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CRIB or CRIB-II to predict neonatal mortality

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Introduction: We wanted to compare the power to predict death prior to discharge in VLBW ($<$ 1500 g) infants for the Clinical Risk Index for Babies (CRIB) [BW, GA, congenital malformations, worst base excess (BE), perceived oxygen requirements] and the CRIB-II [BW, GA, sex, temperature , BE at admission].

Methods: On 1485 neonates admitted between 1/1/1991 and 31/12/2006 who survived for at least 12h, CRIB and CRIB-II calculation was possible in 1358 (92%). Predictive power of variables was assessed by comparing areas under receiver operator characteristics curves (AUC).

Results: CRIB (AUC + 95% CI 0.82 [0.78–0.86]) performed significantly better than birth weight (0.74 [0.69–0.79]) or GA (0.71 [0.66–0.76]). CRIB-II (0.69 [0.64–0.74]) was inferior to CRIB and did not differ significantly from birth weight or GA.

Conclusions: CRIB-II does not result in improved estimation of mortality risk in VLBW infants, as compared to CRIB, BW or GA.

Debriefing and evaluation of neonatal resuscitation a pilot study of video-recording

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Introduction: To ensure quality of delivery room management and to provide an optimal resuscitation training, a standard evaluation process is required. We therefore wanted to test feasibility of video-recording of resuscitation with a subsequent evaluation process.

Methods: A webcam is used to record patient and hands of medical staff. Debriefing: the resuscitation team meets to watch and discuss the interventions. Quality-check: a check-list based on resuscitation guidelines was developed, which distinguishes between mandatory, important and suggested items. Records are evaluated by the quality-team and results are presented at neonatal staff meetings. Records are deleted thereafter, or, parental consent is obtained to use the records for educational purposes.

Results: 30 resuscitations were recorded. The most senior neonatologist of the resuscitation team is in charge of the debriefing, junior staff and nurses are asked for strengths and weaknesses of the intervention. The quality check-list could be used for debriefing.

Conclusions: To improve quality and teaching, a structured two phase process of post-intervention debriefing and quality management is suggested. Practical and legal aspects have to be considered. www.neonatal-research-dresden.de

Ischemia-modified albumin levels in normal and intrauterine growth restricted full term neonates

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Introduction: Ischemia-modified albumin-(IMA) is a sensitive biomarker of cardiac ischemia. Intrauterine growth restriction (IUGR) implies chronic fetal hypoxia, resulting in blood flow redistribution. We therefore hypothesized that cord blood IMA levels should not differ between IUGR and appropriate-for-gestational-age-(AGA) term pregnancies.

Methods: IMA was measured in blood samples from doubly-clamped umbilical cords (representing fetal state) of 110 AGA and 57 asymmetric IUGR pregnancies.

Results: No differences in IMA levels were documented between AGA and IUGR groups. IMA levels were elevated in cases of elective caesarean section ($p = 0.03$), and offspring of multigravidas ($p = 0.02$).

Conclusions: The 'brain sparing effect' is possibly responsible for the lack of differences in cord blood IMA levels between IUGR and AGA groups at term. Higher oxidative stress could account for the elevated IMA levels in cases of elective cesarean section and offspring of multigravidas.

Maternal allopurinol reduces neonatal brain damage after fetal hypoxia as indicated by S100-B

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Introduction: Allopurinol (ALLO) inhibits xanthine oxidase, reducing free radical formation after birth asphyxia. Efficacy of postnatal ALLO is questionable because administration may be too late to prevent early reperfusion related free radical production. We evaluated placental passage and reduction of brain injury in newborns after maternal ALLO-treatment for fetal hypoxia.

Methods: Women in labor with fetal hypoxia (GA $>$ 36wks) were treated with ALLO or vehicle (double-blind randomised). ALLO and oxypurinol (OXY) lactate, and S100-B concentrations and non protein bound iron (NPBP), isoprostane, hydroperoxide, thiolgroups were determined in maternal and arterial cord blood.

Results: 27 mothers were treated with ALLO (500 mg iv), 27 with a vehicle. ALLO and OXY levels were within therapeutic range in mothers but not always in fetuses. The ALLO group was divided in a therapeutic ($ALLO^+$: $>$2.5ug/ml, $n = 15$) and a subtherapeutic ($ALLO^-$: $<$2,5ug/ml, $n = 12$) group. Fetal hypoxia was comparable between groups as expressed by lactate (vehicle: 8,4+2,9; $ALLO^-$: 7,8 $\pm$ 2,3; $ALLO^+$: 8,7 $\pm$ 2,4 mmol/l). Free radical formation was lower in $ALLO^+$ compared to vehicle. S100-B was lower in $ALLO^+$ versus vehicle/$ALLO^-$ fetuses (vehicle: 1.05 $\pm$ 0.48 ug/l; $ALLO^-$:1.29 $\pm$ 0.61; $ALLO^+$: 0.61 $\pm$ 0.20, $p < 0.05$). Significantly less newborns of $ALLO^+$ treated mothers ($n = 5$) had to be admitted to the NICU compared to newborns of vehicle treated mothers ($n = 17$).

Conclusions: Fetal ALLO concentrations were not always in the therapeutic range. $ALLO^+$ newborns seem to have less brain damage. Maternal ALLO treatment in case of fetal hypoxia may reduce hypoxia-induced brain damage in newborns.

Plasma unbound bilirubin and ibuprofen in preterms

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Introduction: Ibuprofen (IBU) is highly albumin-bound and may displace bilirubin. We tested whether unbound plasma bilirubin is increased in IBU-treated neonates compared to placebo.

Methods: Frozen plasma from 113 neonates (BW 500–1000g, GA 24–30 weeks) from the NICHD PPRU Ibuprofen Randomized Trial were used for plasma total (TB) and unbound bili (UB) by horse radish peroxidase assay. 55 had IBU (10 mg/kg then 5 mg/kg/day x 2) and 58 received placebo (saline). Plasma TB, UB and IBU (Cp IBU by HPLC) were obtained 1 and 48 h post-first IBU or P dose. Data were analyzed by linear regression, Mann-Whitney U and Wilcoxon Signed Rank Sum test.

Results: TB was lower in IBU at 48 h ($p = 0.04$). UB was low and constant in both groups. UB was higher in IBU than P at 1 h ($p = 0.05$) and at 48 hrs ($p = 0.05$). CpIBU had no correlation with TB or UB at 1 or 48 hrs ($r = 0.01$) *Conclusions:* Higher UB in IBU treated newborns suggests potential IBU-albumin-bili interactions or pre-existing higher UB and its clinical relevance remains to be determined.

Displacement of bilirubin from albumin by ibuprofen

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Introduction: Ibuprofen is strongly bound to albumin, and could displace bilirubin from albumin to cause bilirubin toxicity. Most clinical studies have not shown increased concentrations of unbound bilirubin (UB) in plasma from infants treated with ibuprofen. This could be due to *in vivo* equilibrium between different compartments. *In vitro* studies have not been equally conclusive.

Methods: Total bilirubin and UB were measured *in vitro* in pooled plasma samples from jaundiced newborn infants with the peroxidase method (UB-Analyzer UA-1, Arrows Co Ltd, Japan) after addition of ibuprofen or sulfisoxazole as bilirubin displacers. Ibuprofen concentrations varied from 100–600 μg/ml. Bilirubin concentrations varied from 176–708 μmol/l by adding bilirubin to plasma samples.

Results: Ibuprofen caused a linear increase in UB up to +59% at a concentration of 600 μg/ml, compared to an increase of 87.3% by sulfisoxazole (350 μg/ml). A double reciprocal plot of bound bilirubin (BB) versus UB at concentrations ranging from 176 to708 μmol/l showed competitive displacement of bilirubin by ibuprofen. *Conclusions:* Ibuprofen is a competitive *in vitro* displacer of bilirubin and should probably used cautiously in newborns with a significant jaundice.

Higher doses of ibuprofen for effective closure of patent ductus arteriosus at advanced postnatal age

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Introduction: Efficacy of ibuprofen for closure of a ductus arteriosus (DA) is influenced by many factors. Large intersubject variability in ibuprofen pharmacokinetics and increased clearance with postnatal age have been documented.

Methods: Evaluation of ibuprofen pharmacokinetics and influencing variables by development of a population pharmacokinetic and pharmacostatistic model, and by investigating relationships between ibuprofen concentrations Area under the curve (AUC), efficacy and effects.

Results: In 66 neonates (median BW 1015g; GA 28 w), ibuprofen pharmacokinetics were described by a one-compartment model with linear elimination. Clearance increased with postnatal age. DA closure was significantly higher in the 57 infants with an elevated AUC after the 1st or after all 3 doses, and with advanced GA as compared to the 9 without DA closure ($p = 0.02$). Closure occurred in 50% of neonates with AUC_1 <600 mg.h/L and in 91% with AUC_1 > 600 mg.h/L ($p = 0.006$). No correlation between AUC and side-effects was demonstrated.

Conclusions: To achieve optimal AUCs in infants of 25–34w GA, three doses q24 h are recommended: 10–5–5 mg/kg < 70h, 14–7–7 mg/kg for 70–108 h, and 18–9–9 mg/kg when 108–180 h.

Amniotic fluid cefazolin equilibration half life reflects maturation of fetal renal drug clearance

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Introduction: Cefazolin is administered during *in utero* surgery, but data on amniotic fluid (AF) disposition are limited. Such observations likely reflect fetal renal drug handling.

Methods: Newly collected and reported studies on cefazolin (plasma, AF) were pooled. Nonlinear mixed

effect modelling was applied. A two-compartment linear disposition model was used to fit maternal cefazolin plasma, a third compartment to model AF.

Results: Data were available in 82 pregnancies. Cefazolin clearance was 7.44 L/h. Equilibration half life (Teq) between maternal plasma and AF at term was 4.4 h, increased with decreasing GA and was 9.09 times longer in cases with polyhydramnios.

Conclusions: Fetal cefazolin elimination clearance increases with GA, reflecting perinatal renal maturation.

Neonatal onset of nephrogenic syndrome of inappropriate-antidiuresis

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Case report: The authors describe the 4th case observed and the 1st in the neonatal period, of a new syndrome characterized by unusual, severe, persistent hyponatremia associated with hyposmolarity, euvolemia, inappropriately concentrated urine and elevated natriuresis. The latter features resemble those typically observed in inappropriate antidiuretic hormone secretion (SIADH), although high Arginine Vasopressin (AVP) levels are lacking. The findings led the authors to hypothesise a Nephrogenic Syndrome of Inappropriate Antidiuresis (NSIAD). The previously described R137C gain-of-function mutation was detected by means of mutation analysis of the V2R gene.

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Postnatal BMI adaptation is regulated during a fixed time period and mainly depends on maternal BMI

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Introduction: To determine the time periods of BMI shift towards under- and overweight from birth to 6 years (y) and associated pre- and postnatal factors.

Methods: 43 children who fulfilled the following criteria were included in the study: BMI at birth $<$10th percentile; BMI 6 y $<$10th percentile; BMI at birth $<$10th percentile; BMI 6 y $>$90th percentile; BMI at birth $<$10th percentile; BMI 6 y $>$90th percentile; BMI at birth $>$90th percentile; BMI 6 y $>$90th percentile. A random sample of 14 children with a BMI between the 25th and the 75th percentiles both at birth and the age of 6 y served as controls. For the selected children body measurements from birth to 6 y, diet during infancy and school age, parental body measurements, social data, maternal diseases and diet during pregnancy were ascertained retrospectively.

Results: Children with extreme rise or fall in postnatal BMI already cross the BMI percentiles during their first y. At 5 y, BMI again moves towards under- or overweight. Independent of the children's BMI at birth mothers of overweight 6y old children are also overweight whereas mothers of underweight 6y olds have a below normal BMI.

Conclusions: The BMI development follows a fixed genetic program and mainly depends on maternal BMI.

Nirture: Glycaemia control, insulin and neonatal outcome

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Introduction: Progress in neonatal intensive care has lead to increasing survival rates amongst VLBW infants. Such survival implies short-term disruptions in the developmental trajectories and may have long-term sequelae. Glycaemia control and insulin could be amongst the key-players in improving nutritional status and reducing catabolic state.

No consensus exists on the use of insulin in VLBW infants due to a lack of randomised controlled trials.

Methods: In this perspective, the NIRTURE trial was set up.

Results: In our own cohort, we observed an improved non-protein caloric intake, better weight gain and decreased incidence of any ROP.

Conclusions: Glycaemia control and insulin may improve neonatal outcome.

Association between mucosal colonization with opportunistic pathogens and blood stream infections in the two NICU-s in Estonia

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Introduction: We aimed to study mucosal colonization of neonates with potentially pathogenic microorganisms in order to find out whether and how this is associated with blood stream infections (BSI).

Methods: In all newborns admitted to one of both Estonian NICUs within the first 72 hours of life and needing empiric antibacterial therapy, nasopharyngeal and rectal swabs were collected on admission and thereafter twice weekly until day 60 or discharge.

Results: A total of 278 patients (144 with BW$<$1500 g) were enrolled from Aug 2006 until July 2007. The most colonizing Gramm-negative microorganizms were *K.pneumoniae* (23%), *E.coli* (15%), *K.oxytoca* (14%) and *A.baumanni* (13%). 45 of 54 BSI were of nosocomial origin (58% G-positive, 40% by G-negative bacteria). The rate of infection per 100 days of colonization was the highest for *MRSA* (4,6) followed by 1,4;1,0; 0,8; 0,8 and 0,8 for *A.baumanni, E.cloacae, E.coli, K.pneumoniae* and *Serratia spp* respectively.

Conclusions: In NICU mucosal colonization by *MRSA* and to lesser extent by *A.baumanni* and *E.cloacae* carries a significant risk for BSI.

Impact of pasteurization on human milk composition and neonatal gut colonization

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Growing evidence favours the use of human milk for the feeding of neonates because of its many beneficial effects related to improvements in host defence, neurodevelopment, digestion and absorption of nutrients as well as psychological effects on the mother-child bonding. It is the preferred feeding for all infants, including sick and premature newborns. Preterm infants will be fed expressed mother's milk via nasogastric tubes because neurological immaturity or respiratory distress prevents them from sucking the breast directly. However, expressed breast milk is a possible source of pathogens as contamination frequently occurs. Pasteurization can be applied to prevent transmission of micro-organisms, but the process of heat treatment reduces the content and function of important immunological components. The neonatal gut is sterile at birth but starts to be colonized with bacteria within the first day. The type of feeding is an important factor in the development of the intestinal flora which plays a key role in the adequate induction of the immune system. Bifidobacteria dominate the flora of breast-fed term infants and suppress the growth of pathogenic bacteria. Few studies have determined the developmental aspects of intestinal colonisation in VLBW infants. However, these infants are at risk for systemic infections caused by bacterial translocation from the gut into the bloodstream; a mechanism which is facilitated by an increased intestinal permeability, a poor gut motility and an impaired general and mucosal defense. The aim of this study is to describe the type and timing of intestinal colonisation in VLBW-infants ($<$1500 g or $<$32 wk) fed with formula milk or mother's milk. The infants whose mothers intend to breastfeed are randomly assigned to receive either pasteurized or raw milk. The type of enteral nutrition and the colonisation pattern will be correlated with the occurrence of late-onset septicaemia.

Physiological variables for the neonatal cerebral oxygenation

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Introduction: With near-infrared spectroscopy, using spatially resolved spectroscopy, new parameters of cerebral oxygenation like TOI (tissue oxygenation index) and FTOE (fractional tissue oxygen extraction) can be measured and are increasingly used in studies and daily clinical practice. The different physiological influences on these parameters are measured.

Methods: In neonates the effect of pCO2, glycaemia and peripheral oxygen saturation on TOI and FTOE was measured in order to become a better interpretation of these parameters in daily practice.

Results: A positive correlation between pCO2 and TOI and a negative correlation between glycaemia and TOI were found. The effect of blood pressure on TOI and FTOE is individually different due to autoregulation and this can be studied by measuring the relation between TOI and blood pressure. Autoregulation is not only different interindividually but also over time. The effect of changes in pO2 and peripheral oxygen saturation on TOI can be interpreted by using FTOE.

Conclusions: These new parameters can be used to improve interpretation of the effect of different treatments on the cerebral circulation and oxygenation of neonates.

Correlation between fractional anisotropy (FA) and apparent coefficient of diffusion (ADC) on diffusion tensor imaging, and early neurological outcome in neonates with hypoxic-ischemic encephalopathy (HIE)

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Introduction: Diffusion Tensor Imaging (DTI) provides information on diffusions' orientation. Fractional Anisotropy (FA) and Apparent Diffusion Coefficient (ADC) reflect brain microstructure. The current study investigates the neurological prognostic value of FA and ADC values in white (posterior limb of the internal capsule PLIC, cerebral peduncles CP) and grey (basal ganglia BG) matter in the first days of life in term neonates with brain damage likely to lead to HIE.

Methods: We prospectively enrolled 16 consecutives neonates (10 females, 6 males; mean GA 39.6 wks $+/-$ 8.1 d; median 40 wks, BW 3249 $+/-$ 470 g). One baby was excluded. MRI scans were obtained between D2-8 after birth. Neurological assessment with Amiel-Tison score (group A favourable outcome; group B unfavourable outcome) was performed on day 10.2 $+/-$ 4.13 on average.

Results: 11 babies were in group A and 4 in group B, 3 died. Statistical differences were observed regarding outcome and ADC data on PLIC and BG but not on CP. No difference was noted on outcome and FA values on PLIC and BG whereas significant differences existed between early outcome and FA values in CP.

Conclusions: DTI parameters in specific brain areas, showing strong correlation with early neurological outcome in babies with HIE, may reflect a consistent underlying neural mechanism. These indices may represent robust parameters for long term outcome.

End-Tidal carbon dioxide monitoring in ventilated preterm infants

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Introduction: Capnography is of limited accuracy for monitoring PCO_2 in preterm infants. Monitoring end-tidal CO_2 ($EtCO_2$) using low-flow sidestream capnography (S-capno) may be more accurate than using previous techniques.

Objectives: To determine the accuracy of S-capno. To compare $EtCO_2$from S-capno and transcutaneous CO2 ($TcCO_2$) for detecting low(< 45 mmHg) or high venous CO_2 pressure ($PvCO_2$) (> 60 mmHg).

Methods: Simultaneous recordings of $EtCO_2$and $TcCO_2$and measurement of $PvCO_2$ in 38 ventilated preterm infants (BW$<$1500g). The Intra-class Correlation Coefficient (ICC), the $EtCO_2$ - $PvCO_2$gradient, and the area under the curve (AUC) were calculated.

Results: 144 $EtCO_2$/ $PvCO_2$ pairs were studied. 1) The ICC for all pairs was 0.28. 2) The mean $EtCO_2$ - $PvCO_2$gradient was -11 ± 7.8 mmHg. 3) AUC of $EtCO_2$and of $TcCO_2$ similarly detected high or low $PvCO_2$(0.82vs0.89, $p = 0.18$ and 0.89 vs 0.90, p=0.71).

Conclusions: Despite a poor $EtCO_2$- PvCO2 correlation, S-capno detected low and high CO2 levels, and may therefore be of some clinical interest.

Antenatal prediction of lung development in isolated congenital diaphragmatic hernia

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The most important impact of CDH is progressive lung hypoplasia, determining morbidity and mortality.

Typically predictors of outcome are based on anatomical lung assessment, i.e. lung sizing. The best validated method is 2D-ultrasound measurement of the contralateral lung area over head circumference, expressed as a ratio (LHR). This is most accurate by tracing the lung contour. When expressed as observed/expected LHR (O/E LHR) , the effect of different growth of lung and head during gestation is discounted. It is currently debated whether position of the liver is an independent predictor. Later measurements are more accurate, but usually clinically irrelevant, and O/E LHR also predicts early mortality. Three dimensional measurement of both lungs is most accurate by fetal MRI, 3D ultrasound does not have this potential. This is mainly because spatial resolution of MRI allows appropriate measurement of the contralateral lung. Observed measurements are expressed as a ratio to what is expected in a normal fetus, most accurately matched by measurement of the body volume. In utero assessment of lung vasculature by measuring number of branches, vessel diameters, flow velocimetry or flow volume are also currently used, but they are less validated and difficult to reproduce. A more functional approach is by measurement of pulmonary artery reactivity following maternal hyperoxygenation.

Intratracheal pressure during high frequency oscillatory ventilation (HFOV) of newborns across small endotracheal tubes

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Introduction: Because of uncertainty about the effective pressure swings at tracheal level 2 mathematical models for calculation of intratracheal pressure were validated in a laboratory model of HFOV.

Methods: Ventilation of a passive lung model through an anatomically shaped ET tube of 3.0 and 4.0 mm inner diameter (ETT3, ETT4) with a HFOV ventilator using different combinations of mean airway pressure (MAP), frequency and amplitude. Measurement of flow with an ultrasonic device, pressure measurement with 2 piezoelectric transducers.

Results: Pressure drop across the ETT was a function of amplitude, frequency and ETT size. Using an I:E ratio of 1:2 throughout the study the pressure drop during inspiration/expiration was 28.1–51.8%/23.8–40.7% for ETT3 and 9.5–24.7%/3.3–16.4% for ETT4. With both mathematical models the pressure drop was underestimated by about 22 or 38% ($p < 0.001$).

Conclusions: Other than in CV pressure drop during HFOV in very small ETTs cannot be calculated by known mathematical models. Normograms are helpful if a precise estimation of tracheal pressure is mandatory.

Prevalence and severity of bronchopulmonary dysplasia (BPD) in a national cohort of extremely premature infants

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Objective: To study prevalence and severity of BPD in a cohort of infants with a high rate of prenatal steroid (86%) and surfactant (84%) treatment.

Methods: BPD was analyzed in a national cohort of premature infants with gestational age (GA) of 22 to 27 completed weeks (wks) or BW of 500 to 999 g, BPD was classified as mild; ventilatory support and/or oxygen at 28 days, moderate; oxygen at 36 wks, and severe; ventilatory support at 36 wks.

Results: No infant with GA 22-25 wks survived without BPD. Moderate or severe BPD was seen in 80% of infant with GA 22–23 wks, 75% in GA 24 wks and 59% in GA 25 wks. Moderate or severe BPD was more common in boys (51%) than in girls (36%) ($p = 0.001$). This sex difference also remained in infants with GA 26–28 wks, (girls 29%, boys 46%, $p = 0.005$). However, for infants with GA 22–25 wks no such difference was seen (girls 64%, boys 71%, $p = 0.45$).

Conclusions: BPD remains a severe problem in spite of prenatal steroids and surfactant treatment. Although BPD is in general more commonly seen in boys than girls, boys and girls of 22–25 wks are equally affected.

Surfactant via gastric tube in spontaneously breathing vlbw infants on nasal CPAP. Multicenter data of a genetic neonatal network

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Introduction: CPAP is a widely adopted strategy to reduce lung injury. However, a large proportion of infants <1000 g suffer from surfactant deficiency and need replacement therapy. We wanted to evaluate effectiveness/safety of surfactant instillation by gastric tube.

Methods: We report German multicenter experience with this approach in 321 infants with RDS on nCPAP from a cohort of 1536 VLBW infants ⩽30 GA that were monitored in 2003-2007 in a genetic study (www.vlbw.de). Characteristics and outcome data were compared to standard treatment.

Results: The method (surfactant (SF)/no intubation) is used increasingly in German centers. In 2007 25% of the infants ≤30 weeks were treated with SF/no intubation.

Conclusions: Multicenter data on surfactant by gastric tube are encouraging, reducing the need for mechanical ventilation and hopefully also the incidence of BPD. A randomised controlled study is ongoing. (www.controlled-trials.com).

Congenital diaphragmatic hernia: Management and outcome in 10 years

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Introduction: Owing to technological advances and new therapies, survival of patients with congenital diaphragmatic hernia (CDH) improved. We wanted to assess effectiveness of management in a cohort of CDH infants.

Methods: A cohort of neonates with CDH (1997–2006) was assessed. Since 2003 a new treatment protocol has been practiced.

Results: 61 newborns; 30M/31F; BW 2800g (880–3770); GA 38 weeks (28-41) including 23% preterms, 75% inborn; 69% with prenatal diagnosis; 3% chromosomal anomalies; 5% other congenital anomalies; 2% non-immune hydrops fetalis. Diaphragmatic defect was left sided in 90%, right sided in 10%. Corrective surgery was performed in 70%. New therapies were used: HFOV 13%; inhaled nitric oxide 13%; sildenafil 7% . The overall survival was 43%. Since 2003 this rate has improved to 61% in term neonates without other congenital or chromosomal anomalies. Follow-up in survivors revealed: deceased 4%; failure to thrive 23%, neurodevelopmental delay 8%, cerebral palsy 4%, gastro-oesophageal reflux 12%, respiratory problems 15% musculoskeletal abnormalities 12%, recurrence of hernia 8% and patch rejection 4%.

Conclusions: Survival rate of CDH has improved over the last decade, associated with a new treatment protocol including new therapies. Survivors of CDH remain a complex patient population throughout infancy and childhood, requiring long-term follow up.

A placebo controlled study on lung mechanics after intra amniotic injection of VEGF in preterm rabbits

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*Introduction:*Vascular Endothelial Growth Factor (VEGF) is critical for angiogenesis, vasculogenesis and alveolar type II cell differentiation. We aimed to study functional pulmonary effects of antenatal intra-amniotic VEGF administration in a preterm rabbit model.

Methods: At 26 d (GA term = 31–32 d), 60 μg recombinant rat $VEGF_{164}$ in 250 μL vehicle or 250 μL placebo were injected intra-amniotically. Unexposed littermates served as internal control. At 28 d GA, fetuses were harvested (11 VEGF, 10 placebo, 10 control) for morphologic assessment or ventilated (11VEGF, 9 placebo, 8 control) with a Flexivent (Scireq, Montreal) ventilator allowing measurement of total lung capacity, resistance, compliance. Morphologic assessment includes airway and vascular morphometry and immunohistochemistry for Sp B, Flk 1, apoptotic (caspase3) and proliferative markers (PCNA).

Results: Lung mechanics as well as number of Flk-1 positive cells were higher in treated pups than in placebo and control animals (ANOVA $p < 0.05$).

Conclusions: Intra-amniotic injection of VEGF at canalicular phase results in a significant improvement in lung mechanics and a higher number of Flk-1 positive cells at 28 d (saccular stage).

Effect of angiotensin converting enzyme (ACE) gene polymorphism on diaphragmatic strength and endurance in infants

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Introduction: The human ACE gene contains a polymorphism consisting of either the presence (I) or absence (D) of a 287-base fragment. The ACE I-allele is associated with enhanced muscle fatigue resistance. Diaphragmatic tension-time index (TTdi) is a measure of diaphragmatic endurance and a high TTdi can predict diaphragmatic fatigue. Diaphragmatic strength can be assessed by measuring transdiaphragmatic pressure during crying (cPdi). The aim was to compare diaphragmatic strength and endurance in infants with ACE I, ID or DD alleles.

Results: One hundred-twenty infants were studied. ACE genotyping was performed by PCR amplification. cPdi was measured using a pressure catheter. TTdi was calculated as the product of the mean to the maximum transdiaphragmatic pressure and the inspiratory duty cycle. Infants with the ACE I-allele compared with infants with the ACE ID or DD alleles had significantly lower TTdi, but not different cPdi.

Conclusions: These results suggest that the ACE genotypes affect diaphragmatic endurance, but not strength in infants.

Preserved assembly of complex III despite decreased bcs1l content in GRACILE syndrome fibroblasts

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Introduction: A homozygous mutation (A232G) in *BCS1L*, encoding a mitochondrial protein assembling the Rieske FeS subunit (RISP) into respiratory chain complex III (CIII), causes GRACILE syndrome. We investigated the subcellular localization of BCS1L and the assembly of CIII in fibroblasts of GRACILE patients.

Methods: Fibroblasts from GRACILE patients ($n = 5$) and age matched controls ($n = 3$) were assessed with transmission electron microscopy (TEM) and immunoelectron microscopy (IEM) to detect localization of BCS1L and CIII subunit Core I in mitochondria. Incorporation of RISP into CIII was assessed by Blue Native PAGE with immunoblotting.TEM demonstrated that GRACILE and control fibroblasts had similar numbers and structure of mitochondria.

Results: IEM showed that despite decreased amount of BCS1L in patient fibroblasts, Core I was present in CIII in similar amounts as in controls. In Blue Native PAGE, all respiratory chain complexes were present in similar amount as in controls. RISP incorporation into CIII was normal in GRACILE fibroblasts.

Conclusions: GRACILE fibroblasts contain normal numbers of viable mitochondria with decreased BCS1L amount that may reflect a shorter half life of mutated BCS1L. RISP subunit incorporation into CIII was unaffected in patient fibroblasts, suggesting tissue specific variations in respiratory chain complexes.

Single-center versus population-based outcome data of extremely preterm infants at the limits of viability

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Introduction: Counselling parents requires recent data on mortality and long-term morbidity, but published reports utilize diverse formats and are rarely based on GA. A notable exception is the population-based EPICure study. We wanted to compare outcome of preterm infants in the AAP grey zone (GA $\geqslant$ 23 and $<$ 25 weeks) cared for in a single tertiary care center 2000-2004 in Essen, Germany, to those of the population-based EPICure study.

Methods: Tools and definitions of the EPICure study.

Results: 39/45 live-born infants with a GA $\geqslant$ 23 and $<$ 25 weeks were admitted to intensive care (87%), as opposed to 69% (429/623) in the EPICure study ($p = 0.012$), and 59% (23/35) survived, as opposed to 29% (126/429) in EPICure ($p < 0.001$). More infants survived without severe disability than in the EPICure study (38%, 17/45 vs. 14%, 90/623, $p < 0.001$) while the percentage of all liveborn infants who survived without overall disability was similar (13%, 6/45 vs. 9%, 56/623, $p = 0.294$).

Conclusions: The more proactive approach in the single tertiary center may have increased survival and survival without severe disability but not survival without disability.

Posttraumatic stress disorder (PTSD) symptoms among mothers of VLBW infants

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Introduction: Little is known about PTSD symptoms among mothers of VLBW infants and the associated factors. We therefore valuated the mothers' PTSD symptoms to determine how these symptoms were related to mother and infant characteristics, mothers' interaction with their infant and infant cognitive development.

Methods: Data were collected on mothers' PTSD symptoms when the infants (BW $<$ 1500 g) were 6 months corrected age. Maternal posttraumatic stress was assessed with the *Perinatal PTSD Questionnaire* (*PPQ*). Mother-infant interaction was assessed with the *Emotional Availability Scales.* The *Revised Nursery Neurobiological Risk Score* was used for illness severity and the *Bayley Scales for Infant Development.*

Results: Mothers' mean PPQ score was 3.9 (SD = 3.3), 25% of mothers had scores in the abnormal range (i.e., above 6). Mothers with higher PPQ scores had infants with lower BW ($r = 0.67$), were born more premature ($r = 0.68$), experienced more medical complications ($r = 0.55$), were hospitalized longer ($r = 0.73$) and spent more days on oxygen ($r = 0.62$). Mothers who had more PTSD symptoms at 6 months were less sensitive ($r = -0.50$) and less effective at structuring interactions ($r = 0.49$) with their infants. Maternal PTSD symptoms were not related to Bayley scores.

Conclusions: Mothers of infants with neonatal complications are at greater risk for developing PTSD, which may adversely affect mother-infant relationship.

Neurodevelopmental outcome after intrauterine red cell transfusion for severe fetal anemia and fetal hydrops

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Introduction: To evaluate neurodevelopmental outcome after intrauterine transfusion for severe fetal anemia due to fetal hemolytic disease or Parvovirus B19 infection.

Methods: 20 children after severe Rhesus hemolytic disease (fetal hemoglobin 1.4–6.0 g/dl) and 20 children after fetal Parvovirus B19 infection (fetal hemoglobin 2.2–8.5 g/dl) and fetal hydrops were investigated at a median age of 47 months and 52 months respectively. In addition to physical and neurological examination, age-appropriated developmental tests were used (Griffiths Scales, Kaufman-ABC and Snijders-Oomen Non-Verbal Intelligence Test).

Results: Children after Rhesus hemolytic disease had a median intelligence quotient (IQ) of 101 (67–130), two children having persistent neurological sequelae. All children in the Parvovirus group were neurologically normal with a median IQ of 101 (86–116).

Conclusions: Though intrauterine treatment was started in fetuses with severe anemia or hydrops, a successful transfusion therapy lead to normal development till early childhood in 38/40 children.

Popular culture in mediterranean countries: What about children care and the over natural protection

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Introduction: Some popular beliefs on birth, marriage, pregnancy, childbearing, and death are commonly applied to most components of everyday life. The beliefs, despite their differences due to religious thought, have many connections in many Mediterranean countries. In all of those the child's wellbeing needs over natural support. Parents must protect her offspring

against any harmful influence. To discover how the popular culture can "protect" newborns and infants from the risk of life, beyond the medical care.

Methods: Authors have independently studied 5368 newborn infants, in order to document events of newborn protection by popular and religious objects.

Results: 57 "pictorial" proofs concerning "protective" popular and/or religious objects to the newborns were documented.

*Conclusion*s: In our multiethnical and multiracial world we should be aware of and respectful for religious or parental thoughts.

Emea, the european initiative on drugs and the neonatologist

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The use of medicines in pediatrics, especially in the NICU remains as a rule "off-label" or unlicensed: most drugs prescribed by neonatologists (up to 90%) have no specific indication for this age group. This attitude is not without risk: unknown adverse events, poorly established efficacy, hazardous dose calculation and inappropriate formulation. In the USA (1998) and recently in Europe (2006) efforts have been undertaken to offer safer drugs to children. The Regulation 1901/2006 stipulates that for new drugs, industry has to develop in parallel with their adult medicine program, a program called pediatric investigation or development plan (PIP). This PIP is a full pediatric program to be elaborated as soon as the drug enter Phase II. The underlying question in this PIP include: is this potential new drug of any interest for children in any similar or nearby indication? The decision to start investigation in the different age groups remains a case by case decision. This regulation has major implications as new potentially beneficial drugs in newborns need among others, an appropriate formulation, juvenile toxicity studies in appropriate animal species and phase II and III clinical studies. A Paediatric Committee composed by 1 representative per member state evaluates and amend the proposed PIP. More than 320 PIP's have been evaluated in the first year.