EFFECTS OF MATERNAL CDP-CHOLINE, ADMINISTERED EITHER ALONE OR IN COMBINATION WITH A STEROID, ON LUNG INJURY IN A NEONATAL RAT MODEL OF HYPEROXIA

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Background: Bronchopulmonary dysplasia (BPD) is the major cause of chronic lung disease in preterm infants. As current management approaches have little efficacy due to multifactorial pathogenesis, novel preventive and therapeutic options are required. CDP-choline, an endogenous intermediate in phosphatidylcholine (PC) synthesis was shown to reduce hyperoxia-induced severe lung damage when injected to newborn rats. However, the effect of maternal CDP-choline on neonatal lung structure was not evaluated yet. The aim of this study was to evaluate the effect of maternal administration of CDP-choline, alone or in combination with betamethasone, for prevention of hyperoxic lung injury in newborn rats.

Methods: Pregnant Spraque-Dawley rats were grouped to receive either single or combined therapies of CDP-choline and/or betamethasone. Pups born to these dams were subjected to hyperoxia for 10 days after the first day of life. After decapitation at 11 days of life; lung phospholipid levels, apoptotic cell death and alveolarization were evaluated. Radial alveolar count was used for determination of alveolarization. Both total phospholipd and PC levels were established in lung tissues. Western blot analysis was performed for evaluation of apoptotic cell death.

Results: Maternal CDP-choline administration significantly enhanced total phospholipids and PC levels, improved alveolarization, and reduced apoptosis in rat pups subjected to hyperoxic lung injury. Antenatal betamethasone significantly increased lung phospholipid levels, but had no significant effect on apoptosis and alveolarization. The lung phospholipid levels were significantly higher and apoptosis was potently reduced in pups whose dams received the combination of betamethasone and CDP-choline, compared to single administration of both agents.

Conclusions: This is the first study that shows the preventive effect of maternal CDP-choline treatment on hyperoxic lung injury in newborn rats. Our findings show that the combination of betamethasone and CDP-choline provides greater benefit in reducing neonatal hyperoxic lung injury by both increasing phospholipid levels and improving alveolarization and decreasing apoptosis. These data suggest the clinical utility of this combination for prevention of BPD.

Keywords: antenatal steroid; antenatal CDP-choline; combination therapy; hyperoxic lung injury

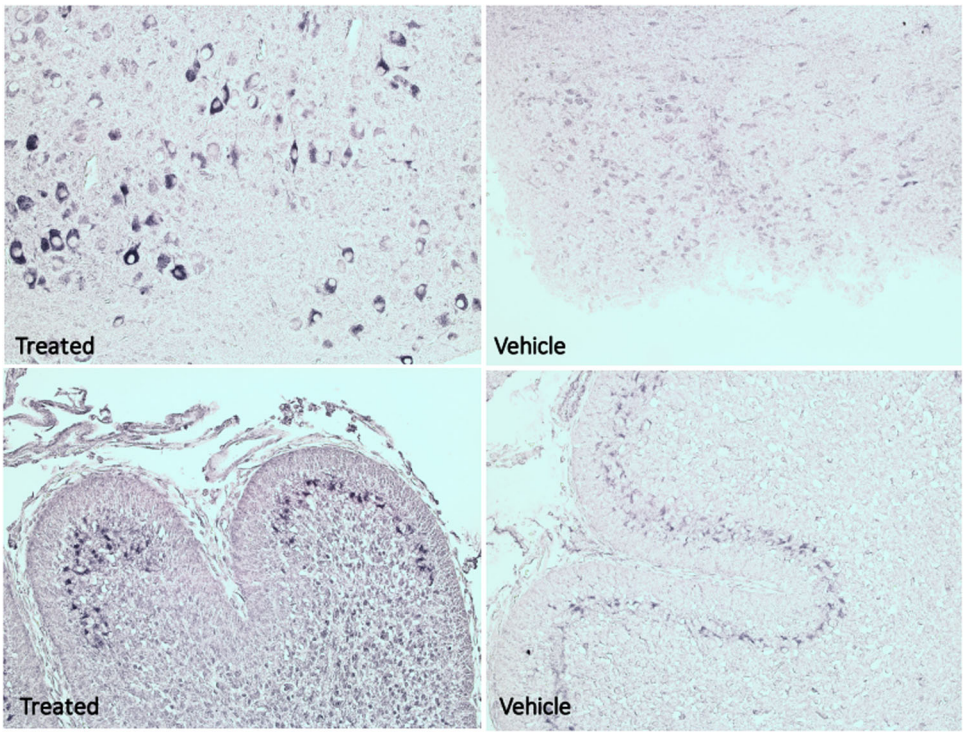
Disclosures: None declared

ORAL PRESENTATIONS—NEONATAL PULMONOLOGY, NEONATAL RESPIRATORY SUPPORT, RESUSCITATION

	30% O_2	100% O_2	*p*-value
	n = 24	n = 20	
Average tidal volumes in first 5 min (mL/kg)[a]	3.8 ± 3.7	4.8 ± 3.8	0.006
Average MIFR in first 5 min (mL/kg/s)[b]	7.8 (3.3 – 13.3)	12.7 (5.7 – 18.0)	0.014
Respiratory rate in first 5 min (breaths/min)[b]	26 (11 – 36)	33 (14 – 52)	0.099
Time of mask ventilation in the first 10 min (s)[b]	108.3 (46.4 – 205.1)	23.6 (0.0 – 122.2)	0.021
Duration of hypoxia in first 10 min (sec)[b]	158 (116 – 184)	73 (0 – 189)	0.018
Duration of hyperoxia in first 10 min (sec)[b]	79 (15 – 152)	99 (24 – 215)	0.394

Data are presented as mean ± SD (ª) and median (IQR) for non-parametric data (ª). MIFR: Mean inspiratory flow rate.

[71] Table 1 Results of breathing effort and oxygenation



[71] Table 1 Results of breathing effort and oxygenation

71. THE EFFECT OF INITIAL HIGH VERSUS LOW FIO2 ON BREATHING EFFORT IN PRETERM INFANTS AT BIRTH: A RANDOMIZED CONTROLLED TRIAL

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Background: Non-invasive ventilation in preterm infants at birth is hampered by closure of the glottis between breaths when breathing is intermittent. Infants are currently stabilized with initial low FiO2 (0.21–0.3) which increases the risk of hypoxia and suppression of breathing in the first minutes after birth. We hypothesized that stabilization of preterm infants at birth with an initial high FiO2 (1.0), followed by titration, would improve breathing effort when compared to an initial low FiO2.

Methods: In a bi-centre randomized controlled trial, infants < 30 weeks GA were stabilized at birth with an initial FiO2 of 0.3 or 1.0, after which oxygen was titrated using the reference ranges described by Dawson et al.(2010). Primary outcome was minute volume of spontaneous breathing. We also assessed tidal volumes,

mean inspiratory flow rate (MIFR) and respiratory rate with a respiratory function monitor. Pulse oximetry was used to measure heart rate and SpO2 values. Hypoxia was defined as SpO2 95%. Differences in breathing effort and oxygenation parameters were tested with a Student's t-test or Mann-Whitney u-test, depending on the distribution. The interaction of breathing effort parameters with time was analysed with a linear mixed model.

Results: 52 infants were randomized (26 in 100% O2-group, 26 in 30% O2-group) and recordings were obtained in 44 infants (20 infants in 100% O2-group, 24 infants in 30% O2-group). Minute volumes (mL/kg) were significantly higher in the 100% O2-group (146.34 ± 112.68 mL/kg/min) compared to 30% O2-group (74.43 ± 52.19 mL/kg/min), $p = 0.014$. Average tidal volumes and MIFR in the first 5 min after birth were significantly higher in the 100% group, while the duration of mask ventilation given was significantly shorter (Table 1). Oxygenation was significantly higher in infants in the 100% O2-group (85 (64–93)%) compared to the 30% O2-group (58 (46–67)%) ($p < 0.001$) in the first 5 min after birth. The duration of hypoxia was significantly shorter in the 100% O2-group, while the duration of hyperoxia was not different between groups (Table 1).

Conclusions: Initiating stabilization of preterm infants at birth with 100% oxygen led to a higher breathing effort, improved oxygenation, and a shorter duration of mask ventilation as compared to 30% oxygen, without increasing the risk for hyperoxia.

Keywords: Breathing effort, oxygen, resuscitation, preterm infant

Disclosures: None declared.

72. PREMATURITY AFFECTS LUNG DEVELOPMENT IN NEONATAL RABBITS

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Background: Improved survival and changing practices in neonatology have altered the phenotype of bronchopulmonary dysplasia (BPD) from a more fibrotic disease to a developmental delay. Nevertheless post-prematurity respiratory disease (PRD) remains an important consequence of preterm birth, although the need for supplemental oxygen was not a good predictor for it. The constant factor in the pathophysiology of BPD and PRD is prematurity, however most of the preclinical research in this field focusses on the effect of hyperoxia or mechanical ventilation, mainly in term rodents. In this study we wanted to evaluate the effect of prematurity alone on lung function and structure in rabbits.

Methods: Rabbit dams were randomized to either a C-section on day 31 (term, alveolar stage of lung development) or day 28 (preterm, saccular stage). Fetal lungs were harvested immediately after birth for morphometry and qPCR in a subset of animals. All others received incubator care (T 32 °C, 50% humidity and 21% FiO2), with gavage feeding twice daily. In vivo microCT and X-ray dark field imaging were performed on day 0, 3, 5 and 7 for preterm or day 0, 2 and 4 for term pups. Lung function was measured and lungs were harvested for morphometry on day 7 for preterm pups and on day 4 for term pups (same corrected age).

Results: At birth preterm rabbit lungs have increased alveolar septal wall thickness ($p < 0.0001$) and a lower total gas exchange surface ($p = 0.04$), in comparison with term rabbits at birth. Preterm fetal lungs exhibit lower mRNA-expression of surfactant protein B and C ($p = 0.005$ and $p = 0.03$). MicroCT reveals a significantly higher proportion of non-aereated lung volume and a higher mean voxel density in the preterm pups in comparison to term pups at all time points, reflecting delayed alveolar recruitment and lung fluid clearance. This is confirmed on dark field images. At the corrected age of 4 days gas exchange surface is smaller in survivors of preterm birth ($p = 0.02$), mainly due to a difference in lung volume ($p = 0.004$). Additionally pups born prematurely had higher values for tissue damping ($p = 0.008$) and elastance ($p = 0.02$) at forced oscillation.

Conclusions: Preterm rabbits exhibit structural and functional immaturity at birth, which, even in the absence of hyperoxia, lead to persistent pulmonary abnormalities. This shows that preterm birth affects lung development, and advocates for a paradigm shift in preclinical BPD research towards disease models studying prematurity. Further studies should focus on identifying the developmental pathways that are disturbed by preterm birth.

Keywords: bronchopulmonary dysplasia, prematurity

Disclosures: None declared

ORAL PRESENTATIONS—NEUROLOGY

73. MODULATION OF MYELOID CELL POLARIZATION BY THERAPEUTIC HYPOTHERMIA IN NEONATAL HYPOXIC-ISCHAEMIC BRAIN INJURY

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Background: Hypoxic-ischaemic encephalopathy (HIE), is one of the leading causes of death and disability in children. Therapeutic hypothermia (HT) is the only recommended therapy, which is however limited. A better knowledge of hypothermia's effector mechanisms is needed to guide the rational design of combination treatments. Inflammation is a major hallmark of HIE pathophysiology involving myeloid cells which reveal a high degree of phenotypic plasticity either participating in progression or resolution of injury-induced inflammation. The purpose of this study was to investigate the impact of HT on the temporal and spatial dynamics of microglia/macrophage cell polarization after neonatal HIE.

Methods: Postnatal day 9 (P9) C57BL/6 mice were exposed to hypoxia-ischaemia (HI) through occlusion of the right common carotid artery followed by one hour hypoxia (10% oxygen). Immediately after HI, animals were cooled for 4 h (HT, Trectal = 32 °C). Controls (normothermia, NT) were kept on a warming mat to maintain physiological body core temperatures (Trectal = 35 °C). Brain injury, neuronal cell loss, apoptosis and microglia activation were assessed by immunohistochemistry 1, 3 and 7 days post HI. To analyse a broad set of typical genes associated with both classical (M1) and alternative polarization (M2) phenotypes CD11b+ microglia/macrophages cells were sorted by magnetic activated cell sorting followed by mRNA expression analysis via real time PCR 1, 3 and 7 days post HI.

Results: Acute HT significantly reduced HI-induced brain injury and neuronal loss at 7 days post HI whereas only mild non-significant protection from HI-induced apoptosis was observed at 1 and 3 days post injury. Microglia activation revealed by Iba-1 immunoreactivity was not modulated at 1 day post HI. However, a significant HI-induced upregulation of Iba-1 was observed at 3 days which declined at 7 days. HT did not modulate Iba-1 immunoreactivity at any time point. Gene expression analysis in ex vivo isolated CD11b+ cells demonstrated a strong and

significant upregulation of the majority of M1 but also M2 marker genes 1 day after HI, which was significantly reduced by HT. These acute changes following HI were diminished for most of the genes at 3 and 7 days post HI, resulting in no significant differences between HT-treated and normothermia-treated control animals.

Conclusions: These data demonstrate that HT inhibits secondary neuronal degeneration, which is preceded by acute suppression of HI-induced upregulation of pro- and anti-inflammatory genes representing an important effector mechanism of HT, though the early HI-induced mixed gene response in myeloid cells indicates that the traditional M1/M2 classification scheme oversimplifies the concept of distinct inflammatory cell phenotypes in vivo.

Keywords: neonatal hypoxic-ischaemic brain injury, hypothermia, myeloid cell polarisation

Disclosures: None declared.

NEUROLOGY

74. MONITORING SLEEP THROUGH EEG IN PREMATURE INFANTS: THE 'SLEEPI' STUDY

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Background: Sleep is essential for neurosensory cortical development, physical growth and brain formation in the preterm infant. Deprivation of sleep has been associated with impaired development and loss of brain plasticity. In the NICU emphasis is on recording of cardiorespiratory vitals with less placed on monitoring neurodevelopment. Electroencephalogram (EEG) makes a valuable contribution to assessment of neurologic status when infant is sleeping. The aim of this study is to assess the number of overnight sleep wake cycles (SWC) in mid to late preterm infants (MLP) and to quantify the number of forced versus spontaneous awakenings during active and quiet sleep and the reason for same.

Methods: This is a single centre observational study (pilot) carried out in southern Ireland. Participants were healthy/clinically stable MLP infants (32–36 + 6 weeks gestation), admitted to the neonatal unit at birth. An overnight video EEG was carried out before 36 + 6 week's gestation and prior to discharge. Lifelines EEG monitors were used for all recordings. A modified neonatal version of the international 10/20 system was used, which provided recordings from 11 electrodes: F4, F3, C4, Cz, C3, T4, T3, O2, O1, reference and ground. ECG and respiratory activity were also monitored. A standardised 12 h time period was analysed and annotated for all recordings commencing with the onset of active sleep. Standard of care was not altered whilst recordings were in progress.

Results: The mean gestational age of MLP at birth was 34.48 ± 1.29 weeks and weight recorded at 2.12 ± 0.37(Kg). Whilst the majority of infants were nursed in a cot during monitoring (60%), the high numbers nursed in incubators were in part attributed to the fact that 20% (6) underwent phototherapy during monitoring. A median (IQR) of 4 (4–4) feeds were given to each infant during EEG. 46.7% of infants fed orally, 10% via nasogastric tube and 43.3% a mixture of both. Throughout recording only 20% of infants woke/ left to wake spontaneously for all feeds.

A median (IQR) of 6(5–7) SWCs were identified for each infant on EEG. In total, 51 forced awakenings were seen in the 30 recordings, with a median (IQR) of 2(1–3) per infant - the greater majority of which occurred during active sleep (70%). Feeding was the main reason for forced awakenings (66.7%) with parental handling also provoking awakenings.

Conclusions: This study provides baseline information regarding sleep and feeding in pre discharge MLP infants. Further study is required to determine the most favourable strategy for feeding in terms of sleep optimisation and developmental impact, and consider whether forced or spontaneous awakening for feeds pre discharge serve the best interest of the MLP infant. Routine EEG monitoring for MLP's is a valuable adjunct to a pre discharge clinical assessment.

Keywords: mid to late premature, sleep-wake cycling, EEG/aEEG, active sleep, quiet sleep

Disclosures: None Declared

75. PRENATAL STRESS HAS STRAIN-SPECIFIC EFFECT ON SERUM CORTICOSTERONE LEVELS

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Background: Prenatal exposure to stress is associated with an increased risk for neurodevelopmental disorders such as anxiety, schizophrenia, autism spectrum disorder, and attention deficit hyperactivity disorder.

Results from human and animal research show that early-life exposure to stress affects the regulation of the neuroendocrine response to stress and thus represents an important risk factor for a broad range of pathologies. Although most research is performed on male subjects, a sexually dimorphic response to the programming of the hypothalamic-pituitary-adrenal (HPA) axis has been found in animals. The mechanisms remain to be elucidated, but the interaction between HPA and hypothalamic-pituitary-gonadal (HPG) axes seems to be involved. Similarly, few studies report differences in the response to stress in different strains of mice. Glucocorticoids are tightly regulated by the HPA system and play a pivotal role in stress response. Corticosterone, the main stress steroid produced in non-human animals, is a major indicator of stress. The aim of this study was to determine the effect of prenatal stress on strain and gender in a mouse model of prenatal stress.

Methods: The effect of prenatal stress was examined in a mouse model using CD1 and C57Bl6 mice. Beginning on gestational day 14, pregnant dams were subjected to an 8-day schedule of variable stressors including restraint, swim stress, social stress, bedding-free cage, and alteration of light and dark cycles. A variable stress paradigm was implemented to prevent habituation. Body weights and blood from pups and mothers were obtained. Serum corticosterone levels were measured in duplicate by immunoassay (Corticosterone Enzyme Immunoassay, Arbor Assays). DNA was extracted for PCR sex determination. Behavioral testing performed at set times in young adult offspring. All procedures were approved by the Institutional Animal Care and Use Committee at Biomedical Research Institute of New Jersey.

Results: We have analyzed data for 8 litters; 4 exposed to prenatal stress and 4 controls. Pups exposed to prenatal stress had decreased weight at P1 compared to controls. In CD1 pups, prenatal stress was associated with an increased serum corticosterone on P1 (527 pg/mL v 143 pg/mL, $p < 0.001$). No such effect was seen in C57 mice (706 pg/mL v 392 pg/mL, $p = 0.29$). There was no difference in serum corticosterone levels between males and females after exposure to prenatal stress in either CD1 (609

pg/mL v 374 pg/mL, p = 0.50) or C57 mice (965 pg/mL v 1153 pg/mL, p = 0.29). When accounting for birth weight, prenatal stress increased serum corticosterone in FEMALE CD1 mice (743 pg/mL v 150 pg/mL, p = 0.0004) but not in FEMALE C57 mice (564 pg/mL v 1183 pg/mL, p = 0.099). Offspring exposed to prenatal stress showed abnormal behavioral testing consistent with depression.

Conclusions: Exposure to stress during gestation caused a reduction in the birth weight of the offspring. Behavioral test results in early adulthood in our rodent model validate our model and confirm reports that prenatal stress exposure can cause depressive-like behavior in mice.

Our findings show a strain difference in the neuroendocrine response to prenatal stress in P1 mice.

No difference was observed on corticosterone levels between males and females.

Disclosures: None declared

76. TREATMENT WITH INSULIN-LIKE GROWTH FACTOR (IGF) -1/IGF BINDING PROTEIN (BP) -3 IN PRETERM RABBIT PUPS - REGIONAL BRAIN DISTRIBUTION OF IGF-1 AND EFFECTS ON CHOROID PLEXUS ANGIOGENESIS AND EXTRACELLULAR MATRIX STRUCTURE

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Background: The preterm rabbit pup model incorporates essential physiological aspects of human preterm birth. Brain maturity at E 29 in the rabbit corresponds to gestational week 25 in the human. Following establishment of the pharmacokinetic (PK) profile of exogenous recombinant human (rh) IGF-1/IGFBP-3 we investigated the regional distribution of IGF-1 in the brain and its effects on genes involved in angiogenesis and extracellular matrix (ECM) structure in the choroid plexus (CP).

Methods: Rabbit pups were delivered by cesarean section at E29, housed in a controlled environment and fed twice daily via gastric tube with bovine colostrum. The PK of 1, 2, 4 and 8 mg/kg sc administered rhIGF-I/IGFBP-3 was evaluated. In a second study, pups were randomized to sc administered rhIGF-1/IGFBP-3, 8 mg/kg or saline, twice daily from birth up to 72 h. CP tissue was sampled and snap frozen at 4, 12, 24, 48 and 72 h after first admin. of rhIGF-1/IGFBP-3 or vehicle. Expression of genes involved in angiogenesis and ECM structure was evaluated using RT PCR arrays in CP tissue. Paraffin sections from in vivo perfusion fixed brains were processed for immunohistochemistry (IHC), using monoclonal antibodies against IGF-1 and IGFBP3.

Results: After sc admin. of rhIGF-1/IGFBP-3 complex at doses of 1, 2, 4 and 8 mg/kg, serum levels peaked between 1 and 4 h and returned to baseline levels at 48 h. A mean (SD) serum IGF-1 level of 264 (17) ng/ml was observed at 4 h after 8 mg/kg (rhIGF-1/IGFBP-3). Brain IHC demonstrated an increased IGF-1 immunoreactivity at 4 h after administration of rhIGF-1/IGFBP-3 (8 mg/kg), with a wide distribution in different brain regions including the choroid plexus in comparison to the more restricted endogenous IGF1 expressing cell populations. In pups receiving IGF-1/IGFBP-3 (8 mg/kg), expression of genes in the CP involved in vessel maturation (eg Angiopoetin-1, Thrombospondin-1) and ECM structure (eg Fibronectin, Versican, Collagens) were upregulated (3–10 fold versus time-matched controls) at 24 h after first dose of the rhIGF-1/IGFBP-3 complex.

Conclusions: Systemic admin. of rhIGF-1/IGFBP-3 at a dose counteracting the endogenous decrease was associated with an increase presence of IGF-1 protein in several brain regions. Exogenous IGF-I/IGFBP-3 caused an up-regulation of genes related to structural and functional vessel maturation. These findings indicate a possible therapeutic effect of rhIGF-1/IGFBP-3 on vascular fragility and thereby a role in prevention of preterm intraventricular hemorrhage.

Keywords: insulin-like growth factor 1, preterm, brain angiogenesis, extracellular matrix

Disclosures: DL and AH hold stock/stock options in Premalux AB, and have received consulting fees from Shire. NB and GC are employees of Shire and own stock/stock options in Shire.

ORAL PRESENTATIONS—NEUROLOGY

77. IMPAIRMENT OF DENDRITOGENESIS OF CORTICAL PYRAMIDAL NEURONS IN POSTNATAL MICE BY OXYGEN TOXICITY AND PROTECTION BY ERYTHROPOIETIN

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Background: Preterm birth is associated with a higher risk for neurological disorders, e.g. autism and others, which correlate with altered dendritogenesis. The increase of O2-levels in preterm infants caused by premature change from hypoxic fetal life in utero into room air environment can affect the developmental program of the brain. So far there is no effective pharmacological therapy available for preterm infants to prevent neurological disabilities. However, preclinical studies have demonstrated neuroprotective properties of erythropoietin (EPO). We investigated whether dendritic growth of cortical pyramidal neurons is inhibited by oxygen and whether rEPO is useful for protection.

Methods: Five-day old healthy C57BL/6-mice were divided into three groups: (A) exposure to 80% O2 for 48 h, (B) parallel to hyperoxia-exposure, administration of 3 injections 5000 I.U./kg bw rEPO s.c. respectively (at the beginning, after 24 and 48 h), (C) untreated control. To analyze dendritic morphogenesis of cortical pyramidal neurons of cingulate, motor and sensory cortex, brains were impregnated with Golgi-Cox staining at postnatal day 23 (P23) and histologically prepared to perform Sholl-analysis with ImageJ-software. For Sholl-analysis 30 concentric circles with a distance of 10 µm each were put centrally around the soma and basal and apical dendrites were counted.

Results: Hyperoxia caused a significant reduction of dendritic branching of basal dendrites of cortical pyramidal neurons in cingulate cortex within a radius of 30 and 50 µm ($p \leq 0{,}05$). A similar reduction was revealed in superficial layers of motor cortex within a radius of 30–80 µm ($p \leq 0{,}01$) at basal dendrites, of 40 µm ($p \leq 0{,}05$) at apical dendrites and in deep layers a radius of 30–110 ($p \leq 0{,}05$) at basal dendrites and of 40–80 and 110–140 µm ($p \leq 0{,}05$) at apical dendrites. The sensory cortex has shown significant reduction of dendritic branching in superficial layers within a radius of 10–90 µm ($p \leq 0{,}05$) at basal dendrites, a radius of 60 µm ($p \leq 0{,}01$) at apical dendrites and in deep layers of 10–80 µm ($p \leq 0{,}05$) at basal dendrites and of 70 µm ($p \leq 0{,}05$) at apical dendrites. Pyramidal neurons treated with rEPO have shown a selective normalization of dendritic branching in all investigated cortical areas.

Conclusions: Neonatal hyperoxia leads to a significant inhibition of dendritic growth of cortical pyramidal cells in cingulate,

	Controls [med (IQR)]	Mild HIE [med (IQR)]
Spectral Power FB1 (μV²)	308.9 (236.4, 409.9)	386.4 (268.1, 712.6)
Spectral Power FB2 (μV²)	17.8 (14.6, 23.8)	18.0 (13.8, 24.6)
Spectral Power FB3 (μV²)	9.3 (8.2, 11.6)	8.1 (5.8, 10.5)
Spectral Power FB4 (μV²)	4.7 (4.1, 5.4)	4.6 (3.5, 7.5)
rEEG median (μV)	50.8 (43.352, 56.445)	46.9 (41.8, 56.3)
rEEG lower margin (μV)	27.0 (21.7, 31.5)	25.2 (22.4, 31.4)
rEEG upper margin (μV)	97.9 (92.6, 110.0)	92.6 (79.8, 104.8)
rEEG asymmetry	0.346 (0.321, 0.374)	0.343 (0.304, 0.373)
Spectral Edge Frequency (Hz)	6.1 (4.9, 6.4)	4.7 (3.3, 5.5)
Spectral Relative Power FB1 (%)	89.5 (88.5, 92.4)	92.0 (90.6, 93.9)
Spectral Relative Power FB2 (%)	5.3 (4.8, 6.5)	4.406 (3.097, 5.220)
Spectral Relative Power FB3 (%)	2.8 (2.4, 3.2)	1.869 (1.501, 2.136)
Spectral Relative Power FB4 (%)	1.4 (1.2, 1.9)	1.3 (0.9, 1.6)
Spectral Flatness FB1	0.432 (0.359, 0.495)	0.362 (0.212, 0.432)
Spectral Flatness FB2	0.894 (0.879, 0.902)	0.878 (0.864, 0.891)
Spectral Flatness FB3	0.890 (0.875, 0.910)	0.890 (0.876, 0.904)
Spectral Flatness FB4	0.766 (0.742, 0.805)	0.780 (0.728, 0.835)
Coherence FB1	0.165 (0.109, 0.191)	0.112 (0.087, 0.189)
Coherence FB2	0.060 (0.052, 0.087)	0.045 (0.035, 0.100)
Coherence FB3	0.047 (0.042, 0.096)	0.042 (0.033, 0.092)
Coherence FB4	0.037 (0.035, 0.052)	0.041 (0.030, 0.071)

FB1 = 0.5 – 4 Hz; FB2 = 4 –7 Hz; FB3 = 7 – 13 Hz; FB4 = 13 – 30 Hz

* Mann-Whitney *U*-tests

[78] Table 1 Quantitative EEG features in Infants with mild HIE compared with control population

motor and sensory cortex. Administration of rEPO prevents the damage on dendritogenesis and may thus be useful for prevention of associated neurological problems in preterm infants.

Disclosures: None declared

78. NEUROPHYSIOLOGICAL ALTERATIONS DURING THE FIRST 6 h IN INFANTS WITH MILD HYPOXIC ISCHAEMIC ENCEPHALOPATHY

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Background: Infants with mild Hypoxic Ischaemic Encephalopathy (HIE) currently do not meet selection criteria for Therapeutic Hypothermia (TH) despite having significant levels of disability on follow up. HIE is an evolving process and often it is difficult, in the short time available, to identify which infants would benefit from TH. In the pre-TH era, electroencephalography(EEG) within 6 h of birth was most predictive of outcome and although this has now been altered with TH, EEG continues to play a key role in HIE management.

This study aims to identify and describe features of early EEG (before 6 h of life) in infants with mild HIE and assess their ability to predict neurodevelopmental outcome.

Methods: This was a retrospective study of infants with mild HIE from 3 previous prospective studies conducted in tertiary maternity hospitals in Cork, Ireland between 2003–2011. Infants >36 weeks gestation with a clinical diagnosis of mild HIE, not undergoing TH with early EEG (before 6 h of life) and heart rate recordings were identified. Control infants were taken from a previous study examining brain activity in normal term infants. EEGs of infants with mild HIE were qualitatively analysed by a neonatal neurophysiologist blinded to outcome. EEGs of infants with mild HIE and controls were quantitatively assessed using multiple features of amplitude, spectral shape and inter-hemispheric connectivity. Quantitative features of the heart rate variability(HRV) analysis were computed for both groups.

Results: 35 infants with mild HIE (4 of which had an abnormal outcome) and 15 healthy term controls were included in this analysis. Median gestation of infants with HIE was 40.28 [IQR 39.29–41.29] and median birth weight was 2.52kg [IQR 3.14–3.75 kg]. Qualitative EEG analysis of infants with mild HIE showed that 45.7% had absent/poor sleep wake cycling, 57.1% had diffuse delta waves and 25.7% were discontinuous. Quantitative EEG analysis revealed significant differences in spectral shape between infants with mild HIE and controls (Table 1). HRV analysis revealed no difference between the groups. When assessing outcome, range-EEG (rEEG) median ($p = 0.046$), rEEG lower margin ($p = 0.046$) and spectral flatness ($p = 0.031$) were associated with abnormal neurodevelopmental outcome at 24 months. Qualitative EEG features and HRV did not correlate with outcome.

Conclusions: Previous studies report that 25% of infants born with mild HIE have significant disability at follow up. Quantitative analysis of early EEG revealed significant differences between control infants and infants with mild HIE. Incorporation of early quantitative EEG features could be considered in future trials of TH in infants with mild HIE to aid the objective identification of cases.

Keywords: Hypoxic Ischaemic Encephalopathy; mild HIE; EEG; Neurodevelopmental Outcome

Disclosures: None declared

79. EARLY EXPOSURE TO PROCEDURAL PAIN IS ASSOCIATED WITH DEVELOPMENT OF THALAMO-INSULA CONNECTIVITY IN VERY PRETERM NEONATES

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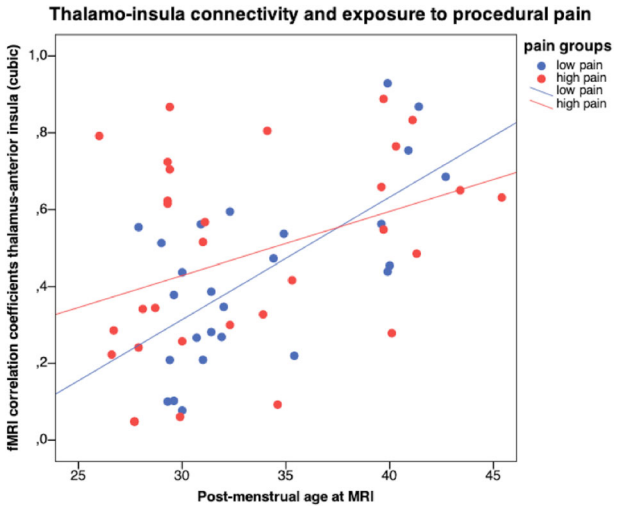

[79] Figure 1 The graph shows the functional correlated activity between the thalamus and the anterior insula (cubic transformation of the values) by postmentrual age at MRI, stratified in 2 groups divided by the median number of invasive procedures

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Background: Early exposure to procedural pain in very-preterm (VPT) neonates (<32 weeks' gestational age [GA]) represents a major concern in the NICU. Recent data suggest that early procedural pain exposure predicts disrupted thalamocortical development. In adults, the anterior insula is central for sensory and affective pain processing, yet the cortical representation of pain in the preterm brain remains unknown. We hypothesized that early procedural pain in VPT neonates would be associated with impaired thalamo-insula connectivity. Our objective was to determine whether neonatal pain is associated with development of functional connectivity between thalamus and insula in VPT neonates.

Methods: Fifty-one neonates (median[IQR] GA 27.6[2.0] weeks) underwent 3 serial MRIs including functional resting-state MRI at median postmenstrual weeks: 29.4, 31.9, and 41.1. Time courses from the independent-component maps in the thalamus and in the anterior and posterior insula were extracted, and correlation coefficients between subcortical and cortical areas were calculated. Pain was operationalized as the total number of invasive procedures over the NICU stay. Generalized Estimating Equations, accounting for repeated measures, assessed the association of procedural pain with functional connectivity between thalamus and insular cortex. Models accounted for postmenstrual age at MRI and clinical factors: GA, days of mechanical ventilation, sepsis, morphine and dexamethasone doses.

Results: High-quality serial fMRI data were available for 27 subjects with a total of 60 scans. Over the period of neonatal intensive care, functional connectivity increased as measured by the strength of correlated activity between thalamus and anterior insula ($r = 0.46$, $p < 0.001$), and thalamus and posterior insula ($r = 0.52$, $p < 0.001$). Procedural pain negatively predicted functional connectivity between thalamus and anterior insula over time (interaction term: invasive procedures and postmenstrual age; $p = 0.004$), independent of relevant clinical factors. This relationship was not observed in the posterior insula.

Conclusions: Robust maturation of thalamo-cortical functional connectivity was observed in the insula over an early sensitive period of brain development. Early exposure to procedural pain was associated with impaired development of thalamo-insular functional connectivity with anatomic specificity, suggesting a role for these specific thalamo-cortical projections in early-life pain processing.

Keywords: functional connectivity, insula, thalamus, preterm brain development

Disclosures: None declared

80. INTRANASAL INSULINE-LIKE GROWTH FACTOR 1 (IGF1) TREATMENT TO COMBAT PRETERM WHITE MATTER INJURY

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Background: White matter injury (WMI) is a common cause of neurological morbidity in the preterm neonate. Previous studies have established that impaired maturation of oligodendrocytes (OLs), followed by myelination failure, is the main underlying pathophysiological mechanism in preterm WMI. IGF1, an endogenous growth factor vital for normal white matter development, is shown to be downregulated following extreme preterm birth. Here we evaluated endogenous IGF1 changes in a mouse model of preterm WMI. Moreover, we explored the potential of intranasal IGF1 treatment to restore myelination in vivo. Furthermore, we assessed in vitro whether IGF1 could support OLs to overcome their maturational arrest.

Methods: WMI was induced in C57Bl/6j mouse pups at postnatal day (P) 5 by combining a hypoxic-ischemic insult with systemic inflammation (1 mg/kg LPS i.p.). Endogenous IGF1 levels were measured in blood and brain between P5–8. Mice were treated with intranasal IGF1 at different dosages during 6 consecutive days following WMI induction. At 3 weeks post-WMI, we assessed motor outcome using the cylinder rearing test. Brain sections were analyzed for myelination (MBP), cerebral inflammation (Iba-1, GFAP) and axonal injury (NF200) by immunohistochemistry. To explore the potential of IGF1 to support OLs in overcoming their maturational arrest, WMI was modelled by subjecting primary cultured immature OLs to inflammatory stimuli.

Results: Induction of preterm WMI led to a transient decrease in endogenous IGF1 levels in both plasma and brain compared to sham-operated control pups. Intranasal treatment with 25ug IGF1 for 6 days post-WMI restored myelination at 3 weeks post-WMI to levels in undamaged sham control mouse pups ($p < 0.001$). Motor function of WMI mice was restored by ~80% after IGF1 treatment compared to vehicle treatment ($p < 0.001$). We did not observe any axonal or neuronal damage in our in vivo model of preterm WMI. Intranasal IGF1 treatment dampened astrocyte activity compared to vehicle-treated WMI animals while microglia activation remained unaffected. ELISA for hIGF1 confirmed the cerebral distribution of IGF1 at 30 min after treatment. In our in vitro model we showed that addition of IGF1 to OLs arrested in maturation directly boosted OL differentiation and subsequently increased myelin production.

Conclusions: Induction of WMI in newborn mice is associated with a transient decrease in endogenous IGF1 levels between P5 and P8, comparable to the human preterm neonate. Restoring IGF1 levels using intranasal administration of IGF1 is a potent new strategy to restore myelination in a mouse model of preterm WMI. IGF1 aids in white matter regeneration after preterm WMI by boosting OL differentiation following OL maturation arrest.

Keywords: Preterm birth
Preterm white matter injury
Encephalopathy of prematurity

Insulin-like growth factor 1
Neuroregeneration
Disclosures: None declared

ORAL PRESENTATIONS—NEUROLOGY

81. NEURODEVELOPMENTAL OUTCOME AT PRESCHOOL AGE AFTER EARLY HIGH-DOSE RECOMBINANT HUMAN ERYTHROPOIETIN IN VERY PRETERM BORN CHILDREN: RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL

Giancarlo Natalucci[1,2], Beatrice Latal[2], Brigitte Maria Koller[1], Christoph Rüegger[1], Beate Sick[3], Leonhard Held[3], Hans Ulrich Bucher[1], Jean-Claude Fauchère[1], on behalf of the 'The Swiss EPO Neuroprotection Trial Group'

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Background: While erythropoietin (EPO) was shown to be neuroprotective in animal experimental and human clinical studies. The findings of the primary outcome analysis of this randomized controlled trial showed that prophylactic early (within the first 2 days of life) high-dose recombinant human (rh) EPO does not improve neurodevelopment of very preterm infants at 2 years. Since rhEPO reduced brain injury assessed by MRI at term equivalent age in a subgroup of study infants, we aimed to determine whether prophylactic early high-dose rhEPO in preterm infants improves neurodevelopmental outcome at preschool age (secondary outcome).

Methods: 448 infants born between 26.0 and 31.9 gestational weeks were enrolled in this randomized, double-blind, placebo-controlled, multi-center trial in Switzerland in 2005–2012. Participants were randomly assigned to receive either rhEPO (3000 IU/kg) or placebo (NaCl 0.9%) intravenously within 3 h, at 12–18 h and 36–42 h after birth. Outcomes at age 5 years (secondary outcomes) were the intellectual development assessed by the Mental Processing Composite [MPC, norm (SD) 100 (15)] of the Kaufman Assessment Battery for Children and survival without severe neurodevelopmental impairment (NDI, MPC < 70, severe cerebral palsy, severe auditory or visual impairment).

Results: Among 448 randomized infants [mean (SD) gestational age 29.0 (1.7) weeks and birth weight 1210 (345) gram; 185 (59%) female], 228 were allocated to rhEPO and 220 to placebo. Outcome data were available for 345 (77%) children at a mean (SD) age of 5.8 (0.4) years. We observed no difference in the mean (SD) MPC between the rhEPO group [96.0 (12.6)] and the placebo group [97.3 (13.0); mean difference (95%-CI) −1.4 (−4.1;1.4), p = 0.338] and in the rate of survival without severe NDI [170/179 in the rhEPO and 157/166 in the placebo group (both 95%), odds ratio (95%-CI) 1.1 (0.4;3.1), p = 1]. Results were similar after adjustment for sex, study center, and socioeconomic status.

Conclusions: Prophylactic early high-dose rhEPO administered immediately after birth and subsequently over the first two days of life is not associated with neurodevelopment in this cohort of very preterm infants at 5 years. An ongoing follow-up study will test whether the previously observed reduced rate of white matter injuries after rhEPO exposition will be reflected in better executive function abilities at age 7–12 years.

Keywords: Erythropoietin, Neuroprotection, Preterm, Neurodevelopment, Preschool age

Disclosures: None declared.

82. ROLE OF INFLAMMATORY BIOMARKERS IN CEREBROSPINAL FLUID IN NEWBORNS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Nuria Carreras[1], Juan Arnaez[2,4], Thais Agut[1], Ana Alarcon[1], Marisol Leon[1], Gemma Arca[3], Alfredo García-Alix[1,4]

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Background: Inflammation plays a crucial role in the pathogenesis of hypoxic-ischemic injury in newborns. Temporal evolution and impact of the inflammatory cascade have been shown in preclinical models. The measurement of biomarkers which correlate with inflammation may be an approach to its characterization in human neonates. β2 microglobulin (β2m) and Neopterin in cerebrospinal fluid (CSF) have been used as surrogate biomarkers of central nervous system inflammation. The aim of this study was to describe the behavior of β2m and Neopterin in CSF in newborns with hypoxic-ischemic encephalopathy (HIE) and to study the association with brain injury in MRI and neurodevelopmental outcomes.

Methods: Infants with HIE born in Sant Joan de Déu and Clínic Hospitals (Barcelona) in a two-year period were prospectively included. The severity of the HIE was classified within 6 h of life. Infants with moderate or severe HIE received whole-body cooling.

		β2m		Neopterin	
Severity of HIE*	Mild	3 (2.25-3)	p = 0.012	31 (26.2-43)	p = 0.001
	Moderate	3 (3-6)		67 (30-111.5)	
	Severe	5 (3.75-7.75)		126 (81.5-292.5)	
Death or BSID score<85 *		5 (4-6.75)	p < 0.001	119.5 (71.2-221.2)	p < 0.001
T1-T2 score		*0.433*	p = 0.057	*0.518*	p = 0.008
DWI score		*0.607*	p = 0.010	*0.606*	p = 0.002
Motor composite scale		*-0.620*	p = 0.018	*-0.713*	p= 0.001
Cognitive composite scale		*-0.615*	p = 0.019	*-0.734*	p = 0.001
Language composite scale		*-0.608*	p = 0.021	*-0.628*	p = 0.007
β2m				*0.719*	p = 0.001
Neopterin		*0.719*	p = 0.001		

*Median (interquartile range)
Data in cursive correspond to the *Spearman correlation rank*

[82] Table 1 Association between biomarkers, severity of HIE and outcomes

Mean total dBA				Mean peak dB			
Outside Incubator		Inside Incubator		Outside Incubator		Inside Incubator	
Transport n= 1468	Inborn n= 8544	Transport n= 1468	Inborn n= 8544	Transport n= 1468	Inborn n= 8544	Transport n= 1468	Inborn n= 8544
65.7 +/-0.2	60.9 +/-0.1	59.8 +/-0.1	61.1 +/-0.1	98.0 +/-0.3	83.5 +/-0.1	97.2 +/- 0.3	84.9 +/-0.1

[83] Table 1 Mean and peak sound exposure inside and outside the incubator for transported and inborn babies

β2m and Neopterin were measured in study patients in CSF obtained 12–72 h after birth and in a control group of newborns with suspicion of sepsis that was finally ruled out. β2m and Neopterin correlated with brain injury on MRI (Rutherford score) evaluated by 2 blinded researchers and with neurodevelopmental outcomes at 2 years assessed by Bayley Scale of Infant Development III (BSID III). The relationship between biomarkers and MRI and BSID III scores was assessed using Spearman's rank correlation coefficient and ROC curves.

Results: Fifty-five neonates were included and biomarkers were determined in CSF in 36. There were 10 infants with mild, 11 with moderate and 15 with severe HIE. Ten patients died. The median values of β2m and Neopterin were 3 mg/L and 46 nmol/L, respectively, both significantly higher than in controls. Only two infants had β2m levels higher than 7 mg/L and only 5 infants had Neopterin levels higher than 200 nmol/L, and all of them had severe HIE. Association between levels of β2m and Neopterin and the severity of HIE and outcomes are described in table 1. Cutoff values of β2m of 3.07 mg/L and Neopterin of 46 nmol/L predicted the composite outcome of death or score <85 in any BSID III domain with a specificity of 91 and 100% and a sensitivity of 76 and 100%.

Conclusions: CSF β2m and Neopterin are raised in infants with HIE, indicating the activation of the inflammation cascade. Infants with severe damage show higher levels. Interestingly, very high levels correspond invariably to severe HIE, but not all infants with severe HIE show high levels, which may reveal diverse mechanisms of injury in HIE. The characterization of inflammation supports further research into anti-inflammatory therapy as cooling coadjutant.

Keywords: Neonatal hypoxic-ischemic injury, Biomarkers, β2 microglobulin, Neopterin

Disclosures: None declared

83. NOISE EXPOSURE REMAINS A SIGNIFICANT PROBLEM FOR PRETERM INFANTS UNDERGOING AMBULANCE TRANSFER

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Background: Excess noise can cause neonatal instability with elevation in heart rate, blood pressure and desaturations. Preterm infants have decreased autonomic self-regulatory mechanisms, predisposing them to instability and fluctuations in cerebral blood flow with loud noxious stimuli, potentially increasing their risk of IVH. The maximum recommended sound level for neonatal units is 45dBA. In the UK, >16,000 neonatal transfers occur per year and it has been known for > 30years to cause excess noise exposure. Inter-hospital transfer of preterm infants is associated with an increased risk of IVH. We aimed to establish current noise exposure on the NICU and during inter-hospital ambulance transfer.

Methods: Preterm babies <32 weeks gestation and <72 h old who either received their early neonatal care at NUH NICU (inborn arm) or were transported to NUH within the first 72 h of life (transported arm) were included in this cohort study. Sound exposure was recorded both inside and outside the incubator for the duration of the transport journey in the transported arm ($n = 5$), or 1.5 h in the inborn group ($n = 15$). Total A weighted amplitude (1/3 Oct Leq dB), peak amplitude (LCPeak) and amplitude of 1/3 octave band (20–20000 Hz) exposure was recorded using a calibrated Svantek sound device. Results were analysed using Prism GraphPad software.

Results: Total A weighted sound exposure outside the incubator and peak sound exposure, in the transported group were elevated compared to the inborn group ($p < 0.001$). However, total A weighted sound within the incubator was higher for the inborn group (p45dB was limited to 20–4000 Hz, with sound reduced to less than 30dB above 8000Hz and almost undetectable by 16,000 Hz. However, within the incubator this attenuation was not seen with sound >45 dB at 20–8000 Hz, remaining >30 dB from 10,000–20,000 Hz.

Conclusions: Noise exposure continues to be excessive particularly during transport with peaks potentially contributing to stress and higher risk of IVH. In addition, within the incubator babies are exposed to a greater frequency range than within their environment indicating sound generation within the incubator. These interim results indicate that noise suppression during transport needs to focus at the baby interface as well as incubator design.

Disclosures: no conflicts of interest

84. AN INTERNATIONAL RANDOMISED CONTROLLED TRIAL OF RANIBIZUMAB COMPARED WITH LASER THERAPY FOR THE TREATMENT OF VERY LOW BIRTHWEIGHT INFANTS WITH RETINOPATHY OF PREMATURITY

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Background: Current therapy does not eradicate ocular morbidity and visual disability following retinopathy of prematurity. Anti-vascular endothelial growth factor treatment provides a potentially new treatment, but research-based evidence has not confirmed ocular efficacy, the appropriate drug and dose, the need for re-treatment, or defined long-term systemic effects from sustained suppression of systemic VEGF in a developing infant.

Methods: RAINBOW, RAnibizumab compared with laser therapy for the treatment of INfants BOrn prematurely With retinopathy of prematurity, was designed to evaluate the efficacy and safety of two doses of ranibizumab against laser therapy in a randomised

open-label study. Infants <1500 g birthweight meeting established criteria for ROP treatment were recruited in 87 centres in 26 countries. We performed a randomised, multicentre, open-label, 3-arm, parallel-group study evaluating efficacy and safety of intravitreal injection of ranibizumab 0.2mg or ranibizumab 0.1mg against laser therapy. The primary outcome was treatment success, defined as survival with no active retinopathy, unfavourable structural outcomes or the need for an additional treatment modality at or before 24 weeks.

Results: Treatment success occurred in 56/70 (80%) infants receiving ranibizumab 0.2 mg compared with 57/76 (75%) receiving ranibizumab 0·1 mg and 45/68 (66%) infants following laser therapy. The odds ratio of a successful outcome following ranibizumab 0.2 mg compared with laser therapy was 2.19 (95% confidence interval 0.99–4·82; $p = 0.051$). One infant had an unfavourable structural outcome following ranibizumab 0.2 mg, compared to five following ranibizumab 0.1 mg and seven after laser therapy. Ranibizumab 0·2 mg was effective in both Zone I and Zone II disease. Ranibizumab 0.1 mg offered no advantage over 0.2 mg. Death, serious and non-serious systemic and ocular adverse events were evenly distributed between the three groups. Sparse sampling identified high VEGF levels and a return of plasma VEGF levels toward baseline by four weeks in all three treatment groups.

Conclusions: In the treatment of retinopathy of prematurity, ranibizumab 0.2 mg was effective with fewer unfavourable ocular outcomes than laser therapy and with an acceptable short-term safety profile.

Keywords: very low birthweight; very preterm; retinopathy of prematurity; VEGF

Funding: Novartis Pharma; RAINBOW ClinicalTrials.gov number, NCT02375971

Disclosures: AS, DL, AF, BF, JDR, MFC and NM received personal fees and travel reimbursement from Novartis Pharma AG during the design and execution of the trial. No fees were paid during the analysis and write up of the study. AS declares personal fees from Novartis.

85. RNA-BINDING PROTEIN RBM3 CAN PREVENT MODERATE HYPOXIA-INDUCED CELL APOPTOSIS AND CELL CYCLE ARREST IN NEURAL STEM CELLS

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Background: Neonatal hypoxia-ischemia is a major cause of long-term neurological impairment. Neural stem cells (NSCs) reside physiologically in hypoxic niches and play important roles in neuro-regeneration after hypoxia-ischemic injury. While mild hypoxia appears to have proliferation-promoting effects on NSCs, moderate to severe hypoxia seems to show reverse effects. The cold-inducible RNA-binding motif protein 3 (RBM3) has multiple cellular functions including the regulation of apoptosis, cell proliferation, and cell cycle and promoting protein translation in NSCs. However, it is controversial whether and how it is participating in the oxygen stress response.

Methods: P10 SD rats were subjected to right common carotid artery ligation and then exposed to 8% O2 for 1 h. Left and right hemispheres were isolated for Western blot. Hypoxia-induced changes in RBM3 gene expression was assessed in mouse NSC line C17.2 by qPCR and Western blot. Cells were exposed for 24 h to different doses of hypoxia (1 to 18% O2) and either stained with Annexin V/propidium iodide (PI) without fixation or labeled with viability staining reagent and PI after fixation and then analyzed by fluorescence-activated cell sorting (FACS). To examine the role of RBM3 in hypoxia-induced apoptosis and cell cycle arrest, C17.2 cells were transfected with empty or RBM3-overexpressing vector and then exposed to hypoxia for 24 h. Statistical analysis: unpaired two-sample t-test ($P < 0.05$).

Results: Hypoxia had a dose-dependent suppressive effect on proliferation of C17.2 NSCs by increasing the number of cells in G1 phase when measured after 24h hours. This resulted in G1 cell cycle arrest under moderate (2.5% O2) and severe hypoxia (1% O2) and to reduced cell survival by increased apoptosis and necrosis. In vivo, RBM3 expression decreased after HI compared to sham group. In ipsilateral site of stroke, RBM3 level was higher compared to contralateral site. In vitro, RBM3 gene expression decreased in NSCs by about 50% under very mild hypoxia and showed only a small further decrease under moderate to severe hypoxia. Exogenous (vector) RBM3 overexpression significantly blocked cell cycle by decreasing the cell number in G1 phase and increased the cell number in S phase compared to controls. Also, RBM3 slightly increased cell viability but had no significant effect on apoptosis

Conclusions: The expression of the cold-inducible protein RBM3 is sensitively regulated in NSCs in response to hypoxia. Exogenous upregulation of RBM3 can prevent NSCs from getting arrested in G1 phase under moderate hypoxia levels. These findings suggest that RBM3 is involved in NSC proliferation in a hypoxic environment.

Keywords: hypoxia; RNA-binding protein; RBM3; apoptosis; cell cycle; neuro-regeneration; stress response; hypoxic-ischemic injury; neural stem cells

Disclosures: None declared

86. MESENCHYMAL STEM CELL-DERIVED VESICLES FOR TREATMENT OF NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY

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Background: Neonatal encephalopathy caused by hypoxia-ischemia (HI) is a major cause of death and disability in newborns. Stem cell-based regenerative therapies seem promising to prevent long-term neurological deficits. Our previous work in neonatal HI revealed unexpected risks of mesenchymal stem cell (MSC) therapy due to interaction with the brains' microenvironment. An alternative to cell therapy may be the use of MSC-derived extracellular vesicles (MSC-EV). According to our recent studies in models of adult stroke and inflammation-induced perinatal brain injury demonstrating therapeutic effects of MSC-EV, we hypothesized that MSC-EV promote neuroregeneration in neonatal HI-induced brain injury.

Methods: Nine day old C57BL/6 mice were exposed to HI through ligation oft the right common carotid artery followed by one hour hypoxia (10% oxygen). MSC-EV (1x10^5 cell equivalents) or vehicle control (0.9% saline) were injected intraperitoneally immediately after HI. Seven days after HI, brain injury was assessed by regional neuropathological scoring and atrophy measurements in cresyl violet stained tissue sections. Immunohistochemistry for NeuN, Olig2 and CD31 was applied to assess effects on neurons, oligodendrocyte and vessel densities, respectively. Cell proliferation was analysed in tissue sections stained for the proliferation marker Ki-67. Analysis was performed via confocal imaging (Nicon

A1plus, Eclipse Ti) followed by automated cell counting with the respective NS1 analysis software.

Results: While total neuropathological scores were not significantly changed, regional analysis of HI-induced brain injury revealed a significant protection from striatal tissue loss in MSC-EV-treated animals seven days after HI. Furthermore, cell-specific analyses via immunohistochemistry demonstrated that reduced tissue atrophy was accompanied by an increased neuronal, oligodendrocyte and endothelial density in the striatum. Interestingly, larger cell densities in MSC-EV-treated mice were associated with a significantly enhanced amount of proliferating cells in the neurogenic sub-ventricular zone close to the striatum.

Conclusions: These data indicate that MSC-EV promote neuroregeneration by inducing cell proliferation in neurogenic niches of the injured neonatal brain resulting in increased cell densities of a variety of CNS cells thereby preventing secondary HI-induced brain tissue loss. Considering potential unforeseen risks of stem cell therapy, these data suggest that MSC-EV may be a promising alternative to cell therapy for neonatal brain injury.

Keywords: neonatal hypoxia-ischemia, mesenchymal stem cells, extracellular vesicles, neuroregeneration

Disclosures: None declared

87. ANTENATAL MAGNESIUM SULPHATE TREATMENT FOR FETAL NEUROPROTECTION: SHORT TERM AND LONG TERM OUTCOMES IN A TERTIARY NICU

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Background: Antenatal magnesium sulphate treatment was identified as one of the most effective interventions in reducing the incidence of intraventricular hemorrhage (IVH), periventricular leukomalacia and cerebral palsy among preterm infants (1). The aim of our study was to compare rates of IVH and cognitive outcomes, in preterm infants who received antenatal magnesium sulphate with those who did not.

Methods: This retrospective study included a cohort of preterm babies ($n = 90$) born between 23 and 32 weeks of gestation ($23–25 + 6$, $n = 7$; $26–28 + 6$, $n = 26$; 29–32, $n = 57$) from January to December 2015 in a single UK tertiary neonatal centre. The treatment group $n = 38$ (18 male) had a median (range) gestation of $29 + 6$ ($23 + 5–32$) weeks, birth weight of 1074 (550–1716) gms and the non-treated group ($n = 52$; 23 male) had a gestation of $29 + 4$ ($23 + 3–32$) weeks, birth weight 1168 (490–1874) gms. Eighty-five infants (94%) received antenatal steroids. The short term outcome was assessed by cranial ultrasounds on day 1, 3 and 7 of life. The highest grade of IVH was recorded. Cognitive outcomes at the corrected age of two years were assessed by the Bayley Scales of Infant Development.

Results: In the treatment group, IVH grade 1 was reported in 6 babies (15%) while the remaining 35 babies (85%) had normal head scans. Among the non-treated group, 28 (54%) were reported to be normal, 14 (27%) with IVH Grade 1; 8 (15%) with IVH Grade 2; 1 (2%) with IVH Grade 3 and 1 (2%) with IVH Grade 4. A two way ANOVA showed a statistically significant interaction between the effects of magnesium sulphate exposure and gestation on IVH Grades on Cranial USS, ($F(2, 84) = 7.816$, $p = 0.001$) (Figure 1). Incidence of any IVH was significantly higher in the non-treated group compared to those treated across the gestational age range ($p = 0.021$).

The mean (SD) Bayley composite cognitive scores in the treated group 10.75(2.217) were not significantly different compared to the scores in the non-treated infants 8.5(3.659), ($p = 0.279$). None of the babies had a diagnosis of cerebral palsy at 2 year follow up.

Conclusions: In this cohort of preterm infants, antenatal magnesium sulphate treatment was associated with a significant reduction in the incidence of intraventricular haemorrhage but no significant differences in 2 year cognitive outcomes.

Disclosures: None declared

Reference:

1. Alonso, L.G., Prieto, M.P., Colmenero, E.G. & Gul;san, A.C. (2018) Prenatal therapy with Magnesium Sulphate and its correlation with neonatal serum magnesium concentration. Am J Perinatol. 35. 170–176.

NICU QUALITY IMPROVEMENT, PARENTS CENTRE CARE

88. NEONATAL OBSERVATIONAL VASCULAR ACCESS (NOVA): AN AUSTRALIAN AUDIT

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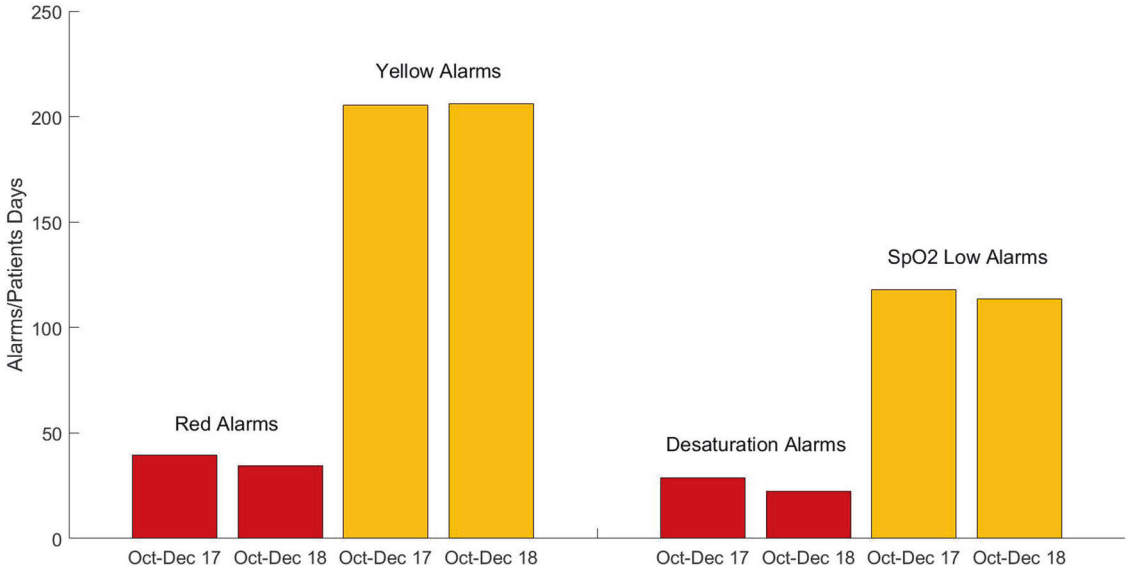
Background: Sick and preterm neonates require the delivery of fluids, medications, nutrition or blood products during hospitalisation. Thus, lifesaving treatment is often dependant on vascular access to deliver these treatments. However, the expected dependability and subsequent complications for a number of neonatal vascular access devices (VADs) is poorly understood. Studies in adults and paediatrics have resulted in evidence-based strategies for VAD insertion and maintenance towards the reduction of preventable complications. This study sought to identify current neonatal VAD practice, utility and complications towards targeted improvement.

Methods: A prospective audit of VAD management and associated complications was conducted over 3 months at the Royal Brisbane and Women's Hospital's, Neonatal Unit (Australia). All neonates requiring a VAD were eligible to participate. Primary outcomes were: (i) VAD complication resulting in catheter failure and (ii) VAD-associated skin complications. Neonates were assessed second daily for primary outcomes, and clinical utility such as frequency of device use. Descriptive statistics have been used, relevant to data characteristics. Associations between VAD-complications and clinical characteristics were assessed using Chi-square, Mann-Whitney U and Kruskall-Wallis tests, as appropriate. Variables with $p < 0.05$ were significant.

Results: In total 140 neonates received 302 VADs, for 1375.3 catheter days. Median age was 33.8 weeks (30.4–37.4) and weight was 2006 (1352–2956) grams. Prematurity (86; 61%) or respiratory failure (73; 52%) were attributed to most admissions. Multiple VADs were needed frequently (62; 44%) with dwell time reported



[89] Table 1 Average number of Alarms/Patients days - Oct-Dec 2017 vs Oct-Dec 2018s

as 2.3 (1.5–3.9) days for peripheral venous; 4.9 (2.7–6.8) days for umbilical venous; and 11.8 (7.9–14.3) days for peripherally inserted central catheters (PICC). VAD failure effected: peripheral venous (68; 36.6%), PICCs (5, 20.0%), umbilical venous devices (6; 11.5%); at a rate of 58.9 (47.4–73.2) per 1000 catheter days. VAD insertions were chiefly for fluids and medications administration (peripheral (184, 98.9%) umbilical venous (52, 100%)). Daily checks reflected high/continuous use (>87%) for VADs and skin complications impacted 12% of patients (23 complications in 17 patients).

Conclusions: VAD's within this study were frequently accessed and often associated with complications. Comparison of results remains difficult, due to inadequate reporting of VAD complications within networks (e.g. ANZNN, VON). Harm associated with VAD complications is an important indicator for prevention of morbidity and mortality. This study has begun to identify causes of neonatal VAD failure which will inform strategies to reduce VAD complications.

Keywords: Neonate, vascular access device, treatment failure, complication

Disclosures: The Royal Brisbane and Women's Foundation Funded this study. No other conflicts of interest to declare.

89. RELEVANCE OF WAVEFORM INFORMATION DISPLAYED ON NURSES' HANDHELD DEVICES IN A SINGLE-FAMILY ROOM NEONATAL INTENSIVE CARE UNIT

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Background: Patient monitoring devices are responsible for producing many false alarms, leading to desensitization and alarm fatigue. More intelligent alarm management can lead to an improved clinical workflow with positive effects on patient safety.

Until recently, the NICU of Máxima Medical Center (MMC), Veldhoven, used a distributed alarm management system and handheld phones for nurses displaying alarm but missing waveform information. This feature gives contextual information about the patient status and can help reduce the number of false alarms.

This study evaluated the effect of Philips CareEvent, a new alarm management solution implemented in Sep 2018, making waveforms accessible from phones.

Methods: MMC has a 22-bed NICU with single-family rooms. Patient monitoring is implemented such that alarms are generated at the bedside and sent to both a central station and handheld phones carried by nurses. Since Sep 2018, phones show waveform information.

Different measures were developed to analyze relevant alarms, labeled as red (critical) or yellow (alerting), in 3-month reference periods: Oct-Dec 2017 (control) and Oct-Dec 2018 (post CareEvent integration). These were chosen in order to remove seasonality effects from the analysis.

The analysis included the average number of all alarms and specific alarms (e.g. desaturation). For all patients, the percentage of time spent outside the target SpO2-range (89 to 95%) was calculated. All results were normalized by the number of patients' days.

Results: The gestational age (GA) and postmenstrual age (PMA) of the patients were similar during both periods (29.3 ± 1.0 vs 29.2 ± 1.1 weeks GA, 32.1 ± 1.0 vs 32.1 ± 1.4 weeks PMA).

A slight decrease in the average number of all alarms per patient day was found in 2018 (245 vs 235.8). This reduction was also found with desaturation (28.8 vs 22.5) and SpO2 low alarms (117.8 vs 113.5), the most frequent red and yellow alarms.

Wilcoxon rank sum test was used to compare the number of these alarms per day in both periods. A significant difference in the two periods was found for the case of desaturation alarms (p-value < 0.001).

The comparison of the two periods showed a reduction in the percentage of time spent with SpO2 values both below 88% (10.5 vs 9.6%, 1.9 vs 1.6% below 80%) and above 95% (42.5 vs 39.3%).

Conclusions: This study showed a decrease in the percentage of time spent by babies below the target SpO2-range and a significant reduction of desaturation alarms after CareEvent implementation.

Nurses have been able to see waveforms from the phones, having more contextual information to provide care to babies.

Future analysis will also take into consideration the severity of illness and can provide new insights about the improvement in alarm load.

Keywords: NICU, alarms, waveforms, handheld devices, alarm management solution

Disclosures: None declared

90. CREATING ROOM AND OPPORTUNITIES ON WARDS FOR NEWBORNS AND THEIR FAMILIES - THE CROWN INITIATIVE. AN INTERNATIONAL STUDY ON IMPLEMENTING CLOSENESS AND FAMILY INTEGRATED CARE IN NEONATAL WARDS IN EUROPE

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Background: Mother-infant separation postnatally and during hospitalization of the infant in the neonatal ward is applied frequently. Family integrated care (FICare) with subsequent less frequent mother-infant separation improves parent and infant outcomes during stay in the neonatal ward. However, much is unknown on the current state of neonatal wards in Europe on mother-infant separation postnatally and the integration of families into care for their infant during hospitalization, specifically. We analysed hospital settings with regard to mother-infant separation after birth and FICare practices in large Neonatal Intensive Care Units (NICUs) in Europe. Secondly, we explored challenges NICU professionals encounter to keep mothers and infants together and to implement FICare during hospital stay.

Methods: A cross-sectional mixed-methods study using structured interviews. (Veteran) parents of preterm and sick infants were included in the design and conduct of this study. We interviewed healthcare professionals of NICUs to describe current practice of mother and infant care, using patient valued outcomes and the pillars of FICare (NICU environment, education, support and participation of parents in care during infant hospital stay and education of healthcare professionals).

Results: In total, 44 units in 18 European countries and 1 unit from Canada participated. Mother-infant separation during periods of maternal or neonatal care is very common (42/45 (93%) units), due to current logistics, organization of care and architecture of wards. In 32/45 (71%) no visiting limitations were present for father and mother. Breastpumping was allowed in 44/45 (98%) units. In 17/45 units (38%) parents were allowed to participate in daily rounds without restrictions. Units reported privacy issues with presence of other parents on the wards and perceived lower efficiency as main reasons for not including parents on rounds. In 16/45 units (36%) structural education sessions for parents were offered. In 22/45 (49%) of units, a formal structured training for healthcare professionals was present.

Conclusions: Integrating the family into neonatal care during hospital stay and decreasing separation between parents and the infant has not been accomplished in a large number of European NICUs due to current logistics, architecture and common caring practice. Specifically including parents during daily rounds, offering parent educational sessions and education of healthcare professionals are not widely and structurally implemented.

Keywords: family integrated care, mother-infant separation, NICU, family centred care, healthcare education, parent education, family centred rounds

Disclosures: NR van Veenendaal is supported by an unrestricted research grant, provided by Nutricia, the Netherlands.

91. PARENTERAL STRESS IN NICU - WHO SUFFER GREATER: MOTHER OR FATHER?

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Background: The admission and treatment of an infant in the neonatal intensive care unit (NICU) is a great challenge for parents. Being separated with the baby, see own infant feeling pain and being sick, together with complexity of the NICU environment, mother and father experience great anxiety and stress. The stress experienced in the NICU can cause fatigue, sleeping disorders and depression after discharge, compromising bond and relationship between parents and child.

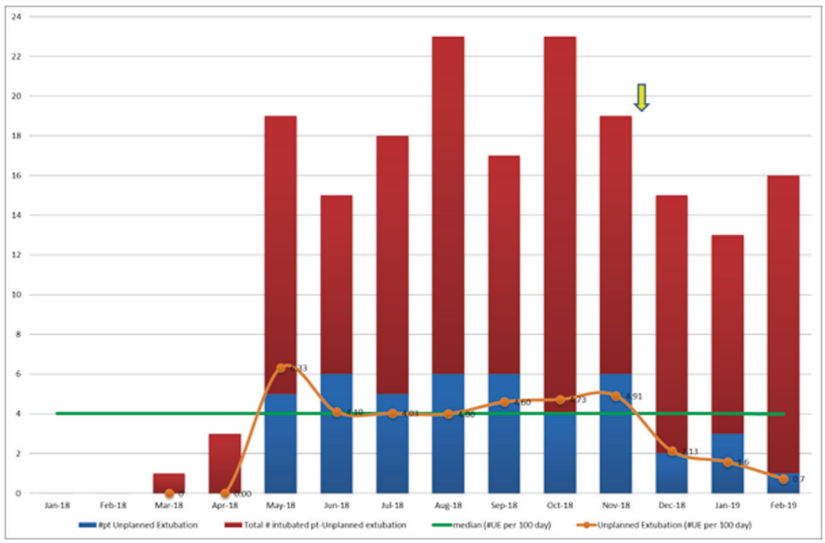
The purpose of the present study was to assess the parenteral stress levels and compare the sources of stress for mothers and fathers.

Methods: Descriptive study with a quantitative approach was conducted in NICUs of Ternopil region, Ukraine. Parents of 40 admitted to NICU infants participated in it. Parenteral stress levels were assessed using the questionnaire Parenteral Stressor Scale: NICU (PSS: NICU). The scale has 26 items, distributed in 3 subscales that measure the stress of parents relating with Sights and Sounds of NICU, Appearance and Behavior of the baby and Parenteral Role Alteration. In a type Likert scale, with a score between 1 and 5, parents indicated how stressful was the experience described in each item. Score "1" refers to not stressful and "5" to extremely stressful.

Mean scores (M) with standard deviation (SD) and t-test ("STATISTICA 13.0. FOR WINDOWS") were used for calculating PSS: NICU scores.

Results: The average PSS:NICU score in mothers was 3,48 with SD = 1,30. Parenteral Role Alteration was the most stressful for mothers (M = 3,90; SD = 1,12) followed by Infant Appearance (M = 3,58; SD = 1,22). The least stressful subscale - Sights and Sounds (M = 2,61; SD = 1,34). The same sequence of stressors were observed in fathers: M = 3,45, SD = 1,31; M = 3,12, SD = 1,29; M = 2,28, SD = 1,31 respectively; the average score (M = 3,04; SD = 1,36) was lower comparing to mother's one, $p < 0,05$.

The most stressful item in Parenteral Role Alteration for both mother and father was "Feeling helpless to protect baby from pain" (M = 4,18; SD = 1,05 and M = 3,80; SD = 1,15; $p < 0,05$). The most stressful item in Infant Appearance subscale for mothers—"Bruises on baby", for fathers—"Unusual breathing patterns". The noises of



[ID583] Figure 1 Trend of unplanned extubation (UE) rate from March 2018 to February 2019. Yellow arrow refers to the time when UE prevention bundle was introduced

alarms were the greatest stressors in NICU for mothers and fathers (M = 3,29; SD = 1,30 and M = 2,78; SD = 1,40; p < 0,05).

Conclusions: Parents of newborns admitted in NICU experience significant stress. Level of mothers' stress is higher than fathers' according total scale and each subscale scores. Parenteral role alteration is the greatest stressor for both parents that show the need for interventions and counseling focus on parents role, their early involvement in infants care, and complete family centered care implementation.

Keywords: parenteral stress, Parenteral Stressor Scale: NICU
Disclosures: None declared

92. AIMING FOR ZERO! REDUCING UNPLANNED EXTUBATIONS IN A "GREENFIELD" SINGLE-FAMILY ROOM QUATERNARY NICU

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Background: An unplanned extubation (UE) is defined as dislodgement of the endotracheal tube (ETT) from the trachea in a patient receiving invasive mechanical ventilation at a time not specifically intended. UE can result in significant adverse events, especially in neonates. The international benchmark for pediatric patients is <1 UE per 100 ventilator days. The rate of UE was unacceptably high following activation of Sidra Medicine NICU services. This was a "greenfield" NICU, integrating heterogeneous practices within a highly skilled, but multi-national workforce. Within a quality improvement project, factors associated with UE were identified and a "prevention of UE" care bundle was implemented.

Methods: All UE in NICU from March to November 2018 were retrospectively studied. A standardized assessment form was used to investigate each UE event and the most common risk factors for UE were identified by a multidisciplinary working group. Data collected included gestation, birth weight, position of ETT, route of intubation, fixation device, sedation, time of day and patient care activity at the time of the event. An UE prevention bundle was formalized which included a bedside ETT care checklist, uniform ETT securement along with staff education focused on appropriate positioning and management of agitation. A 3 month prospective review of the quality improvement measures was undertaken following the introduction of the prevention bundle, and the UE trends over the two epochs were compared.

Results: 44 UEs occurred in 182 intubated patients throughout the study period. There was no significant difference in the demographic characteristics of the patients intubated across the two epochs. Mean duration of ventilation per patient was 6.5 days. The most common risk factors associated with UE were suboptimal sedation, lack of personnel when performing complex procedures on the infant, inconsistent ETT securement and lack of regular surveillance of tube fixation. Following the implementation of the prevention bundle in December 2018, UE has decreased from a peak of 6.33 per 100 patient ventilated days in May 2018 to 0.7 in February 2019 (Fig. 1).

Conclusions: High UE rates in a "greenfield" NICU can be reduced by implementing a bundle of interventions supplemented by intensive staff education and surveillance to decrease variability of care practices. A decrease in UE rates was noted over 3 consecutive time points and sustaining this trend is the next challenge. Establishing the right team culture towards patient safety was a key factor in the improvement of this critical quality of care metric.

Keywords: unplanned extubation, Neonate, NICU
Disclosures: None declared

93. CLINICAL PROTOCOL & RESEARCH PROCESS OF STOCKHOLM PRETERM INTERACTION-BASED INTERVENTION, SPIBI

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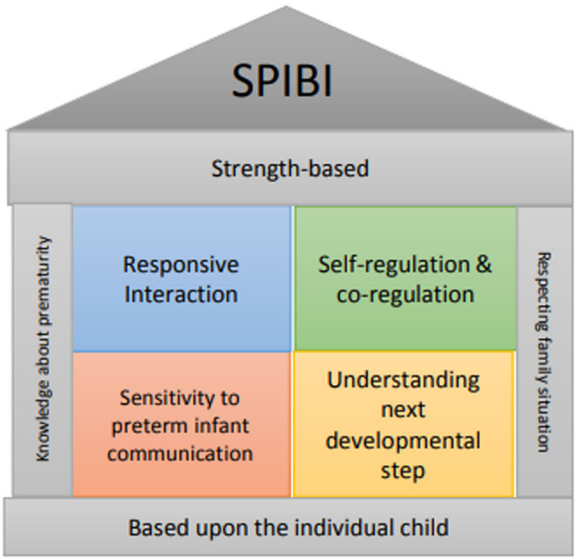

[93] Figure 1 The fundamental content & cornerstones of SPIBI summarized in a house-metaphor

Background: Extremely preterm (EPT) born children are at increased risk of cognitive and neurodevelopmental impairment, neuropsychiatric disorders and academic difficulties. Parents of EPT born children are extra vulnerable for anxiety, posttraumatic stress disorder and depression and the parent-child interaction is negatively affected by prematurity. There is some evidence that early interventions have beneficial effects on neurocognitive and motor outcomes (Spittle A et al. 2015). Based on a previous intervention (Verkerk G et al. 2012) and adjusted to the Swedish context with 480 days paid parental leave, we created a post–discharge intervention, SPIBI, for families of EPT born children.

Methods: The aim of (SPIBI) is to improve the quality of the parent-child interaction, child development and parental mental health in families with EPT born children. SPIBI is a randomized controlled beginning at discharge and lasting until the child is 12 months corrected age. The trial design is a two arm randomized trial with four recruiting sites in Stockholm. Intervention group (target, n = 65) receives 10 visits and two telephone calls from a trained interventionist and the control group (target n = 65) receives treatment as usual plus an extended follow-up program. The SPIBI-team has recruited and trained 6 multi-professional and NICU-experienced interventionists. The training takes one year (0.2 of full time) and the content was both theoretical and practical, including pilot-cases.

Results: SPIBI is an ongoing research project, beginning the 1st of September 2018 and planning to end recruitment the 31st of August 2020 and finishing the home-visits in August 2021. By the end of April 2019, 33 eligible infants had been identified within the four neonatal units in Stockholm; of which 26 children approved and 7 children declined participation. At this stage, three children have dropped out of the study, because of severe social challenges and child death. Identified challenges have been social and medical vulnerability of the EPT-families, finding the optimal multi-professional balance of motoric, psychological, pedagogical and medical kernels of the intervention, ethical considerations when to ask families for participation, lack of long-term discharge-planning of the neonatal units and large geographical spread of NICUs as well as families.

Conclusions: In conclusion, the protocol seem to be feasible and appreciated by parents in the target group. With regard to the small recruitment base, trials of this kind needs a long inclusion time. Since EPT-children and their parents displays a wide scope of difficulties and challenges, multi-professional cooperation is preferable, placing high demands of sensitivity, professional respect and time for long collaborative processes.

Keywords: Child cognitive development, child motor development, early intervention, extreme prematurity, parent-child interaction, parental mental health, self-regulation,

Disclosures: None declared

94. CULTURALLY SENSITIVE NEONATAL CARE PROVISION TO INFANTS OF PARENTS FROM THE TRAVELLER COMMUNITY: A NURSING AND MIDWIFERY PERSPECTIVE ON PROVIDING PARENT CENTRED CARE

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Background: Parents struggle to deal with fears of infant wellbeing in unfamiliar environments such as the neonatal intensive care unit. These challenges are further heightened for parents who do not perceive themselves to be fully integrated into the society in which they are receiving care, e.g. the Irish Traveller community. For nurses/midwives to provide family centred care, they must practice with cultural sensitivity, understanding of Traveller cultural beliefs, perceptions of illness, and past experiences with healthcare providers. There is paucity of focused studies on NICU staff perspectives on cultural issues influencing the care of newborn infants from the Traveller community.

Methods: The aim of this research was to explore neonatal nurses/midwives' experiences of providing culturally sensitive care to infants whose parents are members of the Irish Traveller community. The research sought to: determine views on the significance of attending to cultural needs within a neonatal unit, identify challenges and barriers encountered in providing culturally sensitive care and explore approaches utilised by neonatal nurses and/or midwives to enhance the quality of family centred, culturally sensitive care provision. Following ethical approval, a descriptive qualitative approach was used to conduct face-to-face semi structured interviews with ten nurses/midwives from an NICU in the Mid-West of Ireland.

Results: Four themes identified were, 1. Barriers to breastfeeding for women from the Traveller community included sub-themes of cultural influences, impact of the Beutler test and nurse/midwife assumptions. 2. Cultural Issues around trust, religion, rigidity of the healthcare system and social supports. 3. Educational deficits relating to poor literacy of the Traveller community resulting in barriers to seek health promotion opportunities. 4. Nurses/midwives' concerns, incorporating infant discharge, post-discharge safety and perceived exposure to domestic violence. The influence of the culture of the Traveller group was recognised as having a major influence on decision-making and interactions of these families within the neonatal unit.

Conclusions: Information on challenges, such as reluctance to breast feed, issues of trust, cultural beliefs and 'norms', encountered by neonatal staff in providing culturally sensitive care to the Traveller population would assist in enhancing culturally sensitive neonatal care plans for this sub-population. Discharge planning and follow-up needs to be tailor-made to suit their geographical mobility within Ireland and across Europe.

Keywords: Parent centred care, Cultural sensitivity, Irish Traveller, Barriers to breast feeding, Beutler test, Cultural barriers, Ethnic minorities

Disclosures: None Declared

95. IS EMPATHIC-N SUITABLE FOR NORWEGIAN NICU-PARENTS? TRANSLATION, CULTURAL ADAPTATION AND VALIDATION OF THE NORWEGIAN VERSION OF THE QUESTIONNAIRE EMPOWERMENT OF PARENTS IN THE INTENSIVE CARE—NEONATOLOGY

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Background: EMPATHIC-N is a parent-satisfaction questionnaire in Neonatal Intensive Care Units (NICU) reflecting the values of Family Centred Care (FCC) and is recommended by the European Foundation for the Care of Newborn Infants (EFCNI). It consists of 59 statements on a 6-point scale, organized in 5 domains. It also includes one general satisfaction score and four open questions concerning admission, hospital stay and discharge of their child and general experiences. Translation and validation is performed in Italy, Brazil, Australia, France and Greece/Cyprus.

The aim of this study was to evaluate the EMPHATIC-N in Norwegian NICUs.

Methods: The questionnaire was translated according to Wild's 10 steps for translation and cultural adaptation of instruments for patient-reported outcomes. According to parents' feedback, statements concerning both nurses and doctors were divided resulting in a Norwegian version consisting of 77 statements.

The project was approved by the leadership of the department and the Data Protection Officer at Oslo University Hospital. 500 Norwegian speaking parents voluntarily answered the translated version anonymously.

The internal validity was measured by Cronbach's alpha > 0,75, accepting Correlation > 0.40. The structure of the questionnaire was tested using Structural Equation Modelling analysis (SEM). The data from the four open questions were condensed and analysed qualitatively.

Results: 66 statements in the Norwegian version of EMPATHIC-N were found valid for the Norwegian NICU-parents. 11 statements were not valid within the original domains, mostly because of high missing or "not applicable".

Some statements may not be applicable for the majority NICU population, but important for small groups of patients.

Invalid statements with high clinical importance will be placed in other domains and retested. Dividing the statements concerning doctors and nurses revealed minor differences in parental satisfaction with no importance for quality-improvement-work.

Both mothers and fathers scored high on satisfaction (>5) in all domains, yet, the four open questions provided important information concerning parental frustration with routines and facilities as well as suggestions for improvements.

Conclusions: The Norwegian version of EMPATHIC-N was found valid for parents in Norwegian NICUs.

Parents scored high in satisfaction in all 5 domains, yet the four open questions provided useful information for quality improvement work in the unit.

The EMPATHIC-N questionnaire provides interesting data for studies, but far too much data for quality improvement work in a busy NICU. A short electronic version is needed.

Keywords: NICU, parent-satisfaction, parental satisfaction, patient satisfaction newborn, EMPATHIC-N, FCC

Disclosures: No conflicts to declare

96. SINGLE FAMILY ROOMS AND LATE ONSET SEPSIS IN PRETERM INFANTS - A RETROSPECTIVE COHORT STUDY AND MEDIATION ANALYSIS

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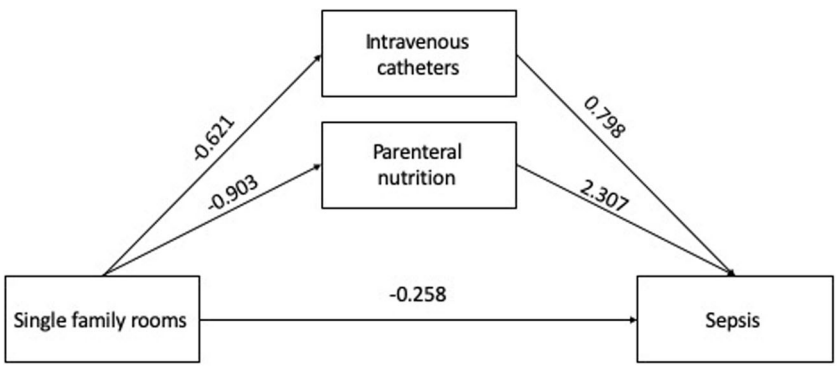
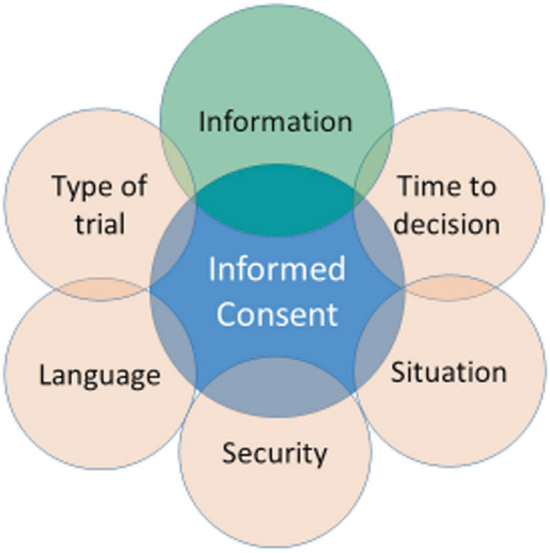
Background: Neonatal late onset sepsis is associated with increased morbidity and mortality, especially in preterm and very low birth weight infants, and has a multifactorial origin. During hospital stay, preterm infants are at increased risk of sepsis and most preventing strategies focus on reducing risk factors. Single family rooms (SFR) are associated with less sepsis events during hospital stay. However, potential mediators in the pathway between SFR and late-onset sepsis remain unidentified. We studied the effect of SFR on the incidence of late onset sepsis in preterm infants compared to open bay units (OBU). Intravenous devices and parenteral feeding were considered as potential mediators.

Methods: A single center retrospective cohort study comparing the period of care in OBU (January 2012 through June 2014) versus care in SFR(January 2015 through December 2016) in our neonatal level 2 department. We included all preterm infants (gestational age < 37 weeks) admitted (born at or transferred) to the hospital with a length of hospital stay ≥3 days. We applied a novel statistical technique with multiple imputation by chained equations for missing data and simple and multiple logistic regression models with 95% bootstrap confidence intervals to study the effect of SFR and potential mediators (with product-of-coefficients indirect effects) on late onset sepsis in our cohort.



[96] Figure 1 The effect of SFR on sepsis—mediation analysis



[97] Figure 1 Important factors for participation in a clinical trial

Secondary outcomes were growth during hospital stay, length of hospital stay and exclusive breastfeeding at discharge.

Results: We analysed 1046 infants (468 in SFR and 578 in OBU, median gestational age 35 + 2 vs 34 + 6 weeks). SFR decreased the incidence of clinical suspected late onset sepsis (3.2 events/1000 vs 5.6/1000 hospitalisation days) and sepsis treated for at least 7 days with antibiotics (1.0 events/1000 vs 2.1/1000 hospitalisation days), also after adjusting for confounding factors (OR 0.492, 95%CI 0.296–0.816, p = 0.0061). Intravenous catheters (indirect effect −1.749, 95%CI −2.751; −1.050) and parenteral nutrition (indirect effect −1.827, 95%CI −2.777; −1.135) were possible mediators of the effect of SFR on clinical and proven sepsis in our cohort. In multiple mediaton models the effect of SFR on sepsis was mainly mediated through parenteral nutrition (73%) and not through intravenous catheters (18%). We found no differences for growth, length of stay and exclusive breastfeeding at discharge.

Conclusions: In our study, single family rooms are associated with a decreased incidence of clinical suspected and proven late onset sepsis, and less use of intravenous devices and parenteral nutrition in preterm infants. Both intravenous catheters and parenteral nutrition were mediators in the pathway between SFR and late onset sepsis. In our analyses, the positive effect of SFR on sepsis was mainly mediated through a decreased use of parenteral nutrition.

Keywords: single family rooms, sepsis, preterm infants, patient centred care, family centred care, parenteral nutrition, mediation analysis

Disclosures: NR van Veenendaal is supported by an unrestricted research grant, provided by Nutricia, the Netherlands.

NURSING AND HEALTHCARE PROFESSIONALS

97. PARENT´S PERCEPTIONS OF THE VERBAL AND WRITTEN INFORMATION GIVEN IN A NEONATAL CLINICAL TRIAL

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Background: Preterm birth is a burdening event for families. In earlier studies, parents expressed that information was one of the most important factors in managing their stress. In this study, we investigated how parents of extremely prematurely born children perceived the information they received in the informed consent process in connection to a clinical trial.

Methods: 201 of 210 infants were included at this interim analysis. Parents either received a questionnaire from the study nurse at two time points or answered on our website when the infants were 7 days and 40 weeks postmenstrual age. Seven questions including the following topics were given: If the information was understandable, if the randomization procedure was clear enough to make a decision about participating, how long time they had for consideration and what influence the information had on parents' sense of security during the trial.

Results: The overall response rate was 78%. On the question "was the patient information clear enough to make a decision to participate?" 88,5% answered yes, 1,5% answered don't know and 10% gave their own comments. On the question "was the randomization process clear enough to make a decision to participate or not?" 65% answered yes,16,5% answered no, 11,5 % answered don´t know and 7% gave their own comments. On the question "if the parents felt completely secure with the information received during the clinical trial" 79% felt completely secure,18% felt rather secure, 2% felt insecure and 1% gave their own comments. Proposals that came up under their own comments was that the time and situation for when the information was given is important and that the information must be repeated throughout the clinical trial.

Conclusions: The results shows that most parents understand what it means to participate in a clinical trial and that they have enough time to make a decision, but that only 65% understood what it means to be randomized. The informed consent process not only depends on well-formulated information, but also on time and situation when the information is given.

Keywords: Parents' perceptions of the verbal and written information given in a neonatal clinical trial.

Disclosures: none declared

98. NATIONAL STUDY GROUP FOR PAIN ON NICU'S: TWENTY FIVE YEARS OF NURSING COLLABORATION IN THE NETHERLANDS, CHANGES IN COMMON HABITS AND POLICIES

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Background: Pain received minor attention until research showed newborn infants and even preterm infants could feel and

remember pain. In 1993 the Dutch National Study Group on Pain in Neonates was formed. In its 25 years of existence the main purpose of this nursing initiative was to achieve a change in knowledge and behaviour among neonatal nurses. Objective of the current study was to asses changes in neonatal pain management during these 25 years.

Methods: In 2019 a survey was performed under the supervision of the National Study Group on pain, to gain insight in common habits and policies among all ten level III NICU's in the Netherlands. The survey aimed at yielding information on preventive, pharmacological and non- pharmacological pain interventions, pain assessment tools used, and availability of written policies and guidelines with regard to pain associated with nine (acute) care interventions, six chronic care situations, and two postoperative situations. Results were compared with similar surveys performed in 1998 and 2016.

Results: Striking were the differences in pharmacological interventions during mechanical ventilation. Nowadays drugs are only prescribed on an individual bases and not as a standard prescription. The drug of choice for pharmacological treatment of pain changed over the years and differences still exist between the ten NICU's. EMLA was used less often, while the use of sucrose for acute interventions has increased. Nursing interventions associated with developmental care, such as supporting, containing and comforting, have become standard of care.

In 1998 none of the NICU's used pain assessment tools whereas in 2006 five out of ten and in 2019 ten out of ten used the ComfortNeo scale. Newborns were all assessed during intensive care treatment but not always in chronic situations. The availability of protocols was rare in 1998 but increased vastly in all NICU's.

Conclusions: This study showed that in the ten Dutch NICU's, prevention, assessment and treatment of pain as well as the availability of policies regarding pain have improved over the last 25 years. However, differences with respect to prevention and treatment of pain still exist. Further research is warranted to identify the background regarding these differences, in our aim to further improve pain management.

Keywords: Newborn, Nursing Care, Pain

Disclosures: None declared

PERINATAL PHARMACOLOGY AND ANETHESIA

99. PROPOFOL FOR ENDOTRACHEAL INTUBATION IN NEONATES CAUSES A DOSE-DEPENDENT PROFOUND AND PROTRACTED DECREASE IN BLOOD PRESSURE

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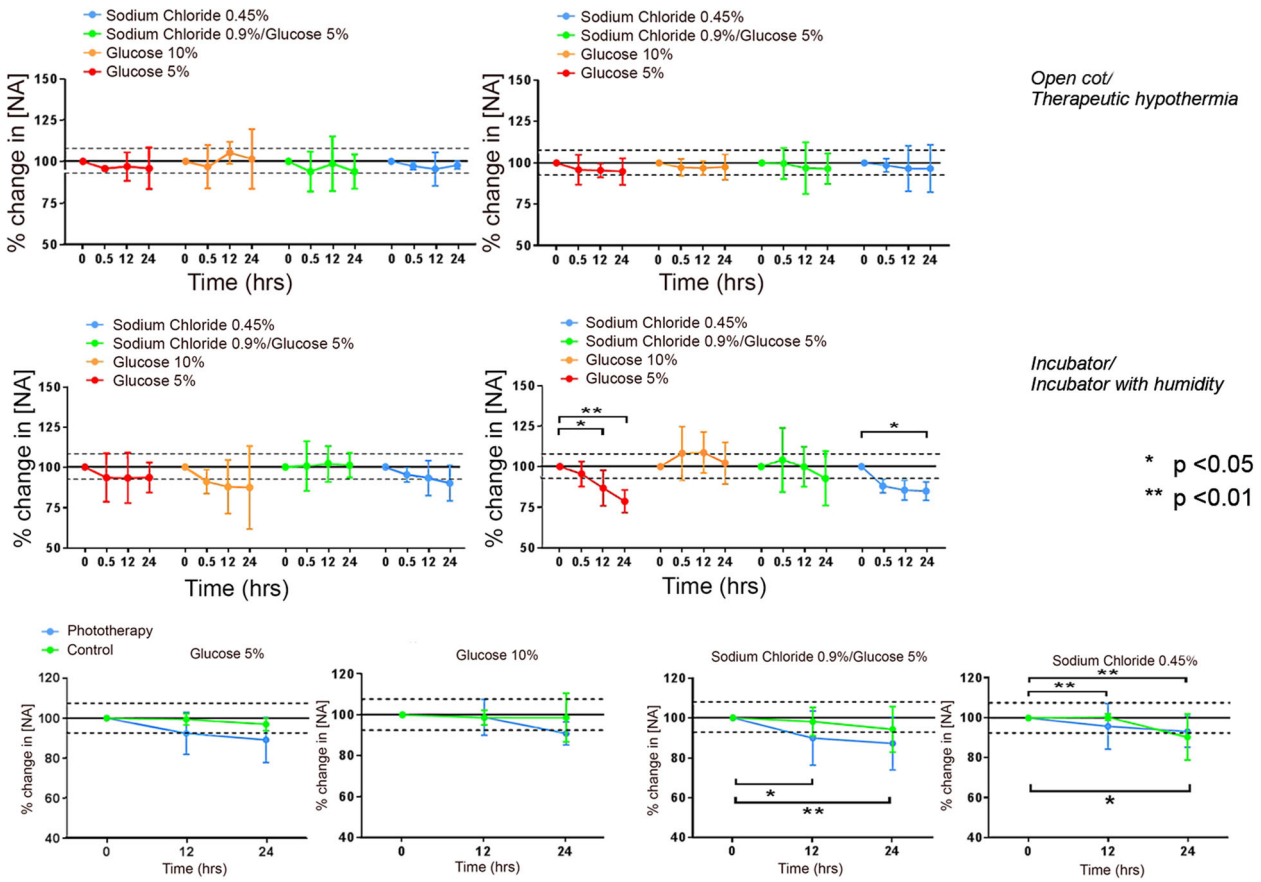
Background: Premedication minimizes the adverse physiological events that accompany endotracheal intubation and increases success rates. Therefore, premedication should always be



[100] Figure 1 Noradrenaline concentration over 24 h in different vehicles/environments

administered before nonemergency endotracheal intubation in neonates. The ideal premedication strategy should be simple to administer, provide good intubating conditions, have a rapid onset of action and short duration, and no adverse effects. In this regard, propofol is considered one of the acceptable options. Results of previous studies have raised concerns about the hypotensive effect of propofol. Aim of this study was to analyze the effect of different propofol doses on blood pressure in neonates.

Methods: A propofol dose-finding study (NEOPROP-2) was previously performed to determine age-specific effective and safe propofol doses for (preterm) neonates. Newborn infants who participated in this study were included in the current post-hoc analyses if they received a propofol starting dose of 1.0, 1.5 or 2.0 mg/kg. Mean blood pressure (MBP) was measured invasively if an indwelling arterial catheter was present or noninvasively by an appropriately sized cuff. MBP data from 5 min before until 60 min after the start of propofol infusion were collected. Outcome measure was the change in MBP in the first hour after the start of propofol infusion compared to baseline in the 3 dosing groups.

Results: Propofol starting doses of 1.0, 1.5 and 2.0 mg/kg were administered to 30, 23 and 26 neonates respectively. Effective sedation was reached significantly more often in the 2.0 mg/kg dosing group (86%), compared to the 1.5 mg/kg (23%; $p < 0.001$) and 1.0 mg/kg (4%; $p < 0.001$) dosing groups. The incidence of hypotension in the 1.0, 1.5 and 2.0 mg/kg dosing groups was comparable (63, 52 and 62%). Figure 1 shows the absolute changes in MBP compared to baseline at different time intervals after the start of propofol infusion for the 3 dosing groups. MBP decreased in all 3 groups compared to baseline and was not completely restored 60 min after start of the propofol infusion. The decrease in MBP was most pronounced in the 2.0 mg/kg dosing group. Correction for volume resuscitation and extra propofol doses yielded almost the same results.

Conclusions: Propofol as premedication for endotracheal intubation causes a dose dependent profound decline in MBP. The MBP decline is mainly dependent on the starting dose, and not on the cumulative administered propofol dose. Caution with the use of propofol as premedication for endotracheal intubation in neonates is warranted. Starting low and adjusting the dose according to an appropriate sedative effect seems the safest strategy.

Keywords: propofol, premedication, intubation, neonates, blood pressure, hypotension

Disclosures: None declared

100. THE STABILITY OF NORADRENALINE INFUSIONS IN THE NICU ENVIRONMENT

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Background: Hypotension is a common problem in preterm and unwell term infants, sometimes associated with sequelae such as renal/hepatic impairment, necrotising enterocolitis, and intraventricular haemorrhage. It can thus lead to adverse neurodevelopmental outcomes.

In UK NICUs, hypotension is increasingly managed with noradrenaline infusions. While available evidence suggests that such infusion solutions retain adequate drug concentrations for at least 24 h, there have been no studies examining their stability in NICU environmental conditions.

This prospective drug stability study aims to establish whether the current practice of changing noradrenaline infusions every 24 h is appropriate.

Methods: Noradrenaline infusions environments (glucose 5%, glucose 10%, sodium chloride 0.45% and sodium chloride 0.9%/glucose 5%) were subjected to a simulated NICU environment over 24 h: incubators with/without humidification, ambient temperature, and conditions associated with the delivery of therapeutic hypothermia. Samples of the noradrenaline solutions were taken at the time of infusion commencement, after 30 min, 12 h and 24 h, and analysed with high-performance liquid chromatography. Furthermore, the impact of phototherapy on infusion stability was also examined.

Results: A percentage loss of >7.5% was deemed significant. At room temperature and associated with therapeutic hypothermia, all infusion vehicles retained acceptable concentrations of noradrenaline. However, when exposed to an incubator, and particularly with humidity, significant changes were noted in all solutions. Noradrenaline concentrations were within limits at 24 h in an incubator, ambient temperature and with therapeutic hypothermia only in sodium chloride 0.9%/glucose 5%; but not in a humidified incubator, where adequate concentration in this diluent was maintained only at 12 h.

When associated with phototherapy, significant concentration degradation was noted in all infusion vehicles.

Conclusions: Definitive recommendations for practice cannot be derived from the results due to inherent wide margins of error, but results suggest that noradrenaline infusion solutions are not stable in the NICU environment. The use of sodium chloride 0.9%/glucose 5% as a diluent may be an adequate strategy to overcome stability issues when phototherapy is not required, but further research in this area is needed.

Disclosures: Lisa Kaiser, Dr Heike Rabe and Dr Bhavik Patel declare that there is no conflict of interest

101. LARYNGEAL MASK AIRWAY VS ENDOTRACHEAL INTUBATION DURING NEONATAL ANAESTHESIA FOR EYE SURGERY

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Background: Endotracheal intubation and mechanical ventilation remains the most common approach for neonates undergoing anesthaesia during surgcial procedures. However, it may be associated with transient reduction of oxygenation (in particular cerebral), tachycardia, hypertension, reflex apnea, and may increase the risk of prolonged ventilation. Hence, less invasive methods of ventilatory support are under investigation. According to the available literature ventilation of a neonate can be effectively carried out using a laryngeal mask airway (LMA) and may potentialy reduce the number of anaesthesia associated complications eg. desaturation, laryngospasm, cough and apnea.

Methods: Neonates undergoing ophtalmologic procedures (laser photocoagulation, injection of ranibizumab and vitrectomy) were randomized in two airway management groups: a) endotracheal intubation (ET) and b) i-gel LMA. The following parameters were monitored: saturation and heart rate (SpO2, HR), % of leak, end-tidal CO2 (EtCO2), NIRS cerebral oxygenation (StO2) and selected haemodynamic parameters measured with electrical

impedance velocimetry (EIV). Anaesthesia was performed with sevoflurane and infusion of remifentanyl.

Results: 41 neonates were enrolled. There were no significant differences in corrected gestational age between groups (median 36.5 (range 30–58) vs 35 (range 33–44) weeks). LMA insertion time was shorter than the intubation time (median 6 (range 6–8) vs 8 (range 5–9)s, $p < 0.05$). The leakage of anesthetic gases was significantly lower with LMA (median a) 17% (range 8–31%) vs b) 13% (range 3–15%), $p < 0.05$). Complications were observed only in the group a) SpO220s (15% of cases). Patients in group a) had significantly greater fluctuations in SpO2 (SD 2.58 vs. 1.73, $p < 0.05$), StO2 (SD 4.51 vs 2.75, $p < 0.05$), HR (SD 6.01 vs 4.74, $p < 0.05$), cardiac output (SD 21.28 vs 14.87, $p < 0.05$) and stroke volume (SD 20.67 vs 7.96; $p < 0.05$). After the procedure LMAs were removed sooner than endotracheal tubes (median 3.25 (range 2.7–3.7) vs 180 (range 60–1800) minutes, $p < 0.05$).

Conclusions: Anaesthesia during neonatal eye surgery performed with LMA seems safe and effective. Lesser leak of gases and fewer respiratory complications were observed with LMA compared with endotracheal intubation. The use of a LMA was associated with more stable cerebral StO2 and hemodynamic parameters. Application of LMA also seems to facilitate a sooner return to spontaneous breathing. These findings warrant further studies.

Keywords: Laryngeal mask airway; endotracheal intubation; neonatal anaesthesia; eye surgery; saturation and heart rate (SpO2, HR), % of leak, end-tidal CO2 (EtCO2), NIRS cerebral oxygenation (StO2); electrical impedance velocimetry (EIV)

Disclosures: None declared

102. THE EFFECT OF PRENATAL SILDENAFIL ADMINISTRATION ON POSTNATAL CEREBRAL AND RENAL TISSUE OXYGENATION IN SEVERE EARLY-ONSET FETAL GROWTH RESTRICTION

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Background: Neonates born after fetal growth restriction (FGR) show higher cerebral oxygenation (rSO2) and ongoing redistribution of cerebral-renal blood flow during the first 3 days after birth. Sildenafil has been under investigation as a potential agent to improve utero-placental blood flow and thereby fetal growth. This could affect cerebral redistribution associated with placental insufficiency. Previous studies showed effects on fetal flow profiles after prenatal sildenafil treatment. However, a large Randomized Controlled Trial was halted during interim analysis due to futility and potential neonatal side effects. This sub-study investigated the effect of prenatal sildenafil on cerebral and renal oxygenation.

Methods: Within the Dutch STRIDER trial, pregnant women with severe early-onset FGR received 25 mg tablets of placebo or sildenafil three times daily. In a random subset of neonates admitted to two neonatal intensive care units, frontal cerebral ($n = 14$ vs $n = 14$) and renal ($n = 5$ vs $n = 6$) rSO2 was continuously measured with near-infrared spectroscopy during the first 72 h after birth. Arterial oxygen saturation (SaO2) was measured simultaneously and fractional tissue oxygen extraction (FTOE = (SaO2-rSO2)/SaO2) was calculated. One hour of good quality of rSO2 per 3-hour intervals was manually selected. Heart rate (HR) and mean arterial blood pressure (MAP) during these periods were extracted. A linear mixed model approach was used providing an intercept ± slope per 3 h interval (=r) per group.

Results: Neonates were born with comparable birthweight (707 ± 46 g vs 659 ± 48 g; $p = 0.48$) and gestational age (28.1 ± 0.4wk vs 28.4 ± 0.7wk; $p = 0.72$). Cerebral rSO2 and FTOE levels were similar between the placebo and sildenafil group and had comparable trends during the first 72 h after birth (Figure 1). Renal rSO2 was similar between groups, but during the first 72 h renal rSO2 decreased less in the sildenafil group (r: −0.91% vs −0.28%; $p < 0.01$). Renal FTOE was elevated in the sildenafil group (intercept: −0.03 vs 0.13; $p = 0.02$) and increased less over time compared with the placebo group (r: 0.015 vs 0.003; $p < 0.001$). HR and MAP were similar between groups, but HR increased slightly more during the first 72 h after birth in the sildenafil group (r: 0.6 bpm vs 1.1 bpm; $p < 0.001$), while MAP increased less over time in the sildenafil group (r: 0.2 mmHg vs 0.1 mmHg; $p < 0.05$).

Conclusions: In this small group of neonates born after severe early-onset FGR, we observed a renal but no cerebral effect in tissue oxygenation during the first 72 h after birth in the sildenafil group compared with the placebo group. These data suggest that prenatal sildenafil may not prevent postnatal cerebral redistribution associated with placental insufficiency and that a different mechanism underlies the observed difference in renal oxygenation.

Keywords: brain; brain sparing; fetal growth retardation; fractional tissue oxygen extraction; kidney; near-infrared spectroscopy; regional oxygenation; sildenafil

Disclosures: None declared.

103. VANCOMYCIN RENAL ELIMINATION CLEARANCE IS MUCH MORE REDUCED IN PRETERM NEONATES TREATED WITH INDOMETHACIN (-55%) COMPARED TO IBUPROFEN (-16%) TO CLOSE A SYMPTOMATIC PATENT DUCTUS ARTERIOSUS

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Background: Ibuprofen and indomethacin are NSAIDs commonly used to induce ductus arteriosus closure in preterm neonates. Our group previously reported that ibuprofen decreased vancomycin clearance by 16%. In this study we quantified the impact of indomethacin co-administration on vancomycin clearance by extending our vancomycin population pharmacokinetic model with a dataset containing vancomycin concentrations measured in preterm neonates co-medicated with indomethacin.

Methods: The modeling dataset includes concentration-time data of vancomycin administrated alone or in combination with either ibuprofen or indomethacin collected in the neonatal intensive care units of UZ Leuven (Leuven, Belgium) and São Francisco Xavier Hospital (Lisbon, Portugal). The derived vancomycin pharmacokinetic model was subsequently used to propose dose adjustments that yield effective vancomycin exposure (i.e., AUC0-24h between 300–550 mg·h/L, with a probability below 0.1 of sub-therapeutic exposure) in preterm neonates with patent ductus arteriosus.

Results: We found indomethacin co-administration to reduce vancomycin clearance by 55%. Model simulations showed that the most recent vancomycin dosing regimen which was based on an

externally validated model, requires a 20 and 60% decrease of the loading and maintenance dose of vancomycin, respectively, when aiming for optimized exposure in the neonatal population.

Conclusions: By analyzing vancomycin data from preterm neonates co-medicated with indomethacin we found a substantial decrease in vancomycin clearance of 55% versus a previously reported 16% for ibuprofen. This decrease in clearance impacts vancomycin dosing and we anticipate that other drugs eliminated by glomerular filtration are likely to be affected to a similar extent as vancomycin.

Keywords: vancomycin, renal clearance, ibuprofen, indomethacin, patent ductus arteriosus

Disclosures: none

104. INTRAVENOUS DEXMEDETOMIDINE FOR SEDATION IN TERM AND TERM-EQUIVALENT PREMATURE NEWBORN UNDERGOING MRI. RESEARCH REPORT

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Background: Dexmedetomidine has gained ground for the sedation of pediatric and adult patients. Dexmedetomidine is a highly selective adrenoceptor agonist and has several favorable features, including: a quite rapid onset of a sedated state mimicking natural (non-REM) sleep; anxiolysis; analgesia; and anesthesia-sparing effects; with no or minimal respiratory side effects. Its use in neonates have a special interest because of side effects related to other sedatives. Brain MRI is a crucial procedure in neonatology for term patients with hypoxic-ischemic encephalopathy or term equivalent ex-preterms with intraventricular hemorrhage or periventricular leukomalacia and its success needs a good sedation.

Methods: A single dose of Dexmedetomidine 1 µg/kg was administered iv in 10 min (and repeated at the same dose when movements occurred during the test) to 15 term or term-equivalent newborns (8 born at term and 7 preterm) just before undergoing a brain MRI for clinical reasons (HIE, IVH or PVL). The sedation status was measured with the N-PASS scale, the time points for measuring sedation with the N-PASS were: at the baseline; 10 min after stopping drug's infusion; and after the newborn returned to the NICU. Vital parameters (SpO2, HR, RR, ABP) were recorded before the iv. administration, then every 5 min during the scan and up to 2 h after completing the MRI. Data were analyzed with Kruskal Wallis test for one-way variance, and Fisher's exact test was used to test the frequency comparison.

Results: The median dose of Dexmedetomidine administered was 3 µg/kg (from 2- to 4). No motion artifacts were seen on the MRI scans obtained with a significant N-PASS score reduction after the administration of the drug up to NICU readmission ($p < 0.0001$). Our population didn't show any significant variation of vital parameters. Blood pressure wasn't significantly modified during the exam. We noticed a slight tendency to heart rate and oxygen saturation reduction without respiratory rate reduction, both those changes are explicable with the expected sedative effect of Dexmedetomedine. In no case these parameters changes were clinically significant, without any medical intervention needed. Allowing to say that we experienced no side effects.

Conclusions: Dexmedetomidine seems safe and effective for use in performing MRI in term and term-equivalent premature newborn, showing no short-term side effects and avoiding neuroapoptosis induced by other sedatives. Its use deserves a larger observational study to confirm this conclusion and identify all its possible applications. End-tidal CO2 is a possible implementation to better understand if the slight SpO2 reduction is related to an increasing CO2.

Keywords: Dexmedetomidine, sedation, newborn

Disclosures: None declared.

105. METHADONE AS TREATMENT FOR NEONATAL REPETITIVE PROCEDURAL PAIN IN A RAT MODEL: ATTENUATION OF ACUTE AND LONG-TERM EFFECTS

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Background: Repetitive pain during early postnatal life affects the postnatal development of the spinal pain transmission network, leading to increased pain sensitivity to re-injury of the same dermatome in adulthood. At the same time, optimal analgesia during the neonatal period including the prevention of long-term changes in nociception is still challenging. The aim of the present study was to identify whether methadone analgesia during neonatal repetitive procedural pain can prevent acute and long-term hypersensitivity in the rat.

Methods: Male and female Sprague-Dawley rat pups underwent 4 needle pricks per day into the left hind-paw from day of birth (postnatal day 0 (P0)) until P7. Methadone (NP+M, 1 mg/kg) was administered before the first needle prick on each day from P0-P7. Sex-matched littermates received saline before the first needle prick (Needle prick; NP). A second control group of sex-matched littermates received saline and a tactile stimulus instead of needle pricks (Tactile control; TC). When adult, animals underwent a paw incision in the ipsilateral hind-paw as a model of acute post-operative pain. Mechanical sensitivity was assessed using Von Frey filaments. Mechanical sensitivity was tested daily from P0-P7; weekly from 3–8 weeks, and until 7 days post-incision; 50% withdrawal thresholds were calculated.

Results: During the neonatal period, NP animals showed significant mechanical hypersensitivity due to the needle pricks as compared to TC animals. Methadone treatment reversed the acute hypersensitivity. After re-injury of the ipsilateral paw in adulthood, NP animals showed increased hypersensitivity on post-operative day 5 compared to TC. NP+M animals showed no differences compared to tactile control.

Conclusions: The results in this study suggest that early treatment with methadone during neonatal repetitive procedural pain may attenuate both acute and long-term mechanical hypersensitivity.

Keywords: early treatment with methadone

Disclosures: none declared

PERINATAL PRACTICES

106. SCHOOL-AGE OUTCOMES OF PRETERM INFANTS WHO RECEIVED ANTENATAL MAGNESIUM SULPHATE THERAPY: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Cochrane library showed that antenatal magnesium sulphate therapy given to women at risk of preterm birth reduced the risk of cerebral palsy in early childhood. However, the effect of antenatal magnesium sulphate therapy on school-age outcomes is still unknown.

Methods: Objective: To evaluate the effects of antenatal magnesium sulphate therapy on school-age outcomes of preterm infants as primary outcome, and short-term outcomes of mothers and preterm infants as secondary outcome.

We conducted a systematic review and meta-analysis according to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" statement. We searched MEDLINE, EMBASE, CENTRAL, CINAHL, and any other accessible relevant databases.

We included randomized controlled trials of antenatal magnesium sulphate therapy in women at risk of preterm birth.

Two reviewers independently assessed the eligibility for inclusion and extracted data.

Results: Two studies (on 1100 babies) were included in primary outcome. Antenatal magnesium sulphate therapy had no relation to death, cerebral palsy, hearing impairment, and neurosensory disability at school-age. However, we were not able to conduct a meta-analysis of mental retardation and visual impairment because the evaluation methods of them were different in the two studies. Seven studies (on 4475 babies) were included in secondary outcome. Antenatal magnesium sulphate therapy increased maternal side effects (relative risk (RR) 18.63; 95% confidence interval 15.48 to 22.42; three trials, 3295 mothers), but it had no relation to neonatal symptom (neonatal asphyxia, use of ventilator or vasopressor, patent ductus arteriosus, intraventricular hemorrhage, periventricular leukomalacia, seizure, and small for gestational age etc).

Conclusions: Antenatal magnesium sulphate therapy had no influence on school-age outcomes of preterm infants. However, further accumulation of data is needed. Regarding short-term outcomes, antenatal magnesium sulphate therapy was associated with maternal side effects but not with neonatal symptom.

Keywords: preterm birth, magnesium sulphate, school-age, development

Disclosures: None declared

107. THE IMMEDIATE PARENT-INFANT SKIN-TO-SKIN STUDY (IPISTOSS): A STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL ON SKIN-TO-SKIN CONTACT BETWEEN VERY PRETERM INFANTS AND THEIR PARENTS

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Background: Skin-to-skin contact (SSC) is an evidence-based place of care for term and stable preterm infants. Evidence is lacking on how soon after birth safe SSC can be commenced for the yet not stable preterm infant. Reviews call for randomized controlled trials (RCTs) to confirm physiological and neurobehavioral benefits of SSC also in unstable infants following birth. Thus, our primary objective in this study is to compare the cardiorespiratory stabilization in very preterm infants exposed to skin-to-skin contact during the first six hours after birth with those in conventional care in incubators. Our secondary objectives are related to short-and long-term consequences of immediate SSC.

Methods: IPISTOSS is a RCT of SSC for very preterm infants born at gestational age 28 + 0–32 + 6 weeks (n = 150). Recruitment and data collection is ongoing at Karolinska University Hospital (Sweden) and Stavanger University Hospital (Norway) since 2018. Infants are randomized to either "immediate SSC" or "conventional care". Medical care is identical in both groups—the place of care differs. In the iSSC group the infant stays in SSC with one parent continuously for the first six hours while the control group infants are cared for in an incubator. After the first six hours, both groups receive SSC according to local guidelines. Exclusion criteria are severe malformations and multiple pregnancy with triplets or more. The study has ethical approval and is registered in ClinicalTrials.gov (NCT03521310).

Results: Primary outcome is infant cardiorespiratory stabilization during first six hours after birth and will be assessed with the "Stability of the cardio-respiratory system in the preterm (SCRIP)" score. Secondary outcomes include short- and long-term outcomes up to 24 months of corrected age such as infant physiology, nutrition and growth, breastfeeding status, infant stress reactivity, neurodevelopment and behavioral organization, mother-infant interaction and parental experiences and mental health. The infant's epigenetic profile will also be studied. We will use descriptive statistics, regression models and mediation-moderation models. Pilot data (n = 54) determined feasibility and safety of practical intervention aspects (unpublished data).

Conclusions: Our study has the potential of filling the knowledge gap on SSC in unstable preterm infants. It will describe the physiological effects of SSC in the very preterm infant in transition from intra-to extrauterine life. Thus, the study may have important implications for initial care of very preterm infants after birth. It will also increase our understanding of how immediate SSC affects very preterm infants and their parents up to 2 years of age.

Keywords: Randomized controlled trial, skin-to-skin contact, socio-emotional development, stabilization, study protocol, very preterm infant

Disclosures: "None declared"

108. INDIVIDUAL RISK PREDICTION FOR SIGHT-THREATENING RETINOPATHY OF PREMATURITY USING BIRTH CHARACTERISTICS AND LONGITUDINAL SCREENING DATA

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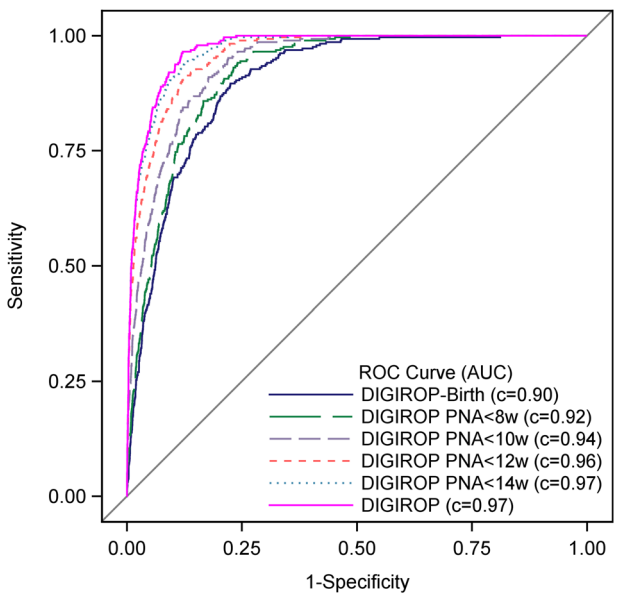

[108] Figure 1 Prediction ability shown by area under the ROC curve for DIGIROP-Birth and DIGIROP model

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Background: Retinopathy of Prematurity (ROP) is a disease potentially leading to blindness which may be prevented by timely treatment. In Sweden, all infants born at a gestational age (GA) < 31w are screened for ROP, only ~6% are treated. Recently, our group created and validated an easily accessible prediction model for ROP treatment, DIGIROP-Birth, based on infants' birth characteristics aimed for use at an early stage of screening. As more screening data is gathered better individual predictions might be done. The aim of this study was to create and validate a statistical model, DIGIROP, predicting ROP treatment for GA 24–30w using both birth characteristics and ROP screening results.

Methods: Data was retrieved from the Swedish National Patient Registry for ROP (SWEDROP) (N = 9135, 2007–2018). Of 7361 (80.6%) infants born at GA 24–30w, 129 (1.8%) were excluded for incomplete data, leaving 7232 (98.2%) in the analyses. Using multivariable Poisson regression for time-varying data momentary individual hazard functions and cumulative risks with 95% CI were estimated for ROP treatment. Predictors were postnatal age (PNA), GA at birth, sex, birth weight SDS, time-updated maximal ROP stage (no ROP/Stage 1 + 2/Stage 3), and significant interactions. Internal and external validation was performed by ROC analysis, cross-validation and calibration plots. Cut-offs to achieve 100% sensitivity were obtained. Comparison to other models was done and a ROP screening program suggested.

Results: Of 7232 infants, 3956 (54.7%) were boys, mean GA was 28.3w, mean birth weight 1146g, 2104 (29.1%) had any ROP and 300 (4.1%) were treated. Nasal ROP at first diagnosis was observed in 735 (34.9%) infants. Among treated infants ROP progression through stages 1 or 2 to 3 was documented in 209 (69.7%), and stage 3 at first diagnosis in 78 (26.0%). DIGIROP had an AUC of 0.97 in both internal (cut-off 0.0656 achieved 100% sensitivity and negative predictive value [NPV], 76.3% specificity, 15.5% positive predicted value [PPV]) and temporal validation compared to AUC 0.90 obtained in DIGIROP-Birth model using only birth characteristics (Figure 1). The AUC was 0.92 using data known up to 8w PNA (cut-off 0.0066 achieved 100% sensitivity and NPV, 51.4% specificity, 8.2% PPV), and 0.96 for data known up to 12w PNA (cut-off 0.0182 achieved 100% sensitivity and NPV, 62.1% specificity, 10.3% PPV).

Conclusions: An update of our DIGIROP-Birth individual prediction model for infants developing ROP needing treatment has been done, including longitudinal data on ROP progression, and successfully validated by internal and external validation. DIGIROP is a strong competitive ROP treatment prediction model compared to other models currently available.

Keywords: Retinopathy of prematurity, preterm, screening, prediction, hazard function, gestational age, birth weight

109. OBSTETRIC MANAGEMENT, COMPLICATIONS AND OUTCOMES OF BIRTH AT EXTREMELY PRETERM GESTATION: A SINGLE CENTRE'S EXPERIENCE

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Background: Obstetric management to reduce neonatal and maternal morbidity of extremely preterm (EP) delivery (22–26 weeks gestational age (GA)) requires appropriate counselling of mothers-to-be. Current evidence for best practice is limited and often focuses on neonatal outcomes. We retrospectively evaluated data regarding labour and delivery from women booked at University College London Hospital (UCLH; ~6500 deliveries/year). We aimed to describe management and short term (maternal and fetal) outcomes and, in particular, to quantify perinatal complications occurring at EP gestations. This will help inform parental counselling and aid clinicians in developing management plans.

Methods: Women with a live fetus at admission to UCLH and in labour or when a decision was made to perform Caesarean section, who delivered at 22–26 weeks GA (1st January 2011–31st December 2013) were included. Case identification used maternity and neonatal admission logs. We collected data on obstetric interventions (ultrasound, cardiotocograph), antenatal steroids (ANS), tocolyis and magnesium sulphate (MgSO4), labour management, and maternal, fetal and neonatal complication via hospital pathology, imaging and neonatal clinical databases cross-referenced with case notes and discharge summaries. Descriptive analyses comparing singleton and multiple pregnancies and women with and without medical complications are reported on a per-baby or per-mother basis, as appropriate, with a cutoff of $p < 0.05$.

Results: Of 132 women, 103 had singleton and 29 (53 live fetuses) had twin pregnancies. Pre-existing medical problems occurred in 30 (23%) women, 110 (83%) had antenatal complications; only 17 (13%) women experienced neither. Postnatal complications (eg post-partum haemorrhage, sepsis, ITU admission) occurred in 35 (27%) women; no statistical differences were seen by twin status or by pre-existing or antenatal obstetric complications. 151 fetuses (97%) were exposed to ANS, 24 (15%) to tocolysis and 70 (45%) to MgSO4. Delivery complications affected 11 fetuses, with 12 deaths in labour or in the delivery room; survival to discharge was 75% (117/156) and increased with GA: 25% (1/4), 75% (18/24), 69% (29/42), 73% (33/45) and 88% (36/41) at 22, 23, 24, 25 and 26 weeks GA respectively ($p = 0.024$). No statistically important impact was seen from twin status, maternal illness or obstetric management.

Conclusions: Despite birth in a large regional referral centre for EP delivery, mothers and fetuses had a high rate of complications. The results support timely transfer of women to a centre with appropriate obstetric and neonatal expertise, and highlight the importance of a team approach by clinicians. Antenatal and postnatal maternal complications were common, emphasising the need to include maternal as well as neonatal outcomes when examining EP birth.

Disclosures: None declared.

110. EFFECT OF 90 VERSUS 60 min OF EARLY SKIN-TO-SKIN CONTACT ON EXCLUSIVE BREASTFEEDING RATE IN HEALTHY INFANTS ≥ 35 WEEKS: AN OPEN-LABEL RANDOMIZED CONTROLLED TRIAL

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Background: Breastfeeding is one of the most cost-effective intervention to decrease under-5 mortality rate. Early skin-to-skin contact (SSC) is one of the key interventions around birth to promote breastfeeding practises and is a standard of care. World Health Organisation (WHO) currently recommends early SSC for a duration of at least 60 min however; the advantage of prolonging this duration is unknown. There is only one retrospective study which concluded that the longer periods of early SSC leads to increased likelihood of exclusive breastfeeding rate during the hospital stay immediately after birth however; there is no randomized controlled trial (RCT) assessing this dose-response relationship.

Methods: The objective was to evaluate if 90 min of early SSC improves exclusive breastfeeding rate in infants ≥35 weeks of gestation as compared to standard 60 min. Healthy infants ≥35 weeks of gestation born by vaginal delivery were randomized at birth to either 90 min (intervention) or 60 min (control) of early SSC. The infants in the intervention group received early SSC for 90 min immediately after birth whereas the control group received standard of care. The infants were followed until 14 weeks of age. The primary outcome was exclusive breastfeeding rate, which was assessed using standard WHO definition at 60 ± 12 h of age before discharge. The secondary outcome was breastfeeding behaviour as measured using modified infant Breast-Feeding Assessment Tool (IBFT).

Results: Both groups had 99 infants each with similar baseline characteristics including maternal age, education, parity, previous breastfeeding experience, socio-economic status and time of first breastfeeding. The mean gestational age and birth weight of the infants were also similar [39 (±1.5) vs. 39 (±1.3) weeks and 3113 (±394) vs. 3055 (±428) in intervention and control group respectively]. The exclusive breastfeeding rate was significantly higher in intervention group as compared to control group at 60 ± 12 h of age [75.7% (75/99) vs. 52.5% (52/99) relative risk (RR): 1.44, 95% confidence interval (95% CI): 1.15–1.79; $p = 0.003$]. The exclusive breastfeeding rate at the time of discharge from the hospital was also same. The IBFT score was also significantly higher in the intervention group as compared to control group [9 [8, 10] vs. 8 [7, 10]; $p = 0.03$].

Conclusions: Ninety minutes of early SSC significantly improved the exclusive breastfeeding rates at 60 ± 12 h of age and at discharge. The infants who received prolonged early SSC were 1.4 times more likely to be on exclusive breastfeeding at the time of discharge than those who received 60 min of early SSC. Moreover, the breastfeeding behaviour as assessed by IBFT tool also significantly better in the prolonged early SSC group (CTRI/2018/09/015632).

Keywords: Early skin-ti-skin contact, infants, breastfeeding rate, breastfeeding behaviour

Disclosures: None declared