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October 10th-14th, 2013 - Porto, Portugal

Abstract Book

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Oral Presentations

EXPRESSION AND LOCALIZATION OF AQUAPORIN 1 AND 5 IN THE CHOROID PLEXUS FOLLOWING PRETERM INTRAVENTRICULAR HAEMORRHAGE.

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Introduction: Intraventricular haemorrhage (IVH) is the most common cause of severe neurodevelopmental outcome in preterm infants. 50% of surviving infants develop post-haemorrhagic ventricular dilatation (PHVD) often requiring lifelong ventriculo-peritoneal shunt. The mechanisms leading to hydrocephalus following IVH are unknown but dysfunction of cerebrospinal fluid (CSF) production by the choroid plexus seems to be a major contributing factor. The aquaporins (AQP) are transmural water transporting proteins which main function is to facilitate water movement across cell membranes. AQP1 is located on the apical membrane of the choroid plexus epithelium and has been implicated as a major contributor to CSF production. AQP5 has not been described in the choroid plexus but it has been described in other organs in the body with secretory functions e.g. lacrimal glands and lung.
Objectives: To characterize the expression and localization of AQP1 and 5 in the choroid plexus following IVH.
Methods: Using a rabbit pup model, the choroid plexus was investigated for mRNA expression and protein levels of AQPs 1 and 5 at 24 and 72 hours following IVH. Furthermore, the subcellular localization of AQP 1 and 5 was examined by electron microscopy (EM) at 72 hours.
Result: Following IVH, mRNA and protein levels of AQP1 were decreased at both 24 and 72h. mRNA expression of AQP5 was increased at corresponding time points (all $p<0.05$)whereas protein levels of AQP5 were decreased at 24 hours but increased at 72 hours. EM staining of AQP5 revealed an increased localisation at the apical surface of the epithelial cells as well as cell membrane budding containing AQP5 following IVH.
Conclusions: IVH in the immature brain and the ensuing hydrocephalus causes a down-regulation of AQP1, the key aquaporin in CSF production. Interestingly, AQP5 is expressed in the choroid plexus and following IVH there is an up-regulation and epithelial cell relocalisation. AQP5 has to our knowledge not previously been described in the choroid plexus and its function and importance has yet to be elucidated. The changes observed in AQP1 and AQP5 expression suggest an adaptive and possibly protective response to the haemorrhagic insult. Further understanding of the molecular basis of hydrocephalus development following IVH is of utmost importance and might provide the key to future targeted therapeutic interventions.

AGONIST-INDUCED NEUROGENESIS RESTORATION AND COGNITIVE IMPROVEMENT IN A MODEL OF CHOLINERGIC DENERVATION

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Background: The increasing survival of ELGA infants is associated with significant neurodevelopmental sequelae. Learning, cognitive and attention deficits are the most common developmental problems in this population. Several studies support the hypothesis that changes in the activity of the forebrain cholinergic system can influence learning, memory and attention. Acetylcholine is involved in brain development and modulation of neurogenesis. Cholinergic neurons in the basal forebrain provide a major source of innervation to the cortical mantle, olfactory bulb, hippocampus and amygdala and may play a prominent role in the mnemonic processing. The restoration of basal forebrain neuroprojections may revert attention and cognitive deficits. Objective: To determine the ability of a muscarinic agonist to trigger neurogenesis and ameliorate cognition deficits after cholinergic damage in a rodent model.
Design/Methods: Selective basal cholinergic lesion was created by cerebroventricular injection of immunotoxin 192IgG saporin in adult female Sprague-Dawley rats. Following the lesion, oxotremorine (OXO), a cholinergic agonist, or saline were infused via an osmotic pump into the left ventricle for 8 weeks. BrdU was administered during the first 2 weeks of treatment. Upon completion of treatment, animals received Fluoro Gold (FG) injection into the CA1 hippocampal region and euthanized one week later. We performed immunohistochemistry for BrdU and different neural markers. Spatial working and reference memory were assessed using an 8 arm radial arm maze.
Result: Severe cholinergic loss and decreased numbers of FG positive cells occur in basal forebrain of lesioned rats. The area devoid of FG labeled neurons was significantly reduced in OXO treated rats. A significantly increased numbers of BrdU positive cells are still apparent in the dentate gyrus following 8 weeks of treatment, indicating their continued survival and suggesting their functional integration. Behavioral studies suggest an improvement in learning and memory in the oxotremorin treated animals.
Conclusions: Administration of an agonist resulted in restoration or preservation of basal forebrain cells projecting to the hippocampus and improved outcome in animals after cholinergic basal forebrain injury. Therapeutic interventions targeting cholinergic systems may enhance plasticity and improve functional recovery and outcome.

MSC-DERIVED EXOSOMES: IMMUNOMODULATORY AND NEUROPROTECTIVE EFFECTS ON INFLAMMATION-INDUCED PRETERM BRAIN INJURY

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Background: Preterm brain injury is a main cause of disability such as cerebral palsy and cognitive disorders. The pathomechanism is considered as multi-factorial and inflammation seems to be mainly involved in the development of brain damage. To date there is no causal therapy. Mesenchymal stem cells (MSCs) show immunomodulatory and neuroprotective features in different experimental settings. Although intravenously administered MSCs mainly get trapped into the lung, therapeutic effects in target tissues are detectable, thereby indicating paracrine mechanisms. A possible mechanism is that these paracrine effects are mediated by exosomes. The aim of this study is to evaluate the immunomodulatory capacity of MSC-derived exosomes on preterm brain damage caused by inflammation.
Methods: Wistar rats were randomized in 4 groups (vehicle/vehicle, vehicle/exosomes, LPS/vehicle, LPS/exosomes). LPS (0,25mg/kg) was administered at P3, exosomes at P3 and P4. At P5 and P11, animals were transcardially perfused, brains were removed and snap-frozen for molecularbiological and immunohistochemical analysis.
Result: At P5 Western blot analyses revealed a significant increase in apoptosis in the LPS-treated animals, whereas additional treatment with exosomes resulted in a significant decrease in apoptosis. At histology level data showed alterations between the LPS treated animals and the animals, who received LPS and exosomes detected with TUNEL staining. At P11 Western blot analyses revealed a significant increased MBP expression as a keyprotein for myelination in the LPS/exosomes treated animal group compared to animals treated solely with LPS.

Conclusions: MSC-derived exosomes showed beneficial effects in an experimental animal model of inflammation-induced brain damage.

INTERACTION OF INFLAMMATION AND HYPEROXIA IN A RAT MODEL OF NEONATAL WHITE MATTER DAMAGE

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Background: Intrauterine infection and inflammation are major reasons for preterm birth. The switch from placenta-mediated to lung-mediated oxygen supply during birth is associated with a sudden rise of tissue oxygen tension that in preterm infants amounts to relative hyperoxia. Both, infection/ inflammation and hyperoxia have been shown to be involved in brain injury of preterm infants. Hypothesizing that they might be additive or synergistic, we investigated the influence of a systemic lipopolysaccharide (LPS) application on hyperoxia-induced white matter damage (WMD) in newborn rats.
Methods: Three-day-old Wistar rat pups received 0.25 mg/kg LPS i.p. and were subjected to 80 % oxygen on P6 for 24 h. The extent of WMD was assessed by immunohistochemistry and western blots. In addition, the effects of LPS and hyperoxia were studied in an in vitro co-culture system of primary rat oligodendrocytes and microglia cells.
Summary: Both noxious stimuli, hyperoxia and LPS, caused hypomyelination as revealed by western blot and immunohistochemistry. Even so, cellular changes resulting in hypomyelination seem to be different. While hyperoxia induces cell death, LPS induces oligodendrocyte maturity arrest without cell death as revealed by TUNEL-staining and immunohistological maturation analysis. In the two-hit scenario cell death is reduced compared with hyperoxia treated animals nevertheless white matter alterations persist. Concordantly with these in vivo findings we demonstrate that LPS pre-incubation reduced premyelinating-oligodendrocyte susceptibility towards hyperoxia in vitro. This protective effect might be caused by upregulation of interleukin-10 and superoxide dismutase expression after LPS stimulation.

Conclusions: The knowledge about mechanisms that trigger hypomyelination, especially the interaction among different injurious stimuli such as inflammation and hyperoxia, might contribute to a better understanding of WMD in premature born infants.

DOCOSAHEXANOIC ACID (DHA) ATTENUATES CASPASE-3 ACTIVITY AFTER HYPOXIA-REOXYGENATION AND MAY HAVE NEUROPROTECTIVE PROPERTIES. A STUDY IN NEWBORN PIGLETS.

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Background: Perinatal hypoxic-ischemic brain damage is a major cause of acute mortality and chronic neurologic morbidity in infants and children. Docosahexanoic acid (DHA) is a major component of brain membrane phospholipids and accumulates during late pregnancy. DHA has a role in neuroprotection after hypoxia and ischemia by regulating multiple molecular pathways and gene expression. Objective: DHA may attenuate hypoxia-ischemia induced caspase-3 activity and offer neuroprotection through DHA involvement in induction of anti-apoptotic activities. We wanted to measure activated caspase-3 in brain- and liver tissue.
Methods: Global hypoxia was induced in newborn piglets (age 12-36h) until Base Excess -20 mmol/L or mean arterial blood pressure <20 mmHg. CO2 was added during hypoxemia, aiming at a PaCO2 of 8.0-9.5 kPa to imitate perinatal asphyxia. One group (n=11) was resuscitated with ambient air (21% group, n=11) and another received in addition DHA 5mg/kg 4 hours after start of resuscitation (21% DHA group, n=10). Throughout the whole experiment, there was a continuous surveillance of blood pressure, SaO2, heart rate, temperature and blood gas measurement. The piglets were followed for 9.5 hours after end of hypoxia. Then tissues from prefrontal cortex, hippocampus and liver were snap frozen in liquid nitrogen and stored by -700 C until analysis. The tissue samples were homogenized and the protein extracted. A Quantikine® KM 300 immunoassay was used to measure activated caspase-3.
Result: DHA given 4 hours after resuscitation achieved lower caspase-3 activity. In liver tissue caspase-3 activity (ng/mg protein) in piglets receiving DHA was 1.03 SEM (0.15) vs. 1.87 (0.15) in the 21% group, $p<0.001$; in hippocampus 0.023 (0.01) vs. 0.060 (0.02), $p<0.05$ and in cortex 0.030 (0.01) vs. 0.068 (0.02), $p=0.061$ There was no difference in heart rate, pCO2, pO2, BE, temperature, pH, and lactate between the two groups. Within each group, the females had higher Hb (1-2g/100ml), but that did not influence on the recovery of lactate, BE and pH after hypoxia. At the end of hypoxia pCO2 correlated with lactate ($r=0.7$, $p=0.001$) and pH ($r=-0.7$, $p=0.001$) but not with MABP and time of hypoxia.
Conclusions: DHA attenuates caspase-3 activity and may promote neuroprotection in a neonatal hypoxia ischemia piglet model. The females had higher Hb (1-2g/100ml), but that did not influence on the recovery of lactate, BE and pH after hypoxia. At the end of hypoxia pCO2 correlated with lactate ($r=0.7$, $p=0.001$) and pH ($r=-0.7$, $p=0.001$) but not with MABP and hypoxiatime.
Conclusions: DHA attenuates caspase-3 activity and may promote neuroprotection in a neonatal hypoxia-ischemia piglet model.

INVOLVEMENT OF AUTOPHAGY IN HYPOXIC-EXCITOTOXIC NEURONAL CELL DEATH

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Background: Macroautophagy or autophagy, a physiological process consisting in the sequestration of organelles and proteins in double-membrane vesicles (autophagosomes) followed by their fusion with lysosomes for degradation (autolysosomes), can be enhanced under some stress conditions and involved in cell death. We previously demonstrated that autophagy is strongly increased in rat models of neonatal cerebral hypoxia/ischemia and suggested that autophagy may be an important mediator in neuronal death.
Methods: Since excitotoxicity is the main death mechanism in neonatal cerebral hypoxia/ischemia and to clarify the role of autophagy we set up an in vitro model combining hypoxia (H, 6%O2) and excitotoxicity (kainate (Ka), 30µM) in primary cortical neuron cultures. Analyzes were done using Western blot, immunocytochemistry and cell death assays. Lentiviral vectors delivering shRNA against autophagy-related genes (Atg) or overexpressing Atg were used to assess the role of autophagy.
Result: Thirty minutes of H/Ka treatment strongly and rapidly induced neuronal death as demonstrated by increased propidium iodide (PI) staining. This severe neuronal death was calcium dependent and mediated by NMDA receptors since it was completely prevented by MK801 and EGTA. Interestingly H/Ka treatment induced an enhancement in autophagic flux as shown by an increase in 1) the autophagosome marker LC3-II, 2) the degradation of p62 (a protein specifically degraded by autophagy), 3) the autophagosome-lysosome fusion as shown using an RFP-GFP-LC3 plasmid and 4) LC3-II levels upon lysosomal degradation inhibitors such as pepstatinA/E64. We then evaluated the role of enhanced autophagy by applying both pharmacological autophagy inhibitors (3-methyladenine (3-MA) or pepstatinA/E64) and lentiviral vectors delivering shRNAs Beclin1 (mammalian homologue of Atg6) and Atg7. Both pharmacological inhibitors and lentivirals vectors delivering shRNA against Beclin1 and Atg7 were shown to reduce neuronal death as shown by decrease in PI staining. Complementary experiments using lentiviral vectors overexpressing Atg6 and Atg7 showed enhanced autophagy and sensitization to H/Ka-induced neuronal death. We then revealed that in vivo inhibition of autophagy by intrastriatal injection of lentiviral vectors delivering shRNA against Beclin-1 reduced the striatal lesion in a rat model of neonatal cerebral hypoxia-ischemia.
Conclusions: All together these results demonstrated that H/Ka treatment enhanced autophagy and that autophagy is involved in H/Ka-induced neuronal death. By giving fundamental understanding on the role of autophagy in both in vitro and in vivo models of hypoxic-excitotoxic neuronal death, this study suggests that autophagy inhibition should be considered as a neuroprotective strategy to reduce neuronal damage following neonatal hypoxia/ischemia. Supported by a grant of the Swiss National Science Foundation.

ASTROCYTE-NEURON INTERACTIONS AND DE NOVO SYNTHESIS OF GLUTAMINE AND GLUTAMATE IN THE REPERFUSION PHASE AFTER NEONATAL HYPOXIC-ISCHEMIC BRAIN INJURY.

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Background: In the adult brain, ischemia disturbs metabolic interactions between neurons and astrocytes and reduces de novo synthesis (anaplerosis) of glutamine, glutamate and GABA. Pyruvate carboxylase (PC), the main anaplerotic enzyme in the brain, is predominantly located in astrocytes. In the neonatal brain, amounts of glutamate are much lower than in the adult brain. Consequently, the neurons rely on pyruvate carboxylation in astrocytes to build up to adult levels of glutamate. In the present study we explored glucose metabolism, the glutamate-glutamine cycle and pyruvate carboxylation in the neonatal brain after hypoxic-ischemic brain injury (HI).
Methods: HI was induced in 7-day-old rats by unilateral severing of the carotid artery and subsequent exposure to hypoxia (8%O2) for 90 minutes. Animals were injected with [1 13C]glucose and [1,2 13C]acetate directly after end of hypoxia or with [1,2 13C]glucose 30 minutes later. Simultaneous injection of [13C]labelled glucose, which is, at the acetyl CoA stage, metabolised in neurons to a larger extent than in astrocytes, and [13C]labelled acetate which probes astrocyte metabolism, makes it possible to study the metabolic interactions between neurons and astrocytes. [1,2 13C]glucose allows for simultaneous investigation of pyruvate metabolism via PC and Pyruvate Dehydrogenase (PDH). Extracts of the ipsilateral hemispheres from animals subjected to HI and sham animals were analysed with 1H- and 13C Nuclear Magnetic Resonance Spectroscopy and High Performance Liquid Chromatography.
Result: 13C labelling from glucose and amounts of lactate and alanine were increased after HI. In contrast, amounts of glutamate, glutamine and aspartate were reduced along with labelling from [13C]glucose via PC and PDH. Also, labelling of glutamate and glutamine from [1,2-13C]acetate was reduced. There was no quantifiable PC related labelling in GABA in HI or control animals. In glutamate, labelling via PDH was more reduced than via PC. Moreover, the ratio of [1,2-13C]acetate label incorporation in glutamate over per cent 13C enrichment in glutamine, indicating transfer from astrocytes to neurons, was preserved after HI.
Conclusions: Mitochondrial pyruvate metabolism from glucose via PDH was reduced in both astrocytes and neurons in HI. Moreover, anaplerosis in astrocytes was impaired. However, the combination of PC related 13C labelling in glutamate and the maintained transfer of glutamine from astrocytes to neurons may indicate that astrocytes continue to provide metabolic support for the neurons during the early reperfusion phase in the neonatal brain.

DOES PASSIVE COOLING WORK?-A RETROSPECTIVE COHORT STUDY OF NEONATES COOLED DURING NEONATAL TRANSPORT FOR NEONATAL ENCEPHALOPATHY

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Background: Therapeutic hypothermia is a time critical intervention needing to be started within 6 hours of birth. Neonates born outside cooling centres are passively cooled and transported to a regional cooling centre. 12/21 transport teams in the UK use passive cooling to achieve neuro-therapeutic temperatures of 33-34C. The question is how efficacious is passive cooling in neonatal transport? The CenTre transport team covers the Trent Perinatal and Central Newborn Networks in the United Kingdom. This study was performed to assess the efficacy of passive cooling by a transport team experienced in using the TOBY passive cooling guideline.
Methods: A retrospective study analysed data of a cohort of neonates using of all cooling transfers in the CenTre catchment over a 14 months period in 2011-12. A record was made of temperatures of the baby at referral, arrival at the referring centre and arrival at the cooling centre. In addition referral times, stabilisation times and transfer times were also recorded. Statistical analysis was performed to analyse if babies cooled down significantly during the process. For the cohort of neonates achieving a neuro-therapeutic temperature factors critical to its achievement were analysed.
Result: Data on 55 infants revealed, median (range) birth-weight 3.3kg (1.9-5.4) and median (range) gestation 40 weeks (346-42). The time from birth to referral was median (range) 144 minutes (82-219), stabilisation time was median (range) 121 minutes (32-400) and age of baby at arrival at the cooling centre was median (range) 496 minutes (250-883). On arrival at the cooling centre 62% of neonates =34C, 16% had a temperature <33C and one <32C. Only 53% of neonates had a temperature =34C at 6 hours of age. Infants referred within 2 hours of birth were more likely to reach a cooling centre within 6 hours from birth (36% vs 7.5%; p=0.016 Fisher exact test). 50% of neonates referred within 2 hours reached a cooling centre within the network with a temperature = 34C within 6 hours as compared to none referred after 2 hours (p=0.02). Infants arriving with temperature =34C had been stabilised for longer (Median 143 vs 97min p=0.02). Of neonates stabilised for 2 hours or more 62% moved from being outside to inside therapeutic range, or remained between 33-34C, as compared to 21% stabilised for less than 2 hours (p=0.036).
Discussion: This study demonstrates a statistically significant drop in temperature at every stage from referral to arrival at a regional cooling centre. Only 53% of neonates were neuro-therapeutic at 6 hours of age. Longer stabilising times are associated with increased rate of achieving therapeutic temperatures. Infants referred earlier were more likely to arrive at a cooling centre within 6 hours with a therapeutic temperature.
Conclusion: This is the largest and only study to date demonstrating the effectiveness of passive cooling at each stage of the transfer. Passive cooling before and during transport is successful in achieving satisfactory temperatures in many but not all cases. The importance of early referral in improved thermal and neurological outcomes may be key during the transport process.

NEURODEVELOPMENTAL PREDICTORS OF SPECIFIC MATHEMATIC ABILITIES IN NEONATAL AT-RISK CHILDREN AT 8;5 YEARS

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Introduction/Background: Impairments in mathematic skills in neonatal at-risk children are specific and not explained by global deficits in cognitive function. The aim is to investigate the relations between early neurodevelopmental predictors and specific mathematic abilities in middle childhood.
Patients and Methods: 947 children ranging from 23 to 41 weeks gestational age (GA) were studied from birth to 8;5 years as part of a prospective geographically defined longitudinal investigation of neonatal at-risk children in South Germany (Bavarian Longitudinal Study). In addition to GA, infant neonatal risk was assessed via a comprehensive postnatal optimality index including 21 items (e.g. intubation, severe anaemia, cerebral haemorrhage), as well as duration of ventilation and initial hospitalization. At 20 months of corrected age, children's cognitive development was measured with the Griffiths Scales. At age 6;3 years, attention regulation abilities and motor impairment were assessed by paediatricians and psychologists. At 8;5 years, children's cognitive and mathematic abilities were measured with the K-ABC MPC score and with a standardized mathematics test including estimation, reasoning, arithmetic, and mental rotation abilities.
Results: Residuals of a linear regression predicting children's math test scores by IQ (K-ABC MPC score) at 8;5 years were used to identify specific mathematic abilities that are independent of general IQ. The relationship between GA and these specific math abilities was curvilinear with a turning point at around 33 weeks of gestation where the impact of one lost week of gestation had a highly increased adverse impact. Multivariate linear regressions showed that infant neonatal risk variables were the only significant predictors of specific math abilities at 8;5 years after statistically controlling for child sex and parents' SES, early cognitive development, attention regulation, and motor impairment. Subgroup analyses revealed that the variance explained (R^2) in specific math abilities by infant neonatal risk increased with decreasing GA from 1% in healthy full term children to 10% in very preterm children.
Conclusion: Neonatal at-risk children's impairments in specific mathematic abilities increase exponentially with decreasing GA. Children with specific mathematic impairments that are independent of general IQ are a special group characterized by severe neonatal risk and low developmental plasticity. These findings have implications for routine cognitive follow-up and research into brain reorganization after preterm birth.

RANDOMIZED CONTROLLED TRIAL TO ASSESS THE EARLY USE OF EXOGENOUS SURFACTANT IN COMBINATION WITH INHALED NITRIC OXIDE IN THE TREATMENT OF NEWBORNS WITH HYPOXEMIC RESPIRATORY FAILURE

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Background: Hypoxemic respiratory failure (HRF) is a leading cause of neonatal morbidity and mortality among term and near term infants. Few studies have evaluated surfactant therapy in these patients with conflicting results. Objective: To evaluate whether early use of exogenous surfactant in combination with inhaled nitric oxide (iNO) will prevent newborns with moderate hypoxemic respiratory failure from developing severe HRF [Oxygenation Index (OI) = 40]. Design/
Methods: We conducted a randomized double-blind, placebo-controlled trial that enrolled term and near-term (> or= 35 weeks gestational age) newborns with acute HRF (OI>20) excluding lung hypoplasia, admitted to 5 level III NICUs before 72 hours after birth. Infants were randomized to two groups: Surfactant-iNO group: received treatment with 20 parts per million (ppm) of iNO with up to 2 doses of 100 mg/kg of exogenous surfactant (Curosurf) or Control Group: received treatment with 20 ppm of iNO + placebo (air) and standard intensive care, which in both groups included high frequency or conventional mechanical ventilation, inotropic support and sedation. Infants in both groups received open-label surfactant if they developed an OI>40 within the first 48 hrs of study. ECMO was considered in patients with a persistent OI>40.
Result: 96 infants were included. Mean ± SD birthweight was 3473 ± 545 g and gestational age 39 ± 1.6 weeks. Demographic and clinical characteristics including diagnoses and severity of their initial respiratory diseases were similar among infants of both groups at randomization time. Infants receiving early surfactant + iNO improved their oxygenation faster resulting in a significant lower proportion of infants developing an OI >40: 23% (11/47) compared to 49% (24/49) of the control group, $p<0.02$. ECMO therapy was used in 6 infants (13%) of the surfactant-iNO group and in 11(22%) of the control group (NS). One infant (2%) of the surfactant group died compared to 7(14%) of the control group, $p= 0.06$. Fewer infants of the surfactant-iNO group presented with the combined adverse outcome death or need of ECMO: 15% (7/47) compared to 35% (17/49) of the control group, $p<0.05$.
Conclusions: Early use of surfactant in combination with iNO in infants with HRF improves oxygenation preventing the progression to severe hypoxemic respiratory failure. This may reduce mortality and the need of ECMO therapy.

USE OF INHALED NITRIC OXIDE FOR HYPOXAEMIC RESPIRATORY FAILURE: A FIVE-YEAR STUDY

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Introduction/Background: Inhaled nitric oxide (iNO) is a licensed treatment in term and near-term infants with hypoxaemic respiratory failure with PPHN, but its use in preterm babies < 34 weeks' gestation is unlicensed (‘off-label'). The aim of this study was to describe the use of iNO in our institution, one of the largest neonatal intensive care units (NICUs) in the UK.
Patients and Methods: We retrospectively reviewed data on all babies treated with iNO over a five-year period (2008-2012). Demographic and clinical information was obtained from local records and data submitted to the European Inhaled Nitric Oxide Registry.
Results: 128 babies received iNO during the study period. Of these babies, 83/128 (65%) were preterm and 45/128 (35%) were near term and term. There were 72 (56%) male and 56 (44%) female infants. 45/128 (35%) babies died and 3/128 babies received ECMO. 20/83 (24%) of preterm and 10/46 (22%) of near term and term babies developed chronic lung disease. RDS was the most common diagnosis in preterm babies and meconium aspiration in the term and near term babies. The median (IQR) baseline oxygenation index (OI) was 33 (20-50) in term and near-term babies and 38 (21-54) in preterm babies (p= 0.71). A short-term response (OI decrease of > 10% within an hour of commencing iNO) was observed in 44% of babies overall. Short-term response was a significant predictor of survival in babies in the term and near term babies but not in less mature babies. Responders were more likely to have a diagnosis of surfactant deficient lung disease. There was no significant difference in responders in any of the other diagnostic groups. Survival was associated with higher gestational age and birth weight but also a higher baseline OI. Within each diagnostic group, a higher proportion of babies with a diagnosis of meconium aspiration or pulmonary hypoplasia survived. A higher proportion of those with a diagnosis of RDS or congenital diaphragmatic hernia died. There was no significant association between starting, maintenance or maximum dose and short or long term outcome.
Conclusions: Off-label, unlicensed use of iNO is common in preterm infants. Short-term response is a useful predictor of survival, but only in term and near-term babies.

USING INHALED NITRIC OXIDE IN PRETERM INFANTS - DOES IT MATTER?

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Introduction: The efficacy of inhaled nitric oxide (iNO) for the treatment of persistent pulmonary hypertension of the newborn in term babies is well established. However evidence to support its use in preterm babies is less robust. Aim: To assess the clinical outcomes in preterm babies treated with iNO at a tertiary NICU.
Patients and Methods: 25 preterm babies (defined as less than 37 weeks gestation) who received iNO during their admission were identified from the NICU nitric oxide database from 01/01/06 to 28/02/13 (7 years and 2 months) at University Hospital, Coventry. The hospital notes and electronic records of these babies were hand searched to identify the requirement of cardio-respiratory support, details of ECHO scans, antenatal scans, survival and morbidity including: chronic lung disease, home oxygen requirement, grade 3 or 4 IVH, NEC, PVL and long term neurological morbidities.
Result: The mean gestational age was 29+6 (range 23+1 to 36+5) with a birth weight of 1346g (range 474 to 2980). Seven babies had intrauterine growth restriction (defined as having a birth weight lower than the 10th centile for gestational age). 13 out of 25 (52%) babies died prior to discharge. Thirteen babies had oligohydramnios, 11 pregnancies were associated with PPROM and 19 babies were delivered via caesarean section. The mean 1 and 5 minute APGAR scores respectively were 5 (range 1 to 9) and 7 (range 3 to 9). No babies required chest compressions or drugs during resuscitation. The mean days of ventilation was 18 (range 1 to 72), CPAP was 15 (range 0 to 81) and oxygen requirement was 35 (range 1 to 166). iNO was administered for a mean of 4 days (range 1 to 21) at a mean dose of 23ppm (range 5 to 40). Eight babies developed one or more pneumothorax, 4 needed needle aspiration, all 8 needed insertion of a chest drain. 24 babies required surfactant. Pulmonary haemorrhage was diagnosed in 1 baby. Nine babies had CLD and 5 babies needed home oxygen. 23 babies required inotropic support. On echocardiography 11 babies had abnormalities ranging from PFO with right to left shunt or significant tricuspid regurgitation jet velocity suggestive of pulmonary hypertension, structural anomalies and valvular dysfunction. Two babies had grade 3 or 4 IVH, 2 had PVL and 6 babies had suspected or confirmed NEC, 2 of which required surgical intervention. Four babies had delayed development (including Cerebral palsy, learning difficulty, speech delay, hearing or visual impairment).
Conclusions: Preterm babies requiring treatment with iNO have high mortality and significant short term morbidity. 4/25 (16%) in our cohort had long term neurodevelopmental morbidities.

BRONCHOPULMONARY DYSPLASIA AND PULMONARY HYPERTENSION IN PRETERM INFANTS: A NEW THERAPEUTIC APPROACH.

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Background: Bronchopulmonary dysplasia (BPD) is a chronic lung disease due to immaturity, barotrauma and oxygen toxicity, developing in premature infants that requires treatment with oxygen and/or positive pressure ventilation. Its incidence may rise 47% in newborns aged<30 weeks (wks). Pulmonary hypertension (PH) can complicate a BPD and contributes to late morbidity and mortality. Different therapeutic strategies have been adopted to prevent the consequences of severe PH, especially nitric oxide (NO). Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, has been lately introduced in the treatment of BPD associated with PH. Long term treatment with sildenafil has been related to an improvement of the pulmonary hemodynamic but it seems to have no effects on gas exchanges. That being so the small number of data on the use of sildenafil in neonates, we report our experience, focusing on the demographic characteristics of our patients.
Patients And Methods: We considered 12 consecutive newborns who had presented severe respiratory distress syndrome (RDS) evolved in BPD (gestational age (GA) =30wks, weighing<1500 grams) and who were followed in our Pediatric Cardiology Unit from 2009 to 2012.
Results: All the newborns had a GA =30wks (mean 26,8 ±1,9 wks) and weight<1500 g (mean 856 ±286 g). Eleven on 12 (92%) were born from Caesarean, 11 on 12 (92%) had received antenatal steroids. All the infants had severe RDS and received invasive mechanical ventilation. The mean FiO2 value was 45% for average time of 10 ±8 days, then it was gradually lowered to 21% according to the clinical and laboratoristic conditions of the infants. Two newborns (17%) received High Frequency Oscillatory Ventilation (HFOV). The average duration of the ventilation was of 48 ±27 days, the average timing of the hospitalization was of 126 ±57 days. All the 12 infants developed a late onset PH with average right ventricular pressure of 43 mmHg (±15) and received hydrochlorothiazide, sprironolactone and furosemide according to the prevention and treatment protocol of the BPD. The 6 patients with higher right ventricular pressure values, two of whom had previously received NO therapy with only partial benefit, were treated with oral sildenafil at a starting dosage of 0,5 mg/kg to a maximum of 2 mg/kg/dose every 6-8 hours. Sildenafil was started at 58 ±18 days of life and was continued on average for 190 ±135 days. All these 6 infants showed significant lowering of right ventricular pressure (mean value pre-treatment: 56±9 mmHg,; mean value post-treatment 25±4 mmHg; mean ? pressure=32±10 mmHg; p=<0,001). We didn't observe any adverse side effect. A patient who had not received either sildenafil or antenatal steroids died at the age of two years. Eight infants on 12 (67%) needed oxygen home care. Of these 5 patients had received sildenafil and 3 had not received it.
Conclusion: In our series the sildenafil therapy showed a complete efficacy and tolerability so that we consider it as a part of treatment program of lung disease with PH in preterm infants. Our short experience needs further data to confirm the usefulness of this drug in newborns.

ADRENOMEDULLIN DECREASES PROLIFERATION AND APOPTOSIS OF CULTURED HUMAN FETAL PULMONARY ARTERY SMOOTH MUSCLE CELLS

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Background and hypothesis: Adrenomedullin (AM) is a potent vasodilator produced by the endothelial and smooth muscle cells of the systemic and pulmonary vasculature that has shown vascular protective effects. Besides causing endothelium-dependent vasodilation; it may also decrease proliferation and migration of vascular smooth muscle cells and improve the vascular remodeling seen in diseases such as pulmonary hypertension. Little is known about the role of AM in fetal lung vascular development; in the normal fetus, the pulmonary arterial pressures are elevated due to low PaO2 and high levels of vasoconstrictors such as endothelin-1 (ET-1). We hypothesize that AM plays a regulatory role in the development of the human fetal pulmonary vasculature partly by modulating the proliferation and apoptosis of fetal PASMC and we propose to study the effects of AM in vitro by treating fetal pulmonary artery smooth muscle cells (PASMC) cultured in standard conditions and by using ET-1 to promote proliferation and decrease apoptosis.
Methods: Fetal PASMC were isolated from the right pulmonary artery of 18 weeks of gestational age fetus and were identified based on their immunoreactivity against smooth muscle-myosin heavy chain (SM-MHC) antibody. The cells were cultured in Dulbecco's modified eagle media (DMEN) + 10% fetal bovine serum (FBS) and in serum free conditions up to third passage. The cells were treated for 48 h with 100 nM ET-1, 100 nM AM and 100 nM ET-1 + AM. After treatment or vehicle, proliferation was measured by using a commercially available assay (Promega Cell Titer 96® AQueous Non-Radioactive Cell Proliferation Assay). Apoptosis was detected by flow cytometry using Annexin V Alexa Fluor 488 cell apoptosis kit.
Result: ET-1 stimulated proliferation and decreased the apoptosis of fetal PASMC in both serum-free and standard DMEN + 10% FBS conditions. Treatment with AM inhibited the ET-1 induced proliferation of fetal PASMC grown in the presence of 10% FBS, but not when cells were grown in serum-free conditions ($p < 0.01$). AM also inhibited the serum-induced proliferation of fetal PASMC ($p < 0.01$). AM decreased apoptosis of fetal PASMC in the presence of 10% FBS ($p < 0.01$), in addition it blunted ET-1 anti-apoptotic effects but had no effect on apoptosis in serum-free conditions.
Conclusions: AM may play a role in the development of fetal pulmonary vasculature by inhibiting vascular smooth muscle cell proliferation and by decreasing apoptosis. Because AM had no effect in the proliferation of cells grown in the absence of FBS, even when stimulated by ET-1, we speculate that specific growth factors present in serum are involved in the mechanism of AM-induced decrease in proliferation. A decrease in both proliferation and apoptosis may indicate that the fetal PASMC are more differentiated. Further studies are needed to investigate this speculation.

DUCTAL SIZE AND PEAK SYSTOLIC TO DIASTOLIC FLOW VELOCITY RATIO WITHIN 48HRS OF LIFE ARE ASSOCIATED WITH DUCTAL PATENCY IN VERY PRETERM INFANTS??

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Background: Early diagnosis and effective treatment of a significant Patent Ductus Arteriosus (PDA) remains contentious. Various approaches including prophylaxis, early targeted treatment or no treatment at all are advocated. Criteria for an early targeted approach remain inconsistent. ?OBJECTIVE: To determine which clinical and echo parameters are associated with PDA patency in very preterm infants.?
Design/Methods: Preterm infants <32 weeks had an ECHO performed within 48 hours of birth (ECHO 1) and a follow up echo at one month of life (ECHO 2). ECHO parameters and relevant clinical data were documented. Clinicians were unaware of the initial echo findings, but could request an echo at any point if they had a clinical concern. Echo parameters included size determined by colour flow assessment, size determined by non colour assessment, left atrium to aortic ratio, peak ductal systolic flow velocity, peak ductal diastolic flow velocity, ratio of peak systolic to diastolic flow (PSDR)in ductus, peak sytolic flow in left pulmonary artery and presence of diastolic disturbance in main pulmonary artery. Parental consent was obtained in all cases.?
Results: 53 babies were included. Median (range) gestation was 28 (24-31) weeks and birth weight 1090g (470-1800). ECHO 1 demonstrated that 51 babies had a PDA present within 48 hours of birth (96.2%), of which 19 were large (>2mm) (37%) and 32 were small (63%). 5 babies had evidence of significant pulmonary hypertension and 3 babies had died before one month of life. ECHO 2 data reported on 50 newborns revealed that at one month 23 babies still have a PDA (46%), 9 of which were large (18%). Parameters significantly associated with large PDAs at one month were gestational age (26 vs 29 weeks, p=0.01), birth weight (912 vs 1200g, p=0.03) and ventilatory support at 48hrs (92 vs 37%, p=0.01). Echo paramters revealed that mean ductal size on colour doppler (2.5mm vs 1.5mm, p=0.01), mean peak diastolic flow velocity (68m/s vs 121m/s, p=0.01) and PSDR (49% vs 78%, p=0.01) at 48 hrs were associated with patency at 1 month. In a logistic regression model ductal size and low PSDR remained significantly associated with a patent ductus.?
Conclusions: Very preterm infants with a large PDA and a low PSDR within 48hrs are associated with persistent large patent ductus arteriosus at 1 month

LAWS AND RECOMMENDATIONS GOVERNING THE CARE OF VERY PRETERM INFANTS IN 19 EUROPEAN REGIONS : RESULTS FROM THE EPICE PROJECT

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Background: Very preterm infants, born before 32 weeks of gestation, face much higher risks of mortality and long-term developmental impairment than infants born at term. Ensuring that evidence-based medical knowledge is translated into effective perinatal care is essential for optimizing health outcomes for these infants. Many European national and regional governance bodies, including regulatory agencies and professional societies have emitted regulations and guidelines to promote the use of medical practices. Objectives To describe and analyse regional governance affecting the use of evidence-based practices for the delivery and care of very preterm infants in 19 European regions.
Methods: The EPICE project investigates the use of evidence based practices for the care of very preterm babies in neonatal and maternity units in19 regions in 11 EU countries (N=7828 very preterm live births). Nineteen medical interventions were included in the EPICE study based on their clinical importance, strength of the evidence base and the feasibility of comparing their use across regions. We conducted a survey of regional, national or European regulations or recommendations related to these interventions, and published by government structures, health agencies or professional societies.
Results: A total of 69 regulations or recommendations referring to the Epice medical interventions were included in this review. Five additional documents are recommendations from European or other international health professional societies. The majority of the documents included are recommendations published by professional societies (n=36/74). Thirteen were issued by governmental structures and 9 by health agencies. Publication dates varied between 1991 and 2012. Some regions had regulations or recommendations for at least half of the interventions (Italy, Germany, Portugal and the UK) whereas elsewhere there were fewer (regions for Denmark, the Netherlands, Estonia). Obstetrical interventions - such as management of PPROM, use of tocolytics, use of antenatal corticosteroids, in-utero transfers and deliveries by caesarean section - had a higher number of regulations or recommendations than neonatal interventions. The neonatal interventions with the highest number of regulations or recommendations were breastfeeding, use of surfactant replacement therapy and ROP screening and treatment.
Conclusions: There is a wide variation in the regulation of medical interventions on the regional and national levels. This variation might partially explain differences in the use of evidence-based practices between European regions.

REGIONAL DIFFERENCES IN OUTCOMES OF EXTREMELY PRETERM INFANTS IN SWEDEN AT 2.5 YEARS IN RELATION TO THE INTENSITY OF PERINATAL MANAGEMENT (THE EXPRESS STUDY)

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Background: The National EXPRESS study has shown favourable perinatal and 1-year outcomes of extremely preterm infants (EPT, <27weeks) in Sweden compared with similar international studies.
Objective: To determine whether there are regional differences in outcomes at 2.5 years of corrected age and whether outcomes can be related to regional differences in the use of perinatal interventions.
Methods: Population-based prospective study of all EPT children born in Sweden from April 1, 2004, to March 31, 2007. Of 1011 births, 707 infants were born alive, 491 survived to 2.5 years corrected age of whom 456 were followed up at that age. Each region was assigned a perinatal activity score (PAS) based on the rate of selected perinatal interventions. Moderate or severe neurodevelopmental disability was defined as moderate or severe cerebral palsy, moderate or severe visual or hearing impairment or a Bayley-lll cognitive, language or motor score <- 2 SD compared with control children born at term. Mortality and morbidity rates were related to PAS and adjusted for gestational age and background factors.
Results: There were few regional differences in obstetric and neonatal background data. PAS varied from 74 to 100 (median 82) between regions. When 3 regions with higher PAS (median 98) were compared with 4 regions with lower PAS (median 79) the following adjusted odds ratios (AOR) were found for death before 2.5 years. Infants born at 22-26 weeks including stillbirths: AOR 0.7 (95% CI 0.5-0.9); infants born alive, AOR 0.7 (95% CI 0.5-1.0). Infants born at 22-24 weeks including stillbirths: AOR 0.4 (95% CI 0.3-0.7); infants born alive AOR 0.6 (95% CI 0.4-0.9). There were no differences in mortality for infants who were alive at 12 hours of age. There was no difference in high PAS regions compared with low PAS regions in severe neonatal morbidity. At 2.5 years of corrected age, there were no differences in moderate or severe neurodevelopmental disability among infants born at 22-26 weeks from high PAS regions compared with low PAS regions, AOR 0.8 (0.5-1.3) nor among infants born at 22-24 weeks, AOR 1.2 (95% CI 0.8-1.9).
Conclusions: Survival at 2.5 years was higher in regions with higher rates of perinatal interventions. Better survival was not associated with an increase in moderate or severe neurodevelopmental disability.

EVOLUTION OF ETHICAL DECISION-MAKING POLICIES IN EUROPEAN MATERNITY AND NEONATAL UNITS FROM 2003 TO 2012: RESULT FROM THE EPICE PROJECT

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Introduction: European maternity and neonatal units have been shown to have varying policies towards ethical decision-making. As the mortality of very preterm infants has declined in the past decade, we explored whether policies in European units changed between 2003 and 2012.
Methods: Ten regions in Denmark, Belgium, France, Germany, Italy, the Netherlands, Poland, Portugal and the UK participating in the MOSAIC1 and EPICE projects were included in the analysis. A total of 93 (out of 159 fulfilling inclusion criteria) neonatal units with at least 10 admissions of infants 22 to 31weeks' gestational age in 2011-2012 and their associated maternity units (n=81/147) had data from structured questionnaires on policies from 2003 and 2012.
Result: The proportion of neonatal units with written protocols for withdrawing or withholding treatment of extremely preterm babies increased between 2003 (27%) and 2012 (40%), while the percentage of maternity units with protocols for forgoing treatment of extremely preterm deliveries remained stable (29 vs 25%). More maternity units in 2012 (51 units) than in 2003 (40) adopted a limit before or at 25 weeks for performing a caesarean section in case of acute distress of a singleton non-malformed foetus. In cases where parents are against aggressive treatment, more units reported that they perform a caesarean section at 24 (12 vs 6 units) or 25 (9 vs 2) weeks in 2012 than in 2003. A majority of the maternity units called a neonatologist for births before 25 weeks of a singleton non-malformed foetus (55 in 2003 vs 66 in 2012). The number of neonatal units reporting that they withhold/withdraw mechanical ventilation because of poor prognosis (73 vs 78) or because the baby has no chance of survival (73 vs 78) did not change significantly over the study period. A higher proportion of hospitals declared that an ethics committee was available in 2012 (n=70) than in 2003(n=49). Half of the units (53 in 2003, 43 in 2012) follow a policy of multidisciplinary decision-making about active resuscitation before 25 weeks of gestational age. The numbers are higher in case of severe congenital anomalies (61 in 2003, 56 in 2012). More units in 2012 reported that they relied on the neonatologist's decision about active resuscitation of babies less than 25 weeks (23 vs 37) or with severe congenital anomalies (15 vs 28).
Conclusions: Decisions about the active treatment of extremely preterm infants changed little in the last decade. Twenty-four weeks of gestation was the most common lower limit of active treatment in 2003 and 2012, although there are wide variations between individual units. More neonatal units have protocols on ethical decisions in 2012 than in 2003 and the role of the neonatologist in decisions about active resuscitation seems to have increased over time.

BEREAVEMENT, SOCIAL AND MEDICAL SUPPORT IN END-OF LIFE NEONATAL CARE

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Background: Supporting parents when a newborn dies is an important part of neonatal care. We aimed to audit follow up after a baby dies with bereavement services, social work and the medical team to ensure that it was appropriate.
Methods:A review of all infnats born > 22 weeks gestation in the National Maternity Hospital and died between Jan 1st - Dec 31st 2011 was compiled.
Results: 9,459 babies were delivered in the NMH in 2011. 53 patients were included in the study. 46 (87%) of these patients were inborn and there were 39 (74%) males and 14(26%) females. The average age at time of death was 15 days (range 1hour-19 months) but 37 (70%) patients died within the first 72 hours of life. The bereavement team contacted 41(77%) patients by phone to offer condolences and to give information about support services available to bereaved families. Medical social work teams were involved in 13 (25%) cases. The paediatric team followed up with 7 (13%) parents and the obstetric team saw 12 (23%) parents in their OPD. The majority of patients in the study died in the NMH (46 (87%), 5(9%) died in other tertiary referral paediatric hospitals and 2 (9%) died at home. 23 (43%) post mortems were performed. Congenital anomalies accounted for 22 (42%) deaths. It is likely that in other countries, many of these pregnancies would have been terminated which highlights the importance of perinatal end-of-life care in Ireland.
Conclusion: While the majority of patients were followed up by the bereavement team in the NMH, there was no documentation for 23% to demonstrate whether or not they had been contacted. A checklist has been created to ensure that all parents are followed up and offered support, ultimately improving the quality of perinatal care.

MODE OF DYING IN AN IRISH NEONATAL ICU

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Background: Recent categorisation of death and the level of treatment provided at the time of dying have been published from US, Canadian and Dutch neonatal units. No data for Irish neonatal deaths exists to date. Our unit is a tertiary neonatal unit located in the south of Ireland. Objective: To identify the causes of death within our neonatal unit and to categorise the manner in which they died. Design/
Methods: Files of newborn (>22 week gestation) deaths within our unit over a three year period (January 2010- January 2013) were reviewed. Deaths were categorised as to whether they died receiving active cardiopulmonary resuscitation (CPR), died with CPR withheld, extubated in moribund state to die in parents arms or extubated for quality of life reasons. Those said to be moribund were physiologically unstable. To be classified as unstable, babies needed 2 of these criteria: persistent desaturation despite 100% oxygen on mechanical ventilation, hypotension despite volume infusion and inotropes, protracted bradycardia or anuria for >24 hours. All babies that were not unstable according to these criteria were classified as physiologically stable.
Result: There were 64 deaths during this time period. The most common causes of death were congenital anomalies (45%), followed by prematurity related issues (40%) and others including asphyxia and sepsis. The leading congenital anomalies were chromosomal including five cases of trisomy 18, trisomy 13 and 2 cases of triploidy. Other congenital malformations were skeletal dysplasia, hypoplastic lungs and holoprosencephaly. Respiratory insufficiency (59%) and sepsis (22%) contributed to prematurity related causes. The most common place to die is in the NNU (67%). The highest proportion of deaths were in the less than 28 week gestation category (31%). These figures are similar to the findings in prior studies. A high proportion of deaths occurred while receiving active CPR (12.5%) when compared with Dutch (4%) but was similar to Canadian (12%) figures. A smaller proportion of deaths occurred following the extubation of the moribund child (26.5%) when compared with US figures (50%). Extubation for quality of life reasons was (25%) which was comparable to other other countries. Of note there was a high proportion of cases where treatment was withheld (35.9%).
Conclusions: The leading causes of death were congenital anomalies and prematurity as expected. The numbers dying while receiving CPR and those who had treatment withdrawn were similar to other units. However, our overall rates of withholding life sustaining treatment (35.9%) is higher, a reflection of the relatively higher incidence of chromosomal abnormalities in our patient population.

: A COMPARISON OF TWO PERIODS (THE EPI-SEN STUDY).

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Background: Advances in perinatal and neonatal care may influence the rates of survival and major morbidities in extremely low gestational age newborns. It is important to accurately know these changes over time for appropriate decision-making when discussing clinical decision with parents, and for quality improvement audit.Objective: To compare survival and neonatal morbidity for infants born between 22 and 26 weeks' gestation in Spain, during two five-year periods: 2002 to 2006, and 2007 to 2011.Design: Prospective observational population-based study.Setting: Maternity and neonatal units in Spain.
Patients: We studied all infants born alive at 22 to 26 weeks of gestation in the collaborating centres of the Spanish SEN1500 network, or transferred to them in the first 28 days of life. Most regions in Spain were represented, covering about two thirds of all births in the country. Perinatal intervention, clinical management, infant morbidity, and survival to discharge from hospital were studied. Cerebral brain scan abnormality was defined as the presence of severe haemorrhage (grades 3 and 4), cysts or persistent periventricular ecogenicities.
Result: 5470 infants were included (2533 and 2937 in each period, respectively). Main changes in perinatal care were: a lower proportion of infants transferred from another hospital (11.0% v 8.9%; p=0.01), an increase in prenatal steroid administration (69.5% v 80.8%; p<0.001), C-Section delivery (41.8% v 48.3%; p<0.001), and use of nasal CPAP before endotracheal intubation (23.5% v 32.5%; p<0.001). The proportion of infants with 1 minute Apgar score ≤ 3 decreased from 34.4% to 29.0% (p<0.001), and clinical stability in the first 12 hours improved: CRIB I score [median (IQR)]: 7 (4-10) v 6 (3-9). Resuscitation was more active for all gestational ages, except for 22 weekers, and delivery room death decreased from 5.1% to 3.2% (p<0.001). Exclusive breast feeding at discharge increased significantly (18.3% v 36.6%; (p<0.001). Survival and survival without major cerebral scan abnormality by GA among infants admitted to NICU are shown in the Table.

Outcome	GA (weeks)	2002-2006	2007-2011	p
Survival (% of admissions)	22	5.0 (1/20)	14.3 (1/7)	0.419
	23	12.4 (20/161)	20.4 (34/167)	0.053
	24	36.9 (197/534)	36.1 (211/585)	0.775
	25	50.0 (370/740)	59.8 (533/891)	<0.001
	26	65.3 (620/949)	73.4 (876/1193)	<0.001
	Total	**50.2 (1208/2404)**	**58.2 (1655/2843)**	**<0.001**
Survival without major cerebral scan abnormality (% of admissions)	22	5.0 (1/20)	14.3 (1/7)	0.419
	23	8.1 (13/160)	14.1 (23/163)	0.087
	24	29.1 (154/530)	25.9 (149/576)	0.235
	25	38.5 (282/733)	46.7 (407/864)	0.001
	26	52.9 (493/932)	58.2 (669/1150)	0.016
	Total	**39.7 (943/2375)**	**45.3 (1249/2760)**	**<0.001**

Conclusions: Survival and survival without major brain abnormalities increased for infants at the borderline of viability during the two periods studied, but only reached significant differences at 25 and 26 weeks of gestation. AHowever, a more conservative approach was detected for the more immature infants (22 weeks), and more active for the rest of the group.

INTRAUTERINE GROWTH RESTRICTION AS A RISK FACTOR FOR DEVELOPING NEONATAL SEPSIS

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Introduction: The aim of this study was to investigate risk factors for appereance of sepsis in neonates with intrauterine growth restriction regarding gestational age. PATIENTS AND
Methods: In this retrospective-prospective cohort study all neonates born from January 2006 until December 2010 at the Departement for Gynaecology and Obstetrics of Cantonal Hospital in Zenica were analyzed. The data of all neonates with diagnosis of sepsis/meningitis were retrieved from the protocols and analyzed for gestational age, clinical findings, body temperature, laboratory values (CRP, leucocytes, thrombocytes, glucose, calcium, bilirubin, acidobasic status), the results of microbiological analyses, and from mother and neonate depending risks.
Results: The incidence of neonatal sepsis was 10,35/1000 live births and neonatal meningitis 4,033/10000. The male sex was more prevalent (1,37:1), and the increased risk for developing neonatal sepsis was proven in preterm neonates with intrauterine growth restriction (p=0,0171), term neonates with intrauterine growth restriction (p=0,0164), as well as in term hypotrophic neonates with intrauterine growth restriction (p=0,0002). The early onset neonatal sepsis in cohort of neonates with proven systemic infection was present in 32 (20%) of cases with gram-positive bacteria as leading cause. The late onset neonatal sepsis was present in 106 (68%) of cases with leading of Klebsiella pneumoniae, while bacteriemia was proven in the rest of 19 (12%) of cases.
Conclusion: The intrauterine growth restriction has established as statistically significant risk factor for developing of systemic neonatal infection. There was no evidence of a significant association of risk factors from the mother for the occurrence of early neonatal sepsis, as opposed to the possible risk factors of the newborn, as well as premature rupture of membranes less then 18 hours which were proven as risk factors. It is important to improve the screening of pregnant women (vaginal swabs) to the possibility of infection after the 36th weeks gestation, and the screening of high-risk group of infants presented with clinical and antenatal risk for the occurrence of systemic infections due to their appropriate treatment in order to avoid excessive use of high toxic antimicrobial agents and better epidemiological control. KEY WORDS: neonatal sepsis, intrauterine growth restriction, antenatal risk factors, germs

INFLAMATORY AND INATE IMMUNE RESPONSE IN TERM NEWBORN WITH LATE ONSET SEPSIS

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Introduction: Despite continuous progress in the clinical treatment and other supportive care therapies, sepsis remains a leading cause of morbidity and mortality in the intensive care unit with similar outcome throughout the past 50 years. The susceptibility to severe bacterial infection is partially due to newborn immature innate immune system associated to minimal in utero antigen exposure and efector T and B cell impared function. Although the importance of pattern recognition domains such as Toll-like receptors (TLR) in the innate immune system activation has been fully acknowlegded within the last few years its behaviour in front of an in vivo infection cenario is still not completly undestood. Here we analyse the TLR-2 and TLR-4 expression in antigen-presentin cell in healthy and septic newborns. Patients and Methods; This prospective study was conducted during the period from October 2011 until January 2013 at Sao Paulo University, Sao Paulo, Brasil. Fourty-two term newborns without congenital malformation were included from the Newborn Intensive Care Unit at Children's Hospital. As case group 24 newborns who had clinical and laboratory diagnotic of late onset sepsis were included while 18 newborns were evaluated in a non-septic status and included as control group. Cytokines were measured by cytometric bead array in peripheral blood. TLR-2 and TLR-4 were determined by immunophenotyping at peripheral whole blood and analysed on a BD FACSDiva flow cytometer.
Result: Clinical data was similar between septic and non-septic groups except for the infectious status. Microorganisms were identified in 41,6% septic newborns. The infected group had higher levels of pro-inflamatory (IL-8, IL-6, IL-1?) and anti-inflamatory interleukines (IL-10). When it comes to dendritic cells, the expression of TLR-2 and 4 was similar between groups whereas there was lower expression of co-molecule CD86 ($p<0,05$) and similar expression of CD1a and CD80 between infected and non-infected patients. At monocytes, the MFI for TLR-2 and the frequency of TLR-4 expression was higher in infected newborn ($p=0,01$). There were lower levels of total linfocytes in infected patients ($p=0,002$) but no diference was observed in T cells subtypes frequency except for higher levels of efector T cell in infected group with lower expression of CD28 molecule. B cells were similar in number, activation molecules and TLR-2 and 4 expression in both groups.
Conclusions: This study investigated the inate immune response in septic newborn. Interleukine levels 6 and 10 were good indicators of sepsis. Septic newborns, who count most exclusively with innate immune system, had little in vivo response at dendritic cell and monocyte activation leading to an impared immune response and increased susceptibility to infection.

EARLY DIAGNOSIS OF NEONATAL SEPSIS. ROLE OF PCT VERSUS "CLASSICAL MARKERS".

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Introduction: Clinical signs and laboratory tests of neonatal sepsis are non-specific and diagnosis is difficult. Early antibiotic therapy is crucial for treatment success. But incidence of sepsis, in neonate treated for suspected sepsis, is low. Purpose: To evaluate the effect of procalcitonin PCT in early neonatal sepsis diagnose versus other laboratory test(CRP), blood culture, I/T index, WBC and PLT.
Material and Methods: This single-center, prospective, randomized intervention study conducted in a tertiary neonatal intensive care unit, Janary-June 2012, and is still in process. All neonate with suspected sepsis were randomly assigned either to standard treatment based on conventional laboratory parameters (standard group) or to PCT-guided treatment (PCT group) .All neonate with suspected early-onset sepsis were randomly assigned either to standard treatment based on conventional laboratory parameters (standard group) or to PCT-guided treatment (PCT group). Minimum duration of antibiotic therapy was 48-72 h in the standard group, whereas in the PCT group antibiotic therapy was discontinued when two consecutive PCT values were below predefined age-adjusted cut-off values(>2 ng/ml).
Result: 73 newborns were randomly assigned wither to the standard group (n = 34) or the PCT group (n = 39). The two groups were similar for baseline demographics, risk factors for EOS, gestational age, birth weight, Apgar score 1 and 5 minute, and early conventional laboratory findings. PCT show to be more sensitive related to other"classical markers", sensitivity was 90.9% and NPV 96.15%. vs CRP sensitivity 54.54% and NPV 75%. Blood culture show low sensitivity 27.27 %, but high sensibility 85.7%. Low sensitivity show WBC at 12h(38.8%). I/T index has the same role in diagnosis ,sensitivity 27.78 % and NPV 68 %.There was a significant difference in the proportion of newborns treated with antibiotics 72 h between the standard group (85.29%) and the PCT group (59%) (absolute risk reduction 26.3%; odds ratio 0.2 (95% CI 0.07-0.7), p = 0.019). On average, PCT-guided decision-making resulted in a shortening of 40 h of antibiotic therapy in GA >34 weeks newborn. No difference found in antibiotics treatment in neonates with sepsis in two groups. Clinical outcome was better in study group related to secondary sepsis episode.
Conclusions: Use of PCT kit test show to be useful in early sepsis diagnosis. Also seem to be useful in shorten the duration of antibiotic therapy in near-term infants with suspected early-onset sepsis.
Keywords: neonatal sepsis, PCT, CRP, WBC, I/T index, Blood culture, sensitivity, sensibility, NPV, antibiotics.

COLONIZATION STUDIES: ARE THEY OF ANY VALUE? THE AUDIT OF A REFERRAL TERTIARY NICU

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Background: Multidrug-resistant Gram-negative bacteria are a significant source of nosocomial infection. Active microbiological surveillance has been recommended to reduce their transmission, as it allows the adoption of isolation measures to prevent bacterial dissemination. Microbiologists disagree with colonization studies, due to alleged low sensitivity, high costs and mislead antibiotic use.
Aim: To audit the practice of conducting systematic colonization screening for multi-drug resistant bacteria at admission to a tertiary medico-surgical neonatal unit.
Methods: Cross-sectional study of every admission to a single NICU through 2012. Data on the results of the colonization screenings requested in the admission day and bacterial resistance patterns were collected from the intranet clinical data system. Length of stay in a previous neonatal unit (LOS) was hypothesized as the main risk exposure. The main outcomes are multi-drug resistant bacteria colonization rate, number needed to screen (NNS) depending on previous LOS, and cost for each positive screening. Cost assessment was based on the official costs of colonization screenings and estimated costs related to isolation measures.
Result: Out of 174 patients admitted to the NICU, 141 were screened using samples from 244 swabs (pharynx, rectal, axilla or tracheal aspirate). Screening was positive in 41 patients (29%) and 60 isolates were obtained. There was a positive correlation between positive screening and previous LOS (r=0.957). Patients admitted with previous LOS of 29-60 days had the higher rate of positive screening (54.5%), with a NNS of 5 comparing with LOS =7 days and 12 with LOS 8-28 days. Positivity of screening from pharynx and rectal swabs was similar (21% vs. 17%; p=0.263).Nine patients were colonized with multi-drug resistant bacteria, two of them admitted from home: 4 Kl pn ESBL, 4 MRSA and 1 Acinetobacter baumanii. No bloodstream infections caused by these bacteria occurred. The overall costs for each patient colonized with multi-drug resistant bacteria was about 1000 euro.
Conclusions: Criteria for colonization screening for multi-drug resistant bacteria should be narrow, thoroughly defined and customised to each NICU. Even so, costs will be high, with scarce evident gain, even in a tertiary referral medico-surgical neonatal unit. It is difficult to calculate gains of eventually prevented nosocomial sepsis with this policy.

EPIDEMIOLOGY AND DIFFERENTIAL RISK FACTORS FOR COLONIZATION BY COMMUNITY-ASSOCIATED AND HEALTHCARE-ASSOCIATED MRSA IN NICU PATIENTS, PALERMO, ITALY, 2009-2012

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Methicillin resistant Staphylococcus aureus (MRSA) is a major pathogen in neonatal intensive care units (NICUs). Infants in NICU are at increased risk for infection and adverse outcomes, low birth weight, length of stay, parenteral nutrition and use of invasive devices have been described as the most important risk factors for invasive MRSA disease.
The aim of this study was to define epidemiology, clonality and dissemination patterns of community-associated (CA) and healthcare-associated (HA) MRSA in the tertiary NICU of the teaching hospital 'P. Giaccone', Palermo, Italy. Risk factors for colonization with MRSA and for colonization with CA-MRSA vs HA-MRSA were assessed. Prospective surveillance for MRSA colonization was carried out among infants admitted between June 2009 and June 2012. Nares surveillance cultures were collected weekly. Prevalence and risk factors for colonization were assessed. MRSA isolates were submitted to antibiotic susceptibility testing, multilocus variable number tandem repeat fingerprinting (MLVF), staphylococcal chromosome cassette (SCC) mec characterization and multilocus sequence typing (MLST). PCRs for Panton Valentine leukocidin (PVL) and toxic shock syndrome toxin (tst) genes were carried out. Demographic and clinical data were prospectively collected. In the period under study, 187 (25.9%) out of 722 infants were colonized by MRSA. By molecular methods 21 neonates proved to be colonized by CA-MRSA and 166 by HA-MRSA. Prevalence of CA-MRSA significantly increased from the 1st year (1.1%), to the 2nd year (17.6%) and the 3rd (21.5%), chi-square for linear trend 16.134, P = 0.00006. The ST22-MRSA-IVa strain was endemic in the NICU accounting for 100% of the HA-MRSA isolates identified in the three years of surveillance. All the ST22 isolates proved to be susceptible to fluoroquinolones, were PVL negative, but tested positive for tst gene. Among the CA-MRSA isolates, ST1-MRSA-IVa was the most frequently detected (16 isolates), followed by two strains of ST45 and one each of ST7, ST8 and ST97, respectively. ST1-MRSA-IVa disseminated in an epidemic way between April and August 2011, involving 14 infants. Statistically significant risk factors for colonization with CA-MRSA genotypes were: lower gestational age (CA-MRSA vs. HA MRSA, 34.1±4.1 wks vs. 36.6±3.3 wks, P=0.02); more frequent exposure to invasive devices (CA-MRSA vs. HA-MRSA, CVC, 57.1% vs. 23.5%, P=0.001); endotracheal tube (38.1% vs. 17.5%, P=0.03); nCPAP (47.6% vs. 17.5%, P=0.003), more frequent administration of parenteral nutrition (76.2% vs. 38.6%, P=<0.001); more frequent submission to surgical procedures (15.0% vs. 3.1%, P=0.04). CA-MRSA colonized infants were administered more frequently than those with HA-MRSA with systemic antibacterial therapy (66.7% vs. 41.6%, P=0.02). Sepsis was significantly more frequent among CA-MRSA than HA-MRSA colonized infants (28.6% vs. 11.4%, P=0.04). The interval of time between admission and the first positive culture did not differ between the two genotypes: CA-MRSA vs. HA-MRSA, 13.6±11.2 vs. 13.3±17.8, P=0.95. Our findings indicate that CA-MRSA genotypes have entered the environment of our NICU, where they seem to be acquired nosocomially. CA-MRSA strains acquisition proved to be significantly associated to infant- and healthcare delivery risk factors. The atypical epidemiological pattern of CA- and HA-MRSA in our NICU setting warrants further investigation.

UPTAKE OF 'MATCHING MICHIGAN'-TYPE CATHETER CARE BUNDLES IN UK NEONATAL UNITS AND IMPACT ON NEONATAL SKIN ANTISEPTIC USE

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Background: The UK 'Matching Michigan' (MM) interventional programme (2009-2011) introduced care bundles for the insertion and maintenance of central venous catheters (CVCs) in adult and paediatric intensive care units. Skin antisepsis using 2% chlorhexidine gluconate (CHG) in 70% isopropyl alcohol was a central intervention. Successful reductions in bloodstream infections from CVCs were realised. Neonatal intensive care units (NICUs) could participate in MM, but only limited data are available reporting NICUs' experiences. Choice of antiseptics for neonates remains contentious; alcohol-based CHG agents and 2% aqueous CHG have been associated with chemical skin burns in neonates. In 2007, only 7/50 (14%) UK NICUs used alcohol-based antiseptics and none used 2% aqueous CHG. Our aim was to survey prevalence of catheter care bundles and antiseptic use in UK NICUs in the wake of the MM programme. Method In March-April 2013 we conducted a telephone survey of all tertiary-level NICUs in the UK. We asked each unit whether a catheter care bundle was in place for percutaneous CVC (PCVC) insertions, what their chosen topical antiseptic was for skin disinfection prior to PCVC insertion, and whether they had seen chemical skin burns resulting from antiseptic use.
Results: 44/58 (76%) NICUs responded, and 31 (70%) had a MM-type care bundle in place. Seven different cutaneous antiseptics were in use. 22/44 (50%) NICUs now use alcohol-based antiseptics (n=17 the 2% CHG in 70% alcohol; n=5 the 0.5% CHG in 70% alcohol) and one now uses 2% aqueous CHG. Most NICUs (20/23;87%) using these 'stronger' agents did so as part of a catheter care bundle. 19/22 NICUs used alcohol-based CHG agents for PCVC insertions in all infants irrespective of gestational age. 4 (9%) NICUs reported limb skin chemical burns, and 2 of these had subsequently ceased using the 2% CHG in 70% alcohol for very preterm infants.
Conclusion: The recent widespread introduction of catheter care bundles into UK NICUs has led to a significant increase in the adoption on alcohol-based chlorhexidine antiseptics for neonatal skin preparation. The complete lack of safety and efficacy data for antiseptic agents in neonates is of great concern. In the absence of RCTs to examine safety and efficacy in the neonatal population, babies will potentially continue to be put at risk from introduction of antiseptic agents based of safety/efficacy data that were derived solely from adults and older children.

THE UGT1A1*28 ALLELE AND ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDHOOD, A NATIONAL DANISH CASE-CONTROL STUDY.

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Background: A possible risk factor in the development of acute lymphoblastic leukaemia (ALL) in childhood is oxidative stress, as previous studies have shown a relationship between neonatal oxygen supplementation and later development of ALL. Bilirubin is an endogenous antioxidant of possible clinical relevance with documented antioxidative effects both in vivo and in vitro. UGT1A1 is the rate limiting enzyme in bilirubin's metabolism. The UGT1A1*28 allele causes a markedly reduced activity of this enzyme and is main genetic cause of elevated serum bilirubin amongst Caucasians.
Objective: We aimed to test whether the UGT1A1*28 allele is associated with reduced risk of ALL in childhood.
Patients and Methods: The UGT1A1*28 allele was assessed in a case-control study of 710 incident ALL in childhood cases in Denmark 1982-2011 and 1380 controls. Cases were identified in The Danish Registry of Childhood Cancer and data on leukaemia type (pre B cell or T cell), t(12;21) status and age at diagnosis was obtained from the registry of the Nordic Society for Paediatric Haematology and Oncology. Genotypes were obtained through The Danish Newborn Screening Biobank. Association between genotype and outcome was analyzed as sex adjusted odds ratios (OR) using logistic regression under the binary model with wildtype genotype as referent. Sub group analysis was done on age at onset in three groups (0-4 years, 5-9 years and 10-18 years), precursor B cell ALL, T cell ALL and the t(12;21) type ALL.
Result: No association was found between ALL in childhood and UGT1A1*28 genotype with adjusted OR for heterozygotes being 0.96 (0.79-1.16) and for homozygotes OR 1.12 (0.82-1.53). Subgroup analysis also showed no association.
Conclusions: We found no association between the UGT1A1*28 genotype and ALL in childhood.

KNOWLEDGE, ATTITUDE, AND BELIEF OF BURN FIRST AID AMONG CAREGIVERS ATTENDING PEDIATRIC EMERGENCY MEDICINE DEPARTMENTS

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Introduction/Background: Many preventable burn victims with varieties of first aid measures are seen in Emergency Departments. Immediate and effective burn first aid reduces morbidity and determine outcome. Primary burn prevention and first aid knowledge improvement is an important public need. This descriptive study determines the caregivers' current level of knowledge, attitude and belief of burn first aid.
Patients and methods: Caregivers attending four (4) major Pediatric Emergency Departments answered a structured questionnaire detailing demographic, knowledge and the first aid they provide for burn including two case scenarios. Application of cold water for 15-20 min, smothering with clothes caught on fire and covering pot of oil in fire with wet cloth were all considered to be appropriate responses. Main outcome measure is significant proportion of caregivers with appropriate first aid knowledge for burns and non-use of inappropriate remedies. Additional questions on best way of conveying burn educational program were included. Chi-squared tests and logistic regressions were performed to relate knowledge to demographic features, previous history of burn and first aid training.
Result: The interviewed 408 caregivers (55% females) reflected a wide range of age group, occupation and educational level. 60% of respondents have a large family size with 52% had previous history of burn. Overall, 41 % will cool the burn with cool or cold water but 97 % had inappropriate or no knowledge of the duration. While 32% would treat burn with non-scientific remedies alone or in combination, including honey, egg white, toothpaste, white flour, tomato paste, yogurt, tea, sliced potato, butter or ice and 65 % of caregivers cover pot of oil in fire with wet cloth, only 24 % will smother clothes caught on fire. Only 15 % had first aid training. Participants prefer to receive more advises on burn first aid through social media (41%), during hospital visits (30%), and television ads (16%). There was no significant association between age, family size, language, previous history of burn or training and knowledge; however female gender and higher educational level were associated with greater knowledge though statistically was not significant (P = 0.05 and P =0.17 respectively). The logistic regression showed that training was the most influential factor in knowledge of first aid (P <0.01).
Conclusions: Knowledge of burn first aid among caregivers is limited with many non-scientifically based remedies are used. Use of social media, hospital visits, and television ads for first aid training will improve caregivers' awareness. A nationwide educational program emphasizing first aid application of only cold water and reduce the use of inappropriate home remedies for burn injuries is recommended.

DEATH AUDIT FROM URBAN TERTIARY CARE HOSPITAL OF INDIA AND MODIFIABLE FACTORS FOR PREVENTION OF CHILD MORTALITY

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Introduction: India hosts maximum (24%) number of deaths in under-5 children occurring worldwide. Although disease-related or 'biological' factors are important , certain non-biological causes (e.g. administrative, medical personnel and family-related factors) may contribute towards child mortality. We planned this study to evaluate disease-related causes of deaths and to identify socially modifiable factors among hospitalized children aged >1 month-18 years in a tertiary care, referral teaching hospital of North India.
Patients And Methods: We studied the disease-related causes of mortality, retrospectively from 17th March'09 to 30th June'12. We identified socially modifiable factors prospectively from 6th Oct'11 to 30th June'12. Ethical approval was obtained. To study disease-related causes of mortality, we extracted files of all children, aged >1 month-18 years who died in Pediatric emergency ward (PEW) and Pediatric Intensive care unit (PICU) during the study period, from central registration department (CRD). We excluded any missing case records. The 'primary cause' of death (ICD-10 based) was the probable cause that finally led to the death of the child. To study the modifiable causes of child mortality, we enrolled all critically sick children admitted in PEW and PICU. An 'a priori' list of modifiable factors was developed. Modifiable factors were defined as events, actions or omissions contributing to death of a child and which, by means of interventions, could be modified. The modifiable factors were categorized as : family/caregiver-related problems, medical personnel-related problems, and administrative problems. The residents recorded pertinent details regarding these modifiable factors during routine history-taking taken from parents, which was crosschecked by a pediatric consultant. Modifiable factors were identified during the audit meetings which were held fortnightly using death audit profoma and patient records. Each meeting was attended by atleast 3 consulting paediatricians, concerned resident doctors and nursing staff, where deemed necessary. Consensus on causes of death, contributing conditions and modifiable factors were reached during these meetings. Descriptive statistics was used to describe baseline demographic variables and modifiable factors.
Results & Conclusions: We had 5815 admissions (>1-month age) in PEW and PICU over the study duration from 17th March 2009 to 30th June 2012. 493 children died over the study period, giving a case fatality rate of 8.4%. Six files couldn't be traced from CRD. We therefore, analysed 487 deaths for disease-related causes of mortality. Of these 487 deaths, 237 (48.6%) deaths occurred in infants from 1-month to 1-year, 138 (28.3%) in 1-5years and 112 deaths (23%) in children >5 years. Pneumonia, CNS infections and diarrhea were the leading causes of deaths in children accounting for nearly half of total deaths. Severe malnutrition was the major contributing cause, present in 42% of total deaths [Median z-score: -1.94 (95% CI -3.37 to -0.68)]. Socially Modifiable factors We studied socially modifiable factors amongst 107 consecutive deaths. Median duration of hospital stay was 32 hours with 21% deaths occurring within 6 hours and 44% deaths in initial 24 hours.Amongst socially modifiable factors, administrative issues were most common (universal) followed by family/caregiver-related factors (72%) and medical personnel-related factors (41%).

DIAGNOSING ACCURATELY ACUTE ABDOMINAL PAIN IN CHILDREN OUTCOMES OF A QUALITY IMPROVEMENT PROJECT IN A PAEDIATRIC EMERGENCY DEPARTMENT

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Background: Clinical assessment of children suspected of appendicitis is an area of clinical uncertainty where suitable diagnostic aids must be researched. In Dona Estefania Hospital, an urban paediatric hospital with 90.000 annual emergency episodes, the analysis of adverse events concerning missed diagnosis of appendicitis identified contributing factors such as late referral to surgical observation, variations in diagnostic assessment and lack of post discharge follow-up. Aims: To design and implement a protocol able to increase involvement of surgeons in the diagnosis of acute abdominal pain and improve accuracy. To explore barriers and facilitators to the intervention Design: Mixed methods design with a prospective paediatric cohort study of patients with acute abdominal pain attending the emergency department subject to the use of a protocol followed by 18 semi-structured interviews to participants. Intervention: Application of a clinical questionnaire prior to any diagnostic aids. Laboratory tests and surgical observation suggested for patients with = 1 positive variable. Reassessment and imaging requested according to appendicitis suspicion level.
Result: Enrolment retrieved 538 children and physicians complied with the protocol utilization in 417 cases (78%). Appendicitis was diagnosed in 15 patients and all patients had = 1 positive variable in the questionnaire. Surgeons were significantly more involved in the assessment of patients assessed by a compliant paediatrician. Barriers to implementation were overworking for surgeons and conflicts with clinical intuition for paediatricians. Benefits were raised awareness of the problem and a more disciplined clinical process. Application of the protocol to a more restricted group of patients was the most frequent suggestion in all professional groups.
Conclusions: An interdisciplinary team applied a locally designed solution to previously detected systemic problems improving reliability of care. The project introduced standardization of procedures and attitudes and the simultaneous promotion of clinical awareness, self assessment skills and response to reported incidents.

MEASURING HEALTH CARE TRANSITION, ADHERENCE AND SELF-MANAGEMENT IN ADOLESCENTS WITH A PROVIDER-CONFIRMED TOOL: THE TRXANSITION SCALE.

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There is a paucity of validated measures to assess patient outcomes associated disease self-management and health care transition (HCT). The primary limitation of HCT instruments is that the items being measured are disease-specific, making it difficult to use in adolescent patients with multiple co-morbidities. We will present cross-sectional and longitudinal data obtained from nearly 500 adolescents/emerging adults by the TRxANSITION Scale. This 33-item clinically-administered survey has been administered in several specialty clinics (e.g. nephrology, gastroenterology, pulmonology, endocrinology) and it comprises ten knowledge and skill domains: 1) T-type of illness; 2) Rx- medications; 3) A-allergies; 4) N-nutrition; 5) S-self-management; 6) I-informed reproduction; 7) T-trade/school; 8) I-insurance; 9) O-ongoing support; and 10) N-new health providers. For each of the items, the scale administrator rates patients' level of mastery from 0 (not knowledge or skill), 0.5 (some knowledge or skill), to 1.0 (good knowledge or skill) for each item and a summary score from the 33 items (0-33) can then be converted to 0-100 to reflect percentage.

INTEGRATION BETWEEN MEDICAL AND NURSING CHARTS AS A TOOL FOR THE QUALITY IMPROVEMENT AND RISK MANAGEMENT IN NICU

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Background: Clinical documentation is a fundamental tool to get International Standard in terms of patient safety in NICU. Bambino Gesù Children's Hospital obtained for the first time the accreditation by Joint Commission International (JCI) in 2006 within the project of the continuous improving in quality of care. Before 2006 the clinical charts were lacking in nursing information, intervention plans, pain and adverse events monitoring. The prescription of Therapy was reported in different sheets with consequent high risk for medical and nursing errors and adverse events. After JCI accreditation an integrated nursing and medical documentation was designed and applied, looking specifically at the planning of the procedures and at the individualization of care based on specific patient needs. All these aspects have to be reported and well documented in the patient chart. Aims an
Methods: Evaluation of adverse events during the last 18 months in the Department of Medical and Surgical Neonatology (DNMC), through a voluntary communication of adverse events, near miss, or severe events.
Result: In the last 18 months 1005 patients have been discharged by the DNMC. Forty-four adverse events have been documented, of these 8 were near miss events, 36 were adverse events. Eight of these had moderate-severe consequences. The most frequent events (19/44) were therapeutic ones, of whom 16 (84.2%) were due to wrong prescription, that is by far the most risky phase. Following this analysis a new medical-nursing team organization has been developed with the aim of sharing and optimizing the clinical care for sick newborns and reducing the risk for therapeutic adverse events.
Conclusions: Adverse events and medical errors are relatively frequent in NICU and most of them are related to therapy. The weakest phase seems to be drug prescription followed by administration. In both cases, the impact of an organization based on an unique medical-nursing team supported by a culture of a continuous improving in health quality is the fundamental instrument to reduce the risks for patients, family and caregivers.

PREVENTING EARLY POSTNATAL HEAD GROWTH FAILURE IN VERY PRETERM INFANTS: THE RANDOMISED CONTROLLED SCAMP NUTRITION STUDY

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Background: Postnatal head growth failure is well recognised in very preterm infants (VPI), the largest deficit occurs at 3-4 weeks followed by some catch-up growth until 36 weeks corrected gestational age (36wCGA). Head circumference (HC) is correlated with brain volume and later neurodevelopmental outcome. Early nutritional deficits commonly occur in parenteral nutrition (PN) dependent VPI. We have shown that standardising and concentrating neonatal PN can overcome these deficits. We hypothesised that a Standardised, Concentrated with Added Macronutrients Parenteral (SCAMP) nutrition regimen would improve early head growth. Aim: To compare the change in HC (deltaHC) and standard deviation score (deltaHC SDS) achieved at day 28 in VPI randomised to receive SCAMP nutrition (12% glucose, 3.8g/kg/day protein/lipid) or a control standardised, concentrated PN regimen (10% glucose, 2.8g/kg/day protein/lipid).
Methods: The study (ISRCTN: 76597892) received ethical and regulatory approval. Control PN was started within 6 hours of birth. Following parental consent, VPI (birthweight <1200g; gestation <29 weeks) were randomised between day 2 and 5, to either start SCAMP or remain on the control regimen. HC was measured at randomisation, day 7 and then weekly until 36wCGA. Actual daily nutritional intake, biochemical and metabolic data were collected for day 1-28. Weekly growth data and major preterm complications were collected until 36wCGA.
Result: 150/196 eligible infants were randomised at mean age 73.5 hours. Mean (SD) birthweight (g) and gestation (weeks) was: 900(158) versus 884(183) and 26.8(1.3) versus 26.6(1.4) in SCAMP (n=74) and control (n=76) groups respectively. The cumulative mean (SD) actual protein/energy intakes (28 days) were: 89.4 (8.2) g/kg versus 80.7 (8.0) g/kg and 2851 (251) kcal/kg versus 2664 (307) kcal/kg in SCAMP and control groups respectively. Primary outcome: At randomisation, the mean (SD) HC was 240mm (12) with SDS -1.55 (0.70) in the SCAMP group. The HC was 240mm (13) with SDS -1.48 (0.67) in the control group. For the primary outcome in survivors at 28 days, mean (SD) deltaHC (mm) was 31 (9) versus 26 (9) in SCAMP (n=66) and control (n=69) groups respectively. The difference in means (95% CI) was 5mm (2-8) ($p<0.001$). Similarly mean (SD) deltaHC SDS was +0.05 (0.66) versus -0.32 (0.65) in SCAMP and control groups respectively. The difference in means (95% CI) was 0.37 (0.17-0.58) ($p<0.001$). Secondary head growth outcomes: The difference in HC was still detectable in survivors at 36wCGA (n=63 in both groups) with a difference in the mean HC (95% CI) of 5mm (0.1-10) ($p=0.046$) and the mean HC SDS of 0.40 (0.01-79) ($p=0.047$). The 28-day-deltaHC difference equates to 6% difference head/brain volume. Exploratory regression analyses suggested a positive association between protein intake and primary outcome (protein $r=0.4$; calorie $r=0.1$). Other secondary outcomes: There were no statistically significant differences in mortality or major preterm complications in 28 day or 36wCGA survivors.
Conclusions: Early postnatal head growth failure in VPI can be prevented by optimising PN. Standardised, concentrated PN regimens are an effective way to deliver early neonatal nutrition.

STANDARDISING PRETERM INFANT NUTRITION - OPTIMISING NUTRITION AND GROWTH IN PRETERM INFANTS USING AN EVIDENCE-BASED COMPLEX INTERVENTION

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Background: Postnatal growth failure is common in preterm infants and is associated with adverse neurodevelopmental outcomes[1]. One reason for poor growth is that nutritional care is often variable and nutrient intakes suboptimal, despite increasing literature regarding best practice in this area. Optimising nutrient intakes has the potential to improve both growth and developmental outcomes.
Methods: We developed an evidence-based, complex intervention to improve the nutritional care of preterm infants and introduced this in a staged manner. Stage one (August-December 2011) included improved parenteral and enteral nutrition solutions, a multidisciplinary nutrition team and staff education sessions. Stage two (January-December 2012) included comprehensive nutrition guidelines, a nutrition screening tool and 'nutrition nurse champions'. Data on nutrient intakes and growth were collected on all infants less than 30 weeks or 1500g at birth born during the study periods, and compared with a pre-intervention cohort born during 2009. Differences across study periods were analysed by ANOVA with post-hoc analysis using Tukey's method for pairwise differences between study periods (Stata v12.1).
Results: Mean daily intake of the majority of macro- and micro-nutrients increased across study periods, particularly for energy, protein, sodium, calcium, zinc and vitamins D and E (see table 1). Actual mean protein intakes increased from 2.45g/kg/day to 2.82g/kg/day and 2.94g/kg/day respectively. Growth also improved, with the mean change in standard deviation score (SDS) for weight between birth and discharge of -0.90, -0.58 and -0.45 in 2009, 2011 and 2012 respectively ($p<0.01$ for difference between 2009 and 2012 only). Head growth improved slightly, with the mean change in SDS for head circumference between birth and discharge of -0.37, -0.11 and -0.26 in 2009, 2011 and 2012 respectively (NS). 2009 (n=65) 2011 (n=36) 2012 (n=75) Energy 89.1 (18.6) 94.7 (19.6) 96.7 (18.4)* Protein 66.9 (20.5) 75.4 (19.5) 78.2 (18.6)* Carbohydrate 91.1 (19.6) 93.8 (18) 95.3 (17.2) Fat 91 (23.7) 92.9 (20.3) 93.7 (19.8) Sodium 79.5 (17.6) 87.1 (26.2) 92.0 (20.8)* Potassium 162.3 (121.7) 156.8 (81.3) 163.9 (147.8) Calcium 65 (23.4) 76 (20.7)* 78.6 (18.9)* Phosphorous 127.8 (123.5) 131.7 (73.9) 148.2 (148.8) Zinc 72 (17.8) 96.8 (19)* 99.7 (15.7)* Copper 133.1 (128.7) 143.6 (86.4) 156.8 (150.3) Selenium 151.8 (124.6) 154.6 (83.8) 166.1 (148.6) Vitamin A 128.7 (62.3) 111.8 (43.7) 113.4 (39.4) Vitamin D 72.1 (25.4) 107.8 (39)* 101.8 (30.1)* Vitamin E 48.3 (20.9) 64.9 (25.8)* 65.6 (22.9)* Table 1: Mean (SD) daily nutrient intakes across stay in 2009, 2011 and 2011 as a percentage of recommended amounts[2], *$p<0.05$ for difference vs 2009
Conclusion: These results suggest that whilst reformulation of parenteral and enteral feeds significantly improved nutrient intakes, this was further enhanced by full implementation of the complex intervention, including guidelines, nutrition team and screening tool. The complex intervention also resulted in improved growth, with significant improvements in weight gain and a trend towards improved head growth. This suggests that implementing evidence based practice changes can significantly improve care and outcomes. It will be important to see if these improvements are sustained, and whether there is an effect on neurodevelopmental outcomes in later childhood.
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EFFECT OF PROTEIN AND ENERGY INTAKE ON NEURODEVELOPMENTAL OUTCOME OF VLBW INFANTS

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Background: Preterm infants are at risk for developing neurodevelopment impairments. Nutrition may play a key role in early brain development. OBJECTIVE: To evaluate the effect of protein and energy intake consumed during the first 6 months of corrected age on neurodevelopment in a cohort of preterm infants.
Design/Methods: At term corrected age 181 preterm infants (BW=1156.7±239 g, GA=29.9±2.2 weeks) were randomized to receive either a post-discharge formula (75 kcal and 2 g per 100 ml) or a standard term formula (68 kcal and 1.4 g per 100 ml) up to 6 months of corrected age. Energy and protein intake were collected. Weight, length and head circumference were assessed at 1, 3, 6, 12 and 24 months of corrected age. Neurodevelopment was assessed at 24 months of corrected age using the Griffiths Mental Developmental Scale (DS) and related subscales. For analysis infants were grouped in high protein (=2.5 g/kg/day) and low protein group (<2.5 g/kg/day) and high energy (=110 kcal/g/day) and low energy (<110 kcal/g/day) group.
Results: Infants belonging to the high protein group showed higher scores in the locomotor subscale than infants belonging to the low protein one (99.1±10.9 vs 92.8±15.7, p=0.001). With regard to the energy intake, locomotor subscale scores were higher in infants belonging to the high energy group than in infants belonging to the low energy one (100±10.4 vs 92.5±15.5, p=0.006). No difference in the mean developmental score and in the other related subscales was found among groups. After adjusting for confounding variables, protein (beta coefficients 6.43, $p < 0.05$) and energy (beta coefficients 0.3, $p < 0.05$) intakes were independently associated with locomotor subscale scores.
Conclusions: After discharge each g/kg/d in protein intake and each 10 kcal/kg/d in energy intake were associated with 6.43 point increase and 3 point increase in the locomotor subscale scores, respectively.

LOW ENERGY INTAKE DURING THE FIRST FOUR WEEKS OF LIFE INCREASES THE RISK OF SEVERE ROP IN EXTREMELY PRETERM INFANTS

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Background: Retinopathy of prematurity (ROP) is a common complication in very low birthweight infants and may lead to severe visual impairment. Even though vascular and retinal growth is central for the pathogenesis, and it has been shown that poor weight gain is associated with ROP development, the possible impact of early nutrition on ROP has not previously been investigated. AIM: To investigate the effect of macronutrient and energy intakes during the first 4 weeks of life on the risk of severe ROP (= grade 3) in extremely preterm infants.
Method: We used data from the EXPRESS-study, a recent Swedish population-based cohort of extremely preterm infants (< 27 weeks) including ROP diagnosis and comprehensive data on perinatal risk factors. All surviving infants who had been evaluated for ROP were included (n=506). Daily parenteral and enteral nutrient intakes were obtained from hospital records.
Results: The incidence of severe ROP was 29% in this cohort of infants who had an average (±SD) gestational age of 25.3 (1.1) weeks at birth and a birth weight of 765 (170) g. In binary logistic regression models, a low total energy intake during the first 4 weeks of life was the strongest nutritional predictor of ROP ($p<0.001$). Average energy intake during this period was 102 ± 14 kcal/kg/day, which is lower than recommended. In a multivariate model taking possible confounders into account (gestational age, birth weight, respirator treatment, postnatal steroid treatment, postnatal antibiotic treatment, treatment for patent ductus arteriosus (PDA), maternal smoking, antenatal steroid treatment, postnatal weight loss and CRIB-score), energy intake remained a highly significant predictor ($p=0.001$) with an odds ratio of 0.742, based on 10 kcal/kg/day increments. The other remaining significant risk factors were lower birth weight, days of postnatal steroid treatment and PDA ligation.
Conclusions: A low energy intake during the first 4 weeks of life is a significant and independent risk factor for severe ROP in extremely preterm infants. Based on the odds ratio, in our population, an increase of the energy intake by 10% would reduce the incidence of severe ROP with 26%.

THE POSTNATAL GROWTH OF PRETERM INFANTS (PI) WITH BRONCHOPULMONARY DYSPLASIA (BPD) IS NOT INFERIOR TO THAT OF BIRTH WEIGHT (BW) AND GESTATIONAL AGE (GA) MATCHED CONTROLS RECEIVING SIMILAR MACRONUTRIENT AND ENERGY INTAKES: A CASE-CONTROL STUDY.§

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Background: Extra-uterine growth restriction is a well-known problem of BPD infants. The relationship between nutrition, growth and BPD itself is not completely understood yet. Patients and
Methods: We retrospectively reviewed growth data and nutritional intakes of nine hundred thirty-five PI with GA between 240/7 and 316/7, admitted to our NICU between January 2004 and December 2012. Exclusion criteria were: admission after 48 hours of life, death before 36 weeks post-menstrual age (36w-PMA) and major congenital malformations. Data on growth, parenteral nutrition (PN) and enteral feeding (EF) macronutrient and protein intakes were prospectively collected and extracted using a dedicated proprietary software. It is policy of our NICU to increase energy and protein density of the PN and/or EF when fluid restriction is indicated. We compared the Cumulative Fluids Intakes (CFluid.Int), the Cumulative Non-Protein Energy and Protein Intakes (CNPEN.Int and CProt.Int), and growth of the BPD infants (BPDs) with GA and BW-matched Controls (GA&BWCONTRs).
Result: Eight hundred fifteen patients met the inclusion criteria. In this cohort 127 infants were diagnosed as having BPD (Walsh MC J Perinat 2003) and 127 GA&BWCONTRs were selected for comparison using the dedicated software. Because of the study design, anthropometry at birth was not different between the two groups (BPDs vs GA&BWCONTRs: BW 919±260 vs 932±247 g, p=0.7; Total Length (TL) 34.8±3.3 vs 35.3±3.0 cm, p=0.2; Head Circumference (HC) 24.7±2.2 vs 24.7±1.9 cm, p=0.9). No differences were found in anthropometry at 36w-PMA between BPDs and GA&BWCONTRs (WT 1911±366 vs 1938±324 g, p=0.5; TL 42.6±2.6 vs 43.2±2.4 cm, p=0.1; HC 30.5±1.6 vs 30.6±1.4 cm, p=0.3, BPDs vs GA&BWCONTRs respectively). We did not find significant differences in CFluid.Int, macronutrient and energy intakes between BPDs and GA&BWCONTRs (CFluid.Int 8279±1970 vs 8616±2271 ml/kg, p=0.2; CNPEN.Int 5852±1504 vs 5999±1649 kcal/kg, p=0.5; CProt.Int 203±53 vs 211±64 g/kg/d, p=0.3).
Conclusions: We compared nutritional intakes and growth of BPD patients with a control group matched both for GA and BW. BPDs received similar macronutrient and energy intakes, had similar growth and nearly identical anthropometry at 36w-PMA.We speculate that the widespread notion of the "poor" growth of BPD infants lies either in suboptimal nutritional practices or in the erroneous selection of the control infants.

LOW SERUM ADIPONECTIN CONCENTRATIONS ARE ASSOCIATED WITH POSTNATAL GROWTH RETARDATION IN VERY PRETERM INFANTS

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Background: The adipocytokine Adiponectin (APN) enhances insulin-sensitivity and has been suggested to play a role in fetal and postnatal growth. Patients and
Methods: A descriptive cohort study of 64 preterm infants with a mean (SD) gestational age (GA) of 25.7 (1.9) weeks and birth weight (BW) of 853 (276) g. Blood sampling for analysis of serum APN was performed at 72 h of age, at day 7 and then weekly. Standardized measurements of weight, length and head circumference were performed weekly and energy and protein intake were calculated daily from birth until a postmenstrual age (PMA) of 35 weeks. Standard deviation scores (SDS) based on Scandinavian growth curves were calculated for the respective growth parameter.
Result: Concentrations of APN increased rapidly from 6.8 (4.4) µg/L at 72 h of age up to 37.4 (22.2) µg/L at 3 weeks of age with a subsequent decrease thereafter. Mean (SD) APN concentrations during day 3-21 were 26.1 (9.0) µg/L. Mean concentrations of APN during day 3-21 correlated positively with GA at birth ($r=0.46$ $p=0.001$), BW ($r=0.711$ $p<0.001$) and BW SDS ($r=0.42$ $p=0.003$). Further, mean APN concentrations during day 3-21 correlated with SDS weight ($r=0.62$ $p<0.001$), SDS length ($r=0.65$ $p<0.001$) and SDS head circumference ($r=0.62$ $p<0.001$) at a PMA of 35 weeks. The correlations between APN and growth parameters at a PMA of 35 weeks remained significant after adjustment for GA and SDS weight at birth. Energy intake (kcal/kg/d) during day 1-21 correlated with mean APN concentrations day 1-21 ($r=0.34$ $p=0.013$) and remained significant after adjustment for GA at birth, but not after adjustment for both GA and BW SDS. No correlation was observed between mean APN concentrations and protein intake (g/kg/d) during day 1-21.
Conclusions: Lower mean APN-concentrations during the first 3 weeks after very preterm birth are associated with a more pronounced growth retardation of weight, length and head circumference at a PMA of 35 weeks. The steep increase of APN concentrations after birth may be a compensatory mechanism to promote growth during the early postnatal period when deprivation of nutritional intake occurs.

POTENTIALLY HARMFUL EXCIPIENTS IN MEDICINES PRESCRIBED TO EUROPEAN NEONATES - ESNEE POINT PREVALENCE STUDY

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Background: Excipients are essential for many medicines. Some of them have been associated with significant consequences in neonates. At present little is known about the exposure and safety of excipients in that highly vulnerable group of patients, frequently treated with a variety of different medicines, that in itself is a risk of adverse drug reactions (ADR). Our aim was to describe the exposure of neonates to 7 potentially harmful excipients in European NICUs.
Methods: As part of the ESNEE project a Europe-wide point prevalence study (PPS) recording all medicines prescribed to neonates was performed. Data collection was performed in a web-based database within one day chosen by the unit during one of the three fixed two-week study periods of January to February; March or May to June, 2012. Excipients' data in prescribed medicines were identified from international Summaries of Product Characteristics. Based on previous studies on toxicity in neonates the excipients of interest (EOI) included parabens, saccharin sodium, benzalkonium chloride, benzyl alcohol/ benzoic acid/ sodium benzoate, ethanol, propylene glycol, polysorbate 80 and sorbitol. Neonates were stratified by gestational age (GA). Average number of prescriptions and the proportions of those containing EOI for each GA were calculated.
Result: Of 31 invited European countries 21 with 89 NICUs (73% 3rd and 21% 2nd level) joined the study. A total of 624 trade names with 280 active ingredients from 235 manufacturers were used. Neonates =28 days of age (n=726) received 2199 prescriptions, the number of prescriptions per baby being inversely related to GA with average (SD) number per neonate 4.53 (2.33); 3.95 (2.59); 2.68 (1.91) and 2.31 (1.93) in <28; 28-31; 32-36 and >36 weeks of GA band, respectively. Overall, 27% (n=601) of prescriptions and 23% of tradenames (n=144) contained at least one and 10% (n=227) of prescriptions and 13% (n=87) of tradenames more than one EOI. The proportion of prescriptions containing EOI increased with increasing in GA, being 20% (n= 80); 24% (145); 30% (187) and 33% (189) of prescriptions in <28; 28-31; 32-36 and >36 weeks of GA, respectively. Among EOI higher exposure to parabens (42% of neonates), polysorbate 80 (18%) and propylene glycol (15%) was observed, with <10% exposed to the rest of EOI. Enteral and topical formulations made up 67% of paraben, 96% of saccharin sodium, 100% of benzalkonium chloride, 57% of benzyl alcohol/ benzoic acid/ sodium benzoate, 67% of ethanol, 97% of propylene glycol, 78% of polysorbate 80 and 89% of sorbitol containing tradenames.
Conclusions: Potentially toxic excipients are not rare in medicines used in European NICUs with enteral and topical formulations serving as the primary source of exposure. Further integrated assessment of excipients content in neonatal medicines is needed to ensure optimal exposure with drug/ galenic form substitution applied where appropriate.

DEVELOPMENT OF THE LIVERPOOL ADVERSE DRUG REACTION AVOIDABILITY ASSESSMENT TOOL

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Background: The incidence of adverse drug reactions (ADRs) in hospitalised children ranges from 0.6 to 16.8% (1). A recent systematic review of ADRs in children highlighted that few studies performed an avoidability assessment (19/102) (1). There is currently no standardised method for determining avoidability and many of the established tools are not suitable for use in paediatrics and have not been developed systematically (2). We have used an adapted version of the Hallas Scale (3) as a basis for the development of a new avoidability assessment tool (AAT). Objectives 1. To develop and test a new AAT that is more suitable for use in paediatrics but which is also generalisable and applicable to a variety of other settings. 2. To compare individual to group assessments of avoidability
Methods: The initial draft of the AAT was developed via a consensus approach. Phase one consisted of three parts (defining the tool, modifying the tool and refining the tool) involving 2 multidisciplinary teams (MDT) each comprising a research children's nurse, paediatrician and pharmacist. Another researcher observed group process and gathered comments from the participants. Phase two involved the independent assessment of 50 ADR cases from the ADRIC study of adverse drug reactions in paediatric inpatients (4) by six reviewers acting independently.
Results: Phase 1: the assessment of 20 ADR cases by two MDTs showed agreement between the groups on 13/20 cases with a kappa score of 0.29 (95% CI -0.04 to 0.62). Group members commented that a mixture of professions was needed to give a full assessment of avoidability. Phase 2: the individual assessment of 50 ADR case reports by six individual reviewers where pair-wise kappa scores ranged from poor to good (0.12 to 0.75) and percentage exact agreement (%EA) ranged from 52-90%. Stronger agreement was found within professions than between professions.
Conclusion: Avoidability assessment is feasible but needs careful attention to methods. The Liverpool ADR AAT showed mixed inter-rater reliability (IRR) in the individual assessment phase; further testing in a group setting is required to develop and validate the tool. The next step in the development process will be to investigate how to optimise group assessment.
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SPONTANEOUS REPORTING OF ADVERSE DRUG REACTIONS TO MEDICATIONS ADMINISTERED ON NEONATAL UNITS: REPORTS TO THE UK YELLOW CARD SCHEME 2001-2010

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Background: The UK Medicines and Healthcare Regulatory Authority (MHRA) runs a national spontaneous reporting system (Yellow Card, YC, Scheme) for suspected Adverse Drug Reactions (ADRs). Many medications used in neonatology have not undergone regulatory approval so that surveillance for ADRs is imperative. In order to assess the adequacy of spontaneous reports about neonates, YCs submitted during the decade 2001-2010 were analysed to describe the reports and to compare the number of reports to the number of some sentinel events that would be expected in this population according to the literature.
Methods: Data on all UK spontaneous 'suspected' ADRs reported to the MHRA in children aged one year of less between 2001 and 2010 were supplied by the MHRA. The analysis included neonates likely to have received the suspect medication while an in patient on a neonatal unit (NNU) and excluded cases involving vaccinations or congenital anomalies, transplacental or transmammary delivery of the suspected drug. Estimates of the rates of some sentinel neonatal ADRs were estimated from the incidence of ADRs reported in Cochrane reviews combined with annualised estimates of medicines use based on a published survey of medicines use in 49 UK neonatal units (1).
Results: MHRA data: 3511 YC reports on children aged 1 year or less were received during 2001 - 2010. Fifty (1.4%) reports related to babies on a neonatal unit. Reporters suspected 36 different drugs of causing the ADRs in neonates. The most common drugs reported were caffeine (n=5), chlorhexidine (n=5), ibuprofen (n=3), vitamin K (n=3) and indomethacin (n=3). Data on gestation and postnatal age were limited, but 15 (30%) reports were from premature infants. Two fatal reactions were reported (4%). Over the 10 year period approximately 7 million babies were born in the UK giving an apparent incidence of ADRS of 0.0008% and of fatal ADRs of 1 in 3.5 million babies. Cochrane reviews report the incidence of ADRs reports in babies recruited to studies as steroids, hypertrophic cardiomyopathy, 0.9%; indomethacin, intestinal perforation or GI bleed, 3%; dopamine, tachycardia, 5%. Annualised estimates of the number of babies exposed to these medications were: steroids, 1040; indomethacin, 1664; dopamine, 1300. Estimated numbers of these ADRs over 10 years were: steroids and hypertrophic cardiomyopathy, 94; indomethacin and perforation or GI bleed, 500; dopamine and tachycardia, 650. Thus, c. 1250 episodes of these sentinel events alone would be expected in this population during this period, i.e. 25 times more than the total number of reports. Discussion Very few neonatal ADRs were reported using the YC Scheme. Estimated numbers of 3 sentinel neonatal ADRS extrapolated from the literature were much higher than the total number of reports. Underreporting of ADRs on UK neonatal units is probably common. If known ADRs are significantly underreported novel reports may also be missed. Spontaneous reporting of novel events in other countries has led to important developments in neonatal pharmacovigilance. This data suggests a need for increased awareness of, and reporting to, the Yellow Card scheme among UK neonatologists. (1) BMC Pediatr. 2009 Aug 12;9:50.

METHYL AND PROPYL PARABEN CONCENTRATIONS IN PRETERM NEONATES EXPOSED TO CLINICALLY INDICATED MEDICINES FALL WELL WITHIN SAFETY MARGINS FOR OESTROGENIC EFFECTS OF THESE ANTI-MICROBIAL EXCIPIENTS

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Background: Methyl and propyl parabens are widely used as anti-microbial excipients in oral liquid medicines given to neonates. There has been some concern about oestrogenic effects of methyl and propyl parabens. However, parabens are significantly less potent than naturally occurring oestrogens. In breast cancer cells 17ß-oestradiol was a more potent stimulus for proliferation than methyl paraben by a factor of 1.5x107 and propyl paraben by a factor of 1.5 x 106 [1]. This suggests that oestrogenic effects of parabens administered in medicines could be found if the concentrations of parabens were a million times greater than the concentrations of naturally occurring oestrogens. The current study aimed to assess whether paraben concentrations resulting from exposure to parabens in routine clinical practice are likely to cause oestrogenic effects in neonates. The objectives of this study were: 1. To measure circulating concentrations of parabens among neonates administered paraben-containing medicines in routine clinical practice; 2. To compare circulating concentrations of parabens with published circulating concentrations of 17ß-oestradiol in this population.
Methods: Novel data. Neonates in 4 UK and 1 Estonian neonatal units who were prescribed paraben-containing medications were recruited to an excipient kinetic study with parental consent. Parabens were assayed in timed, dried blood spots. Published data. A PubMed review of literature about 17ß-oestradiol concentrations in neonates was supplemented by discussion with experts in paediatric endocrinology.
Results: Novel data. 369 time points were assayed. The maximum methyl paraben concentration in a neonate was 541ng/mL and the maximum propyl paraben concentration was 147ng/mL. 204 (55%) of samples had methyl paraben concentrations below 20ng/mL with 298 (81%) samples of propyl paraben below this threshold. Published data. In a controlled trial of oestrogen in preterm neonates, the placebo group had median circulating 17ß-oestradiol concentrations of 200pg/mL at birth and 30pg/mL 28 days after birth [2]. Discussion. The difference between paraben concentrations in the current study and reported 17ß-oestradiol concentrations in preterm neonates was 10E3 in the worst case while the difference was 10E4 in the majority of cases. Since the difference in potency between 17ß-oestradiol and the parabens was 106, this suggests a 10E3- to 10E4-fold safety margin for parabens for oestrogenic effects in preterm neonates. It is important to avoid infection in this population. The inclusion of parabens allows the safe use of medicines on multiple occasions and and may avoid packaging medicines in single use dosage forms. It may not be necessary to exclude parabens from multiple-use medicines given to neonates because of concerns about oestrogenic effects.
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UMBILICAL CORD AND PLACENTA AS ALTERNATIVE MATRICES FOR COCAINE, OPIOIDS AND METHADONE IN UTERO DRUG-EXPOSURE DETECTION

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Introduction: Drug determination in biological matrices from mother and newborn is an objective measure of maternal and fetal drug-exposure. The aim of this study was to compare mother-hair, meconium, umbilical cord and placenta for detecting in utero drug-exposure to cocaine, opioids, methadone and amphetamines. Method: Mother-hair, meconium, umbilical cord and placenta were collected from 82 mother-newborn dyads. Mother-hair (segmented in trimesters) and meconium specimens were analyzed for cocaine, opioids, methadone and amphetamines. Umbilical cord and placenta specimens were analyzed, if either mother-hair or meconium had tested positive. Analyses were performed by LC-MSMS.
Result: In hair, 13 out of 82 participants tested positive; 11 to cocaine (cocaine 12-50,605pg/mg; benzoylecgonine 9-46,668pg/mg), 4 to methadone (89-26,845pg/mg), 1 to opioids (morphine 1,275-2,398pg/mg; codeine 261-914pg/mg; 6-acetylmorphine 6,061-15657pg/mg). In meconium, 3 out of 82 were positive; 3 to methadone (methadone 326-3,752ng/g; EDDP 5,957-25,179ng/g), 1 to cocaine (cocaine 7ng/g; benzoylecgonine 79ng/g; hydroxi-benzoylecgonine 135ng/g; ecgonine-methylester 56ng/g) and 1 to opioids (morphine 1,025ng/g; morphine-3-glucuronide 22ng/g; codeine 34ng/g). Placenta and umbilical cord were positive 3 out of 13 specimens; 3 to methadone in placenta (methadone 7-543ng/g; EDDP 10-51ng/g) and cord (methadone 17-183ng/g; EDDP 6-109ng/g); 1 to cocaine in placenta (benzoylecgonine 1ng/g; hydroxi-benzoylecgonine 2ng/g) and cord (benzoylecgonine 6ng/g); and 1 to opioids in cord (morphine-3-glucuronide 15ng/g; morphine-6-glucuronide 1ng/g). Meconium, placenta and umbilical cord only tested positive if hair concentrations were >SoHT cutoffs.
Conclusions: Mother-hair is the most sensitive specimen to detect drug consumption during pregnancy. Placenta and umbilical cord could be alternative to meconium to detect high in utero drug-exposure.

HOSPITAL-ACQUIRED HYPONATREMIA IN CHILDREN FOLLOWING HYPOTONIC VERSUS ISOTONIC INTRAVENOUS FLUIDS INFUSION: A SINGLE CENTER EXPERIENCE.

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Background: Parenteral Solutions (PS) may lead to serious, sometimes fatal, electrolyte abnormalities. In pediatric patients, Hospital-Acquired Hyponatremia (HAH) has been reported as one of the most common electrolyte abnormalities following PS administration. Objective: To evaluate the average change in serum sodium levels (mEq/L) within 24 hours of initiation of PS and to assess the incidence of HAH after the infusion of hypotonic vs. isotonic PS. Design/
Methods: A 5 year retrospective chart review was performed. Pediatric patients admitted to the pediatric ward who received PS for at least 12 hours were included. Patients with significant electrolyte disorders (specifically admission sodium <125 mEq/L or >155 mEq/L), moderate or severe dehydration, or those with evidence of renal insufficiency were excluded. Serum sodium levels on admission, as well as after PS infusion, were reported. Hyponatremia was defined as Na = 135mEq/dL. The results were analyzed by statistician.
Result: Over a 5 year period, 786 patients were identified who (1) received PS and (2) had assessment of serum sodium levels at admission and after =12 hours from the initiation of PS. Of those 586 were excluded leaving 200 patients to analyze. Average patient age was 8 years and average weight was 32 kg. There was no significant difference on the serum sodium on admission between the two groups. Of these 200 patients, 98 {49%} received hypotonic PS and 102 {51%} received isotonic PS. On average, patients that received hypotonic PS experienced a mean decrease of serum sodium of 1.74 mEq/dL On average, patients that received isotonic PS experienced an increase in serum sodium of 3.35 mEq/dL. Importantly in patients receiving hypotonic PS, 10 patients developed a serum sodium level =135 mEq/dL, whereas in patients receiving isotonic PS, only one developed a serum sodium of =135 mEq/dL (OR=11.47, 95%CI 1.44-91.45, P=0.02.)
Conclusions: In pediatric patients admitted to a general pediatric ward for treatment of common pediatric illnesses, administration of hypotonic vs. isotonic PS was associated with a > 10 times risk of HAH. This data suggests that the hospitalized pediatric patients receiving hypotonic PS should have intense serial assessment of serum sodium levels. More studies are needed to address the safety of the hypotonic PS in children.

NEW BRONCHOPULMONARY DYSPLASIA AS PREDICTOR OF LUNG FUNCTION AT SCHOOL AGE

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Introduction: Advances in neonatal and antenatal treatment practices have decreased the incidence and severity of respiratory distress syndrome, and improved survival of infants born very preterm. Nevertheless, the overall incidence of bronchopulmonary dysplasia (BPD) has not changed and even infants with mild respiratory distress after birth may develop 'new' BPD. BPD is diagnosed in very preterm infants (< 32-week gestation) who remain oxygen dependent at 28 days. BPD is graded by oxygen requirement at 36 postmenstrual weeks (Gr 1 = mild, room air; Gr 2 = moderate, O2 22-29%; Gr 3 = severe, O2 = 30% or requirement of ventilation). In children born preterm in pre-surfactant era the lung function abnormalities persist in to the adolescence and to the adulthood, particularly in those with BPD. Our aim was to investigate whether the lung function is still affected in school children born very preterm in the era of surfactant therapy, and whether BPD has a severity-dependent influence on lung function. Patients and **Methods:** Altogether 88 children who had been prospectively followed starting from very premature birth (< 32-week gestation), were recruited to the study of lung function at the age 6 to 14 years. Age- and sex-matched control subjects (n=88), born at term (= 37-weeks of gestation) were identified from the population register. Among children born preterm, 49 had had BPD (Gr 1, n=30; Gr 2, n=11; Gr 3, n=8). Spirometry and diffusing capacity for carbon monoxide (DLCO) were recorded for the two groups. The results were expressed as percentage of the national reference (mean±SD). Statistical comparison was performed by paired t-test. The predictive value of BPD grading on forced expiratory volume in 1 second (FEV1) and DLCO was tested by univariate analysis of variance.
Result: Children born preterm had lower airflow values in spirometry compared to the term controls: forced vital capacity (FVC) 91,3±11,2 vs. 95,0±10,1 (P=0,021); FEV1 86,6±11,5 vs. 95,0±10,1 (P<0,001), maximum expiratory flow at 50 % of vital capacity (MEF50) 78,3±20,0 vs. 97,5±22,8 (P<0,001), respectively. DLCO was lower in preterm compared to term children: 87,6±13,9 vs. 93,7±12,0 (P=0,005) expressed as percentage of predicted values. Among the preterm, there was a statistically significant difference in both FEV1 and DLCO between no BPD and Gr 2-3 BPD (P=0,043 and 0,035, respectively), but not between no BPD and Gr 1 BPD groups (P=0,125 and 0,062).
Conclusions: We show that in the surfactant era, the long term effect of very preterm birth to respiratory health is still evident. Both spirometry and diffusing capacity were significantly reduced in children born preterm compared to those born term. The reduction was most striking in values reflecting small airways (MEF50). The prematurity, per se, was associated with reduced lung function. The effect was more marked in children with moderate to severe BPD compared to children without BPD. According to present study, the very preterm birth and the degree of severity of BPD additively predict the decrease in lung function at school age.

VENTILATION-PERFUSION SPECT AND LUNG FUNCTION IN 10 YEAR OLD CHILDREN WITH BRONCHOPULMONARY DYSPLASIA

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Background: Several studies have shown that children with BPD have persistent lung problems at school age. We have previously shown that infants with BPD have significant ventilation perfusion mismatch measured with a scintigraphic technique, 3-D single photon emission computed tomography (SPECT), at the time of clinical grading of BPD; 36 weeks postmenstrual age. In some infants only 20% of the lung parenchyma has a normal V/Q matching. In healthy adults more than 85% of the lung parenchyma has a normal V/Q matching. Objective: To investigate if children who were diagnosed with BPD in infancy have persistent pulmonary abnormalities at school age measured with SPECT and conventional pulmonary function assessment. Design/
Methods: We have examined 26 children with mild, moderate or severe BPD at a mean age of 10,1 years (SD 0,96). Lung function was measured with 3-D ventilation (V)-perfusion (Q) scintigraphy (SPECT). V/Q matching was calculated in the reconstructed three-dimensional image of the lung with a resolution of 7 mm. Functional lung tissue was considered to be areas with a V/Q matching between 0,6-1,4. This was compared with the results from the Static (Body plethysmography) and Dynamic Spirometry.
Result: The average proportion of lung volume with normal V/Q was 71% (range 46,5-81,5%). There were no differences in V/Q values between the mild, moderate and severe groups. Children with BPD had a reduced lung function measured by spirometry. However, the conventional pulmonary function testing value abnormalities were more pronounced in the children with severe BPD. Grading of BPD Mild(10) Moderat(10) Severe(6) Background Gestational age (week) 27 25,7 27,4 Birthweight (gram) 1083 846 1028 Days with CPAP 31 41 51 Days with IPPV 4 12 16 Current status FEV1% of reference 85 79 71 FEV1/FVC 79 81 72 FEF50% 72 72 60 FRC PL % of reference 108 119 129 Asthma medication % 20 50 67 Lung volume with 72 69 72 normal V/Q: [0,6-1,4] %
Conclusions: The main finding in this study was that children with BPD have a reduced proportion of lung tissue within a normal V/Q ratio, compared to healthy adults, 71% versus 85%. The clinical severity grading of BPD at 36 weeks gestation does not correlate with the results on SPECT at 10 years of age. Further, patients with BPD have a worse lung function at 10 years of age measured with conventional spirometry.

A NOVEL ASSOCIATION BETWEEN YKL-40, A MARKER FOR STRUCTURAL LUNG DISEASE, AND SHORT TELOMERE LENGTH IN 10-YEAR OLD CHILDREN WITH BPD

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Introduction/background: Infants with immature lungs, sensitive to oxidative stress are at risk of developing bronchopulmonary dysplasia (BPD), a major cause of long-term morbidity following extreme prematurity. We still lack a biomarker to predict future morbidity of BPD after infancy. Relative telomere length is a biomarker for oxidative stress that has not yet been well studied in preterm infants developing BPD. Short telomere length is associated with increased oxidative stress. Preterm born children are exposed to more oxidative stress during infancy, especially with the need for long periods of oxygen treatment, causing hyperoxia. The chitinase-like protein YKL-40 is is a potential novel serum biomarker associated with airway remodeling and vascular smooth muscle proliferation and migration. We speculate that high levels of YKL-40 is associated with shorter telomeres. Patients and
Methods: Ten year old children were studied in an age- and sex matched controlled cohort study. Cases were children born preterm with bronchopulmonary dysplasia (n=29, mean gestational age of 27 weeks and mean birthweight 1070 ± 78 grams). Controls were children born at term (n=28, mean gestational age week 40 and mean birthweigth 3590 ± 69 grams), that developed phadiatope positive asthma during childhood. Lungfunction (dynamic and static spirometry), inflammation (cytokines and fractional exhaled nitric oxide, FENO) and relative telomere length (RTL) were tested and perinatal data was obtained from chart reviews. RTL was determined by quantitative real-time PCR by extracting DNA from whole blood. Serum levels of YKL-40 was analyzed by ELISA.
Results: Serum YKL-40 was significantly higher in children with BPD compared to children with asthma, 17.8 vs 13.2, p=0.002. No difference between the groups was found for RTL 1.555 vs 1.551, p=0.923. However, in children with BPD there was a significant correlation between shorter RTL and higher levels of serum YKL-40 (r=0,47, p=0,01). School aged children with BPD have significantly lower lung function (dynamic spirometry corrected for length and age, FEV1 76.6 vs 84.4, p=0.013 and FEF 25-75 55.2 vs 70.0, p=0.001) than children with asthma. Lungfunction did not correlate to YKL-40 or RTL. FENO was on a group level significanlty lower in the BPD group, 12.2 vs 23.7, p=0.014, indicating less inflammation compared to choldren with asthma at the time of RTL measurements.
Conclusions: In children growing up with BPD, a more severe structural lung disease may be associated with a genetic alteration, as shorter telomeres were found to correlate to higher levels of YKL-40. High serum levels of YKL-40 suggests an involvement of airway remodeling and fibrosis in BPD, but the correlation to RTL indicate that oxidative stress may play a part. Further studies are needed to elucidate if YKL-40 and telomere length can be used as biomarkers to predict the long-term consequences of BPD.

COMBINED ADVERSE NEONATAL OUTCOME (DEATH OR SURVIVAL WITH SEVERE INTRAVENTRICULAR HEMORRHAGE (IVH) AND/OR CRHONIC LUNG DISEASE (CLD) IN VERY-L0W-GESTATIONAL AGE (VLGA) INFANTS. A EURONEONET STUDY

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Background: Mortality rate for VLGA infants has steadily decrease over the last decade, however the rate of long-term complications related to CLD and/or adverse neurodevelopment has not shown such a clear trend. Aim: To analyse a combined adverse neonatal outcome (CANO: death after admission or survival with grades 3, 4 IVH and/or CLD.) in VLGA infants from a cohort of 37,371 VLBW infants born in 2006-2011 in EuroNeoNet units.
Methods: 12,605 VLGA infants with a gestational age (GA) <32 wks, admitted to NICUs and latter discharged after their 36 wks of corrected GA were studied. Non-parametric independent tests and logistic regression models were performed to predict CANO, using crude and adjusted odd ratios (OR) to determine perinatal associations. Predictive capacity was assessed by Hosmer-Lemeshow test and discrimination by area under ROC curve (AUC).
Result: The overall rate of the CANO was 31.2%, showing an11.5% decreases over the 6 years ($p<0.014$). However, this decrease was less than that observed for neonatal mortality rate (24.6%). Infants with CANO had a lower birth weight (BW) and GA, 1 and 5-min Apgar scores, were more frequently males born from single pregnancies by vaginal deliveries, had lower rates of prenatal care, corticosteroid exposure and more major congenital anomalies. Multiple regression analysis showed that GA BW, gender, 1 and 5-min Apgar scores and major birth defects were independent risk factors for the latter development of CANO ($p=0.036$), AUC(95%CI): 0.74(0.74-0.75) was significantly better than by using only GA and/or BW.
Conclusions: In VLGA infants, the decrease in CANO was smaller than the observed in neonatal mortality, thus, more survivors might latter develop a compromise health and neurodevelopment status.
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PERMISSIVE HYPERCAPNIA FOR EXTREMELY LOW BIRTHWEIGHT INFANTS - A RANDOMISED CONTROLLED MULTICENTRE TRIAL

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Mechanical ventilation for extremely low birthweight infants ist often life-saving, but associated with severe side effects such as bronchopulmonary dysplasia. Animal experiments and secondary analyses of previous studies suggest that ventilator pressures can be lowered and lung injury reduced when higher than usual partial pressures of carbon dioxide (PCO2) are tolerated. This randomized multicenter trial was designed and untertaken to test the hypothesis that higher targets for the PCO2 increase the rate of infants surviving without bronchopulmonary dysplasia (BPD).
Methods: Infants with a birthweight of 400-1000g and gestational age between 23 and 28 6/7 weeks who required endotracheal intubation and mechanical ventilation were randomized to two different target ranges for the PCO2, which were increased according to a schedule for the first 14 days of life but always differed by 15 mmHg between groups.The PCO2 targets in the hypercapnia group were (mmHg) 55-65 (day 1-3), 60-70 (day 4-7) and 65-75 (day 8-14) and in the normocapnia group 40-50 (day 1-3), 45-55 (day 4-7) and 50-60 (day 8-14). The primary outcaome was BPD, defined as requirement mechanical pressure support or supplemental oxygen at 36 weeks postmenstual age, or death before this date. A standardized oxygen rduction test was performed in infants on FiO2 values between 21% and 30%. Scheduled cranial ultrasonograms were centrally evaluated by a single paediatric radiologist.
Result: Recruitment was terminated early after an interim analysis performed on the data of 312 patients because the recruitment rate remained lower than expected due to a declining proportion of infants requiring invasive mechanical ventilation. The results of the interim analysis were as follows (hypercapnia/normocapnia): Number 156/156, Birthweight 714±159 / 710±155, BPD oder death 57 (38%) / 51 (35%), IVH1-4 53 (34%) / 55 (36%), IVH3-4 21 (14%) / 15 (10%). Infants randomized into the hypercapnia arm fell short of their PCO2 target range twice as often (73±19 times per patient) as infants in the normocapnia arm (36±22 times per patient).
Conclusions: Preliminary data of this largest permissive hypercapnia trial in infants to date suggest that the higher PCO2 target range was not associated with a higer rate of survival without BPD. Furthermore, there was no influence on the rate of severe intracranial hemorrhages. Many patients compensated reductions of mechanical ventilatory support by increased breathing efforts and thus fell short of the hypercapnia target ranges. Data collection of all patients and neurodevelopmental follow-up exams are ongoing. Data encompassing all 362 infants will be available before the meeting and will be presented.

HIGH-FLOW NASAL CANNULAE VS. NASAL CPAP FOR POST-EXTUBATION RESPIRATORY SUPPORT OF VERY PRETERM INFANTS: A MULTICENTRE, RANDOMISED, NON-INFERIORITY TRIAL.

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Background: High-flow nasal cannulae (HFNC) are an increasingly popular alternative to nasal continuous positive airway pressure (NCPAP) for non-invasive respiratory support of preterm infants. However, little evidence exists for the efficacy or safety of HFNC in this population.
Methods: We randomly assigned preterm infants born <32 weeks' gestational age (GA) to receive either HFNC or NCPAP as post-extubation support, stratified by GA (<26 weeks, 26 weeks and above) and by centre. Infants received HFNC 5-6 Litres per minute or NCPAP 7 centimetres of water (cm H2O) at extubation. The primary outcome was treatment failure within 7 days, using pre-specified, objective failure criteria. Non-inferiority was determined by calculating the risk difference (95% CI) for the primary outcome; the margin of non-inferiority was 20%. Infants in whom HFNC failed could receive 'rescue' NCPAP 7 cm H2O. They were re-intubated if the failure criteria were again satisfied within the primary outcome period. Infants in whom NCPAP failed were re-intubated. Data were collected until hospital discharge.
Result: 303 infants were randomised at three participating centres. The mean GA and birth weight of infants was 27.7 weeks, 1041 g in the HFNC group (n=152), and 27.5 weeks, 1044 g, in the NCPAP group (n=151). Maternal and other infant demographics were similar. HFNC were non-inferior to NCPAP by our definition: treatment failure occurred in 52/152 (34.2%) of the HFNC group and 39/151 (25.8%) of the NCPAP group: risk difference (95% CI) 8.4 (-1.9, 18.7) %. In infants <26 weeks' GA the risk difference (95% CI) was 20.0 (-1.9, 41.8) %; in infants 26 weeks or above this was 5.0 (-4.9, 14.9) %. Almost half of infants in whom HFNC treatment failed were rescued from re-intubation by NCPAP: 27/152 (17.8%) of the HFNC group were re-intubated within 7 days, compared to 38/151 (25.2%) of the NCPAP group (P=0.12). There was significantly less nasal trauma in the HFNC group (P=0.01), but no difference in any other secondary outcomes including death, bronchopulmonary dysplasia, pneumothorax or duration of hospitalisation.
Conclusions: HFNC therapy was non-inferior to NCPAP as post-extubation support in very preterm infants. HFNC use resulted in no increase in mortality or morbidity, and caused less nasal trauma than NCPAP.

VENTILATORY SETTINGS ON HIGH FREQUENCY OSCILLATORY VENTILATION WITH VN-500 AFTER SWITCH FROM CONVENTIONAL VENTILATION

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Introduction: High frequency oscillatory ventilation (HFOV) is used to treat severe respiratory failure in term and preterm infants. The HFOV mode on the new Babylog VN500 (Draeger, Luebeck, Germany) is more powerful and has the ability to control tidal volume (VT). There is limited information about experience with this device in HFOV mode of ventilation. Aim: The aim of this post-hoc analysis was to see if there are any significant differences after switch from conventional mode of ventilation (CMV) between 1st HFOV settings and optimized HFOV settings in order to validate internal clinical protocol.
Methods: We have analyzed newborns admitted to the level III NICU from January till September 2012. Patients were treated with VN-500 in HFOV mode according to strict clinical protocol. Criteria for HFOV initiation included: PCO2 > 65mmHg on two consecutive arterial blood gases (ABGs) and RR > 60/min. MAP was set at the same level as during CMV and pressure (dPhf) based on the chest movement. Full ABGs with corresponding vent settings, clinical diagnosis, time and patient's weight were prospectively recorded. ANOVA for parametric (Friedman's test) and nonparametric (Dunn's test) distribution was used for comparison of: pH, pCO2, MAP and PIP/dPhf.
Result: There were 26 patients treated with HFV with birth weight = 830.6 + 133.7 g and gestational age = 26.1 + 1.5 weeks (mean + SD). Total of 305 sets of ABGs and ventilatory settings recordings were included and 293 were analyzed. There were no significant differences between 1st HFOV and Optimized HFOV. The only significant difference was noted between 1st HFOV and Post HFOV for dPhf ($p<0.05$).
Conclusions: Lack of significant difference between 1st HFOV and Optimized HFOV suggest that utilized protocol is acceptable. Trend towards lower values of dPhf may suggest use of its' lower settings, which should be verified in larger studies. CMV 1st HFOV Optimized HFOV Post HFOV pH 7.14 7.3 7.27 7.28 pCO2 66.26 40.5 46.33 45.22 MAP 9.79 9.3 8.6 7.96 PIP/dPhf 18.5 18.81* 16.38 15.58* RR/freq 55.81 14.2 14.17 41.65 VT/kg 6.36 2.57 2.28 5.37 *- $p<0.05$

EFFECTS OF THE SYSTEMATIC INTRODUCTION OF A LOW-COST BUBBLE NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE IN A LARGE NEONATAL INTENSIVE CARE UNIT IN NICARAGUA

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Background: In Lower-Middle Income Countries (LMIC), the newborn death rate is still dramatic. The lack of economic and human resources makes its reduction challenging. Nasal Continuous Positive Airway Pressure Ventilation has proven an even greater efficacy than invasive mechanical ventilation requiring intubation and offers the advantage of great cost-effectiveness. The impact of the systematic use of a low-cost bubble nasal continuous positive airway pressure device (bNCPAP) was retrospectively analysed in the newborn intensive care unit of the Bertha Calderon Hospital of Managua, Nicaragua.
Methods: From May 2006, bNCPAP was systematically applied to all newborns requiring ventilatory assistance, starting soon after birth. Data from all patients admitted between May 1 and December 31, 2006 (before the project began), and from May 1 to December 31, 2008 (two years after the project started), were retrospectively and anonymously collected. Children were classified as ventilator assisted (VA) or non-ventilator-assisted (NVA). VA were further divided whether receiving: 1) only mechanical ventilation (MV); 2) only bNCPAP (bNCPAP); 3) bNCPAP before MV (bNCPAP-MV) and 4) MV before bNCPAP (MV-bNCPAP). All patients requiring intubation (MV, bNCPAP-MV, MV-bNCPAP) were further categorised into an additional group called endotracheal tube (ETT). Data regarding gestation, postnatal course, mortality rate, duration of recovery and distribution of the nursing load were finally analysed.
Result: 779 (2008 n=471) cases were included, 613 of which belong to the VA group, with similar proportion between 2006 (n=230, 74,7%) and 2008 (n=383, 81,1%). Among VA, however, bNCPAP increased, from 27.8% in 2006 to 60.8% in 2008 (p <0.0001), while MV decreased, from 50% in 2006 to 10% in 2008 (p=0, 0001), accounting for an overall ETT decrease, from 72% in 2006 to 39% in 2008 (p= 0, 0001). No differences were found in the percentage of MV-bNCPAP patients (p= 0.5467), while the bNCPAP-MV increased from 15.2% to 23% (p=0.02). Mortality rate dramatically reduced, from 31.8% (n=96) in 2006 to 19.7% (n=93) in 2008 (p=0.0003); a significant increase was only recorded in the MV group, from 52.8% in 2006 to 90% in 2008 (p < 0.0001). Considering all VA newborns who died, lower mean gestational age (GA), 30.7 vs 32.5 weeks, and birth weight (BW), 1,383 gr vs 1,633 gr, were observed in 2008 compared with 2006. During both periods, probability of death was inversely related with GA (p <0,0001) and ETT group belonging (p<0.0001). NICU length of admission significantly increased only considering VA, from 14.7 days in 2006 to 17.5 days in 2008 (p=0.048). Nursing workload shifted to the bNCPAP patients, with an estimated increase (hours) of 178% and an hypothetical saving (hours) for ETT patients assistance of 51%. Interpretation: This is the first wide scale study demonstrating the efficacy of the systematic use of a low-cost bNCPAP device in a large NICU from a LMICs.
Results: observed strongly support the early use of bNCPAP as the primary respiratory assistance strategy to provide positive changes in terms of mortality, medical assistance and nursing workload.

EFFICACY OF FLOW SYNCHRONIZED NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION (S-NIPPV) TO TREAT APNOEA OF PREMATURITY (AOP)

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Background: AOP is a common problem in preterm infants which can be treated with nasal ventilation. The most used modes are nasal continuous positive airway pressure (NCPAP) and nasal intermittent positive pressure ventilation (NIPPV). It is unclear whether S-NIPPV would be even more effective for AOP. Our aim was to assess the effects of NCPAP, NIPPV and flow S-NIPPV on the rate of desaturation events and bradycardias in very low birthweight infants and to evaluate the influence of these modes of ventilation on pattern of breathing and gas exchange. Patients and
Methods: Nineteen infants (mean gestational age at time of study 30 weeks, 9 males) receiving NCPAP and caffeine for AOP were enrolled in a randomised controlled trial with a crossover design. The infants were allocated to receive NCPAP, NIPPV and flow S-NIPPV for 4 h each. All nasal ventilation modes were provided by a nasal conventional ventilator (Giulia, GINEVRI srl, Italy) which is able to synchronize the infant's inspiratory efforts to mechanical breaths by mean of a pneumotachograph. Throughout the study were simultaneously monitored and recorded: airway flow, airway pressure, standard thoracic impedance, ECG and beat-to beat HR, SpO2 and pulse waveform, RR and transcutaneous PO2 and PCO2.The primary outcome was the event rate of desaturations (£80%) and bradycardias (£80 bpm) per hour occurring during each mode of ventilation. The incidence of central apneas, scored if the amplitude of chest wall movements fell to <20% of the average amplitude of the preceding breaths for ³10 sec and the airway flow was absent, as well as HR, FiO2, SpO2, transcutaneous blood gases and RR trends during each mode were also evaluated.
Result: The median rate of desaturations/h with NCPAP, NIPPV and flow S-NIPPV was 5, 5.15, and 2.9 respectively (p=0.009 for both compared to flow S-NIPPV). There were no differences in bradycardias events between NIPPV and S-NIPPV (median value=0), while they were significantly more frequent during NCPAP (median value 0.24, p=0.01). Compared to NCPAP and NIPPV, central apneas were significantly less frequent during flow S-NIPPV (3.6, 4.8 and 1.6 respectively, p=0.009) and HR significantly lower (median values: 159, 158 and 156 bpm respectively, p=0.0004). No differences in baseline FiO2 SpO2, RR and transcutaneous blood gases were observed comparing the three ventilation modes.
Conclusions: Flow S-NIPPV seems to be more effective in treating AOP in preterm infants than NCPAP and NIPPV.

VALIDATION OF A FLOW-SENSOR FOR NASAL SYNCHRONIZED VENTILATION IN A SIMULATED NEONATAL MODEL

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Background: Nasal intermittent positive pressure ventilation (NIPPV) is increasingly used to assist breathing in premature infants and many clinical data suggest that synchronization (SNIPPV) may improve its effectiveness. A flow-synchronized nasal neonatal ventilator (Giulia, Ginevri srl - Rome Italy), whose flow-sensor is controlled by a dedicated software, is available in Europe. A common criticism of using a flow sensor for non invasive ventilation is that its reliability can be altered by the continuous flow passing through it generated by the variable leaks from the infant's nostrils and mouth. We set out to demonstrate, in a simulated neonatal model, the reliability of Giulia flow-sensor.
Methods: we developed a SNIPPV simulator to evaluate the performance of the Giulia ventilator with different measured leaks through the flow-sensor. The standard circuit of the ventilator was completed with a high-precision, low-resistance flow-sensor placed between the Giulia flow-sensor and the prongs in order to measure the total flow towards the patient. One of the two prongs was left completely open to create a large leak, whereas the other was connected to a neonatal test-lung contained in a cylinder. The inflation of the test lung was obtained using an electric engine that moves a syringe generating a negative pressure inside the cylinder. The electric engine was programmed so as to generate, in 0.33 seconds, a tidal volume of 5 or 3 ml of air beyond the resting volume of the test lung, mimicking respectively a 'high' and 'low' spontaneous inspiratory flow. The fixed parameters set on the Giulia ventilator were: Ti 0.3 sec, PIP 20 cmH2O, Trigger level 0.2 l/min. By contrast, in order to obtain different leak-flows, we tested the system with increasing PEEP (5 - 8 - 10 cmH2O) and set flow levels (8 - 10 L/min).
Result: the resulting leak-flow using different PEEP and set flows were in the range of 2.8 -4L/min (28 to 46% of the set flows). We took 10 measurements in each experimental condition obtained combining different PEEP and set flow levels with 'high' and 'low' spontaneous inspiratory flow. The Giulia flow-sensor detected 100% of the simulated spontaneous breaths in presence of any tested amount of leak from the prongs. The mean response time, measured from the beginning of spontaneous inspiration to the beginning of the inspiratory pressure rise in the circuit, was 64±(SD)7 ms (range 46-77 ms) and not influenced by the amount of leak. In all the experimental conditions, the minimum spontaneous inspiratory volumes detected by the Giulia flow-sensor to trigger a mechanical breath were 0.021±(SD)0.002 ml and 0.027±(SD)0.004 ml with 'high' and 'low' spontaneous inspiratory flow respectively, while the minimum flow activating the trigger was 3.3 ml/sec.
Conclusions: the Giulia flow-sensor for non invasive ventilation is capable of detecting very small 'spontaneous' inspiratory volumes and flows and its performance is not affected by the leaks. These results are consistent with in vivo observations (1-3).
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WORK OF BREATHING FOR NEONATAL FLOW METERS WITH IN-LINE AND FLOW-THROUGH TECHNIQUE IN SIMULATED BREATHING

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Introduction Measurement of airway flow allows determination of respiratory parameters during ventilatory support and lung function testing. Measurement can be with in-line or flow-through technique and there are several flow meters available. Neonatal flow measurement involves several challenges; 1) an increase in dead space or flow resistance may influence measurement 2) there is a need for high resolution at low flows 3) for premature infants receiving NCPAP treatment there is limited access to in-line measurement and 4) the NCPAP system generates noise. The aim of this in-vitro investigation is to determine the resistance of flow measurement devices. Method Resistance to flow was determined for a sinus flow curve with flow max of 6 l/min and 1 Hz generated by a mechanical lung model (ASL5000). The flow devices were 1) tested at 0-5-10 l/min bias flow and 2) on the expiratory outlet (connected with 20 cm tubing) from a variable flow CPAP generator (Infant Flow) at 3-5-8 cm H2O. The Florian device was also tested with a fixed flow CPAP generator (Neopuff). Imposed work of breathing (iWOB) and pressure swings were determined for 20 cycles. Flow was recorded to evaluate resolution and noise. The tested devices were Fleisch size 0 (pneumotach), Florian (hot-wire) and NDD (ultrasonic flight-of -time, size small).
Results: An increase in bias flow from 0 l/min (corresponding to in-line position) to 10 l/min (corresponding to flow-through position) increased the iWOB: Fleisch 2,1 to 2,5 mJ, Florian 2,6 to 6,7 mJ and NDD 3,2 to 9,6 mJ. The in-line position with 10 l/min bias flow generated a CPAP level of: Fleisch 0,8 cm H2O, Florian 1,5 cm H2O and NDD 2,1 cm H2O. The work of breathing for flow-through placement in combination with the Infant Flow generator (5 cm H2O CPAP) were: Fleisch 4,3 mJ, Florian 6,7 mJ and NDD 7,9 mJ with pressure swings of: Fleisch 1,9 cm H2O, Florian 2,8 cm H2O and NDD 3,3 cm H2O. The iWOB for Florian in combination with 5 cm H2O CPAP generated with Neopuff were: 27,0 mJ (in-line) and 24,4 mJ (flow-through) with pressure swings of 11,5 cm H2O (in-line) and 10,3 cm H2O (flow-through).
Discussion There were large differences in iWOB between the tested flow meters. The flow through technique has the advantage of being dead-space free but the flow resistance of the measuring device will give an increase in iWOB as well as in CPAP level. The lowest flow resistance and generated CPAP were with the Fleisch pneumotach. A flow-through technique with a variable nasal CPAP device seems feasible. Measuring flows with Florian in combination with Neopuff has high iWOB and flow resistance.

FEASIBILITY OF A NEW CARDIO-RESPIRATORY MONITOR IN PRETERM INFANTS: TRANSCUTANEOUS ELECTROMYOGRAPHY OF THE DIAPHRAGM

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Background: Preterm infants often suffer from apnea accompanied by bradycardia and desaturation. These cardio-respiratory events are usually detected by chest impedance (CI) monitoring. However, CI monitoring has limitations in classifying apnea of prematurity, which is important when determining the optimal clinical intervention. Transcutaneous electromyography of the diaphragm (dEMG) might improve detection and classification of apnea as it measures the activity of the diaphragm more directly. However, first the feasibility and repeatability of dEMG for monitoring respiratory rate (RR) and heart rate (HR) in preterm infants needs to be established.
Methods: Preterm infants with a gestational age (GA) between 26 - 32 weeks and on non-invasive respiratory support were enrolled in the study. RR and HR were monitored simultaneously by dEMG (Dipha-16, Inbiolab, Netherlands) and CI (MP90, Philips, Netherlands) for 1-hour on day 1, 3 and 7 after birth. RR and HR recorded by both techniques were calculated 6 times taking 1-minute measurements across the 1-hour recording. Data were compared using Pearson's correlation coefficient (r) and Bland Altman (BA) plots. Subgroup analysis was done for postnatal age (day 1 - 3 - 7) and GA (26/27; 28/29; 30/31 weeks).
Result: Thirty-one preterm infants (GA 29.6 ± 1.8 wk; birth weight 1380 ± 348 g) were included in the study. Electrode placement for dEMG measurements was well tolerated and no skin lesions were observed. Overall dEMG signal quality was good. RR ($r = 0.88$) and HR ($r = 1.00$) correlated significantly ($p < 0.01$) between dEMG and CI. BA-plots showed good agreement between both techniques, with small differences for RR. Subgroup analysis for RR to assess long term repeatability (day 1 - 3 -7) correlated significantly with respectively, $r = 0.82$, $r = 0.89$ and $r = 0.93$. Analysis for GA (26/27; 28/29; 30/31 weeks) correlated significantly with $r = 0.89$, $r = 0.95$ and $r = 0.83$ respectively. Subgroup analyses for HR were all significant with $r > 0.99$.
Conclusions: This study shows feasibility and repeatability of transcutaneous dEMG for cardio-respiratory monitoring of RR and HR in preterm infants. Future studies need to investigate whether this non-invasive and easy applicable tool has additional value in detection and classification of apnea.

ALTERED REGIONAL MICROSTRUCTURE IN THE CORPUS CALLOSUM (CC) IN INFANTS WITH CONGENITAL HEART DEFECTS (CHD)

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Background: Magnetic resonance imaging (MRI) studies have shown that many newborn infants with CHD have preoperative and post-operative white matter brain injury (1). A conventional MR study showed that preoperatively present injury did not progress from the preoperative to postoperative MRIs (2). Abnormal microstructural development assessed by diffusion tensor MRI (DTI) in the genu of the corpus callosum of infants with transposition of the great artery (d-TGA) before and after surgery has been recently reported (3). Aim: To assess the microstructural regional variation in the corpus callosum development in infants with cardiac defects before and after surgery and compared to healthy term infants using DTI. Patients/ **Methods:** Brain MRI were acquired on a 3T GE MR scanner in fifteen infants with TGA (mean (SD) gestational age at birth 39.4 ±1.2 weeks; age at scanning preoperatively 8 ±2 days; postoperatively 29 +/- 5 days) and in twenty healthy term infants (gestational age at birth 39.2 ±1.2 weeks; age at scanning 23 ±6 days). The imaging protocol included a DTI scan using a 35 gradient directions (b_value = 700 [s/mm2], slice thickness 2.5mm, in plane resolution of 0.8±6 x 0.86 mm2). Fractional anisotropy (FA), axial and radial diffusivity and apparent diffusion coefficient maps were calculated using DTI Studio software. ROIs were drawn manually on FA color maps in five parts of the CC: genu (GCC), rostral part body (RCC), body (BCC), isthmus (ICC), splenium (SCC). Significant difference controlling for age between preoperative, postoperative patients and healthy controls was defined as p level <0.05.
Result: Regional variation: Similar pattern of diffusion and anisotropy measures along the five selected parts of the CC was shown in pre-and post-surgery imaging compared to term healthy infants. Lowest FA and axial diffusivity values were found in the isthmus with corresponding high radial and mean diffusivity. Pre-surgery vs healthy term infants: Significant higher axial diffusivity in the RCC, higher radial and mean diffusivity in the GCC, SCC and RCC were found in the infants with CHD before surgery compared to healthy term infants. SCC and GCC FA were significantly lower in infants with CHD compared to healthy term infants. Post-surgery vs healthy term infants: Significant higher radial and mean diffusivity were found in all parts of the CC. Axial diffusivity was significantly higher in the GCC, RCC and BCC in infants with CHD compared to healthy term infants. FA was significantly lower in infants with CHD in all parts of the CC except of the GCC. Pre-vs postsurgery Radial and mean diffusivity were significantly higher in post-surgery scanning in the ICC compared to pre-surgery scanning.
Conclusions: Regional altered microstructure could already be found in pre-surgery imaging in infants with CHD with most prominent changes in the body and isthmus of the CC, suggestive of delayed white matter development and gliosis. After surgery radial and mean diffusivity were higher only in the isthmus of the CC. Neurodevelopmental follow-up of these infants is ongoing. Referenzen: (1) Mahle WT etal, Circulation 2002 (2) Block Aj et al., J of thoracic and cardiovascular surgery 2010 (3) Makki M et al, AJNR 2013

EARLY DETECTION OF VENTILATION-INDUCED BRAIN INJURY USING MAGNETIC RESONANCE SPECTROSCOPY AND DIFFUSION TENSOR IMAGING

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Background: Very preterm infants commonly require respiratory support at birth, but this initial management may be harmful to the immature brain. Injurious ventilation of preterm lambs has adverse effects on the brain, with histological injury evident after only 90 minutes (Polglase et al., 2012). In this study, we aim to investigate whether Magnetic Resonance Spectroscopy (MRS) and/or Diffusion Tensor Imaging (DTI) can be used for early in vivo detection of ventilation-induced brain injury in preterm lambs.
Methods: Lambs (0.85 gestation) were delivered and resuscitated with a 'protective ventilation' strategy (PV, n=7: prophylactic Curosurf®, one sustained inflation, tidal volume (VT) 7mL/kg, positive end expiratory pressure (PEEP) 5cmH2O) or an initial 15 minutes of 'injurious ventilation' (IV, n=10: VT 12mL/kg, no PEEP, late Curosurf®) followed by PV for the remainder of the experiment. At 1 hour, lambs underwent Magnetic Resonance Imaging (Siemens, 3Tesla) for visual analyses of T1- and T2- weighted images. MRS was performed using a localized single-voxel (15x15x20mm, echo time 270ms) encompassing suptratentorial deep grey matter and central white matter. Peak-area ratios for lactate (Lac) relative to N-acetylaspartate (NAA), choline (Cho) and creatine (Cr) were calculated. For measures of Mean/Axial/Radial Diffusivity (MD, AD, RD) and Fractional Anisotropy (FA), 30 direction DTI was performed and regions of interests were investigated in the thalamus, internal capsule, periventricular white matter and the cerebellar vermis. Groups were compared using 2-way RM-ANOVA, Mann-Whitney U-test and Spearman's correlations.
Results: Injuriously ventilated lambs had higher VT and peak inspiratory pressures (PIP) during the first 15min compared to PV lambs (both $p<0.001$). At experimental endpoint, IV lambs had a greater requirement for respiratory support than PV lambs (mean PIP 43±6 vs 30±3, $p<0.001$, mean oxygen saturation 81±9 vs 90±5, $p<0.05$) and were more acidotic (mean pH 7.09±0.2 vs 7.28±0.2, $p<0.05$). Inspection of conventional MR images revealed no gross injuries or abnormalities. Peak-area MRS lactate ratios >1.0 was only seen in IV lambs. In 3/10 IV lambs, Lac/Cr and Lac/Cho ratios were significantly higher compared to the other IV lambs and in comparison to all other animals: Lac/Cr: 2.15±1.5 vs 0.39±0.2 and 2.15±1.5 vs 0.33±0.2, $p<0.05$, Lac/Cho: 2.02±1.6 vs 0.29±0.1 and 2.02±1.6 vs 0.25±0.1, $p<0.05$. At group level, a trend of higher mean ratios for Lac/Cr (0.92±1.1 vs 0.27±0.2, $p<0.1$) and Lac/Cho (0.81±1.1 vs 0.21±0.1, $p<0.1$) was seen, which correlated with lower pH in both groups (rho= -0.496 and rho=-0.492, $p<0.05$). On DTI, IV lambs had higher mean FA (0.20±0.02 vs 0.18±0.02, $p<0.05$) and lower mean RD [(7.8±0.3)x10-4 mm2/sec vs (8.4±0.3)x10-4 mm2/sec, $p<0.05$] in thalamus compared to PV lambs. Two of the IV lambs had significantly higher FA, lower MD, lower AD and lower RD ($p<0.05$ for all) in the cerebellum compared to the other animals, but no overall diffusion differences were seen when comparing the IV group to the PV group.
Conclusion: Acute changes in brain diffusion measures and metabolite peak-area ratios were observed after injurious ventilation, and may reflect the initiation of brain injury. These changes may precede morphological abnormalities that were not detected by conventional MRI.

THE IMPACT OF QUALITY AND POSTPROCESSING METHODS OF DIFFUSION TENSOR IMAGING ON FIBER TRACTOGRAPHY OF THE PRETERM BRAIN

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Introduction: Diffusion Tensor Imaging (DTI) scans enable in vivo, quantitative assessment of the neonatal brain. Because it is thought to provide early biomarkers of outcome, DTI is rising exponentially and has become important for quantification of brain abnormalities. However, because measurement accuracy depends on various aspects, including image acquisition, subject motion and postprocessing, interpretation of neonatal DTI requires a dedicated approach. Current neonatal DTI studies seem to focus too little on these important aspects. Our aims were to study the effects of postprocessing methods on DTI tractography and to perform a systematic review of literature regarding strategies to improve reliability of neonatal DTI analysis. Patients and
Methods: 28 DTI data sets of preterm infants born <29 weeks' of gestation and scanned at 30 weeks' (29 4/7- 30 4/7 weeks) postmenstrual age without evidence of intracranial abnormalities were prospectively collected. MRI procedures were performed according to a previously published dedicated guideline, written informed parental consent was obtained for all subjects. Prior to analysis with Explore DTI (http://www.exploredti.com/), DTI images were corrected for eddy currents, EPI distortions and subject motion. Calculation of DTI parameters was performed according to four different methods of tensor estimation that differ in processing speed and principle: 1) linear least squares (LLS); 2) weighted linear least squares (WLLS); 3) non linear least squares (NLLS), and 4) robust estimation of tensors by outlier rejection (RESTORE). Deterministic fiber tractography of the fornix was performed by placing regions of interest. DTI quality and fiber tracking results were quantitatively and qualitatively evaluated. Systematic review of literature was performed using the following keywords: prematurity, neuroimaging, brain, and DTI. After exclusion of papers that did not comply with our conditions, 58 articles were incorporated for further analysis.
Result: DTI analysis was significantly affected by data quality and method of tensor estimation. The RESTORE approach resulted in a significantly decreased mean FA value in comparison with LLS and WLLS: 0.178 versus 0.185 and 0.184 respectively. Automated rejection of outliers before tensor estimation seemed more precise: standard deviation of mean FA value was significantly decreased: RESTORE: 0.0511; LLS: 0.0587; WLLS: 0.0541; NLLS: 0.0517. Quality of tractography was correlated to data outliers (Spearman's correlation coefficient: -0.46; p-value: <0.01) and was significantly higher for RESTORE, this correlation was particular evident for more corrupted datasets (Fig. 1). According to our systematic review; only 3 studies (5.2%) applied a standardized and well-defined evaluation of corrupted DTI data, estimation of the diffusion tensor was not described by 11 studies and only 1 study performed automated detection of outliers before tensor estimation.
Conclusions: Although quality assessment and postprocessing have considerable impact on neonatal DTI analysis, current literature seems insufficient to provide detailed description of these aspects. Before drawing conclusions regarding neurodevelopmental outcome of preterm infants, future studies should apply dedicated acquisition settings, standardized quality assessment, reliable postprocessing techniques and genuine interpretations of neonatal DTI.

QUANTITATIVE ASSESSMENT OF T1 RELAXATION AND DIFFUSION AS A PROGNOSTIC TOOL FOR BRAIN DEVELOPMENT: A SERIAL STUDY ON HEALTHY PRETERM BABIES

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Background: Despite major advances in care of premature infants, survivors exhibit cognitive deficits in around 40%. Beside severe intraventricular haemorrhages (IVH) and cystic periventricular leucomalacia (PVL), more subtle patterns such as punctuate white matter lesions, diffuse PVL and alteration of brain development might be linked to the cognitive deficits observed. Novel techniques in MR-imaging are emerging, such as MP2RAGE (magnetization prepared dual rapid echo gradient) which produces quantitative T1 relaxation maps and allows to detect tissue anomalies such as dysmyelination. Diffusion tensor imaging (DTI), which reflects white matter maturation, is also widely used, but serial measurement during brain development is missing.
Methods: We included healthy (without IVH grade III/IV and cPVL) preterm infants born before 30 weeks of GA and performed serial MR-imaging at days of life 5, 15 and at term equivalent age (TEA), using DTI and MP2RAGE sequences, on a 3T Magnet Siemens (Trio). Multiple measurements were performed for each exam in 13 defined white and grey matter regions of interest (ROIs). Neurodevelopmental assessments were performed at 6 and 18 months of corrected age (CA).
Result: 48 patients were recruited: mean GA 27 4/7 weeks, mean BW 931g ± 245. 115 MRIs were performed (40 early, 36 late and 39 at TEA). Measures of relaxation time T1 showed a gradual and significant decrease over time (for PLIC 15%, central WM 13%). Measurements of ADC values showed similar monotonous decrease over time, but with a less narrow and precise distribution than T1 map (for PLIC 9%, central WM 16%). There was a strong correlation between relaxation time T1 and ADC values (R^2= 0.73). Early high ADC values in frontal WM were predictive of diffuse PVL at TEA. Measurements of the relaxation time T1 at TEA was significantly different between categories of lesions (healthy preterm at term and diffuse PVL: $p<0.05$). These differences were also observed between male and female at TEA. T1 map values at TEA correlated significantly with WM abnormality scores according to Woodward et al. and with developmental quotient at 6 months of CA.
Conclusions: Serial and quantitative MR imaging in very preterm infants is feasible. On the successive MP2RAGE and DTI sequences, we observed a gradual decrease over time in the described ROIs, reflecting the progressive maturation of the WM micro-structure and interestingly the same process was observed in the grey matter. We speculate that our study will provide normative values for T1map and ADC and might be an early prognostic tool for white matter injury and brain development. The correlation between T1 values at TEA and neurological outcome at 6 months of CA reflects a good predictable tool of T1 relaxation time in regards to myelination. We will further determine if T1 values could be a useful biomarker for monitoring potential neuroprotective therapies such as erythropoietin.
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TRACT-BASED SPATIAL STATISTICS (TBSS) TO ASSESS THE NEUROPROTECTIVE EFFECT OF EARLY ERYTHROPOIETIN ON WHITE MATTER DEVELOPMENT IN PRETERM INFANTS

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Background: Periventricular white matter injury is the most common brain injury in preterm infants (1) and is associated with neurodevelopmental impairments. To date, no neuroprotective intervention to prevent injury or enhance repair of the immature brain has been implemented into clinical practice in preterm infants. Erythropoietin (Epo) has neuroprotective and neuroregenerative effects on the brain (2). A randomised, double-blind placebo-controlled, prospective multicentre study applying EPO in the first 42h after preterm birth 'Does erythropoietin improve outcome in preterm infants' has been conducted in Switzerland (NCT00413946). Aim: to assess the neuroprotective effect of Epo on the development of white matter in preterm infants with TBSS
Methods: The preterm infants were given Epo (3000 IU) or an equivalent volume of placebo (NaCl 0.9%) intravenously before 3 hours of age after birth, at 12-18 and at 36-42 hours after birth. In a subgroup of infants brain MRI was performed at term equivalent age. Here we present data from 58 preterm infants with (mean (SD) gestational age at birth 29.75 (1.44) weeks) at term equivalent age (mean gestational age 41.1 (2.09) weeks). Brain MR imaging was performed with a 3.0 T GE HD.xt MRI scanner (GE Medical Systems, Milwaukee, WI, USA). MR protocol included diffusion tensor imaging (DTI) using a pulsed gradient spin echo EPI sequence (TE = 77 ms, TR = 9 seconds, field of view = 18 cm, matrix=128x128, slice thickness = 3 mm, b=1000). Voxelwise statistical analysis of the FA data was carried out using TBSS (3). After alignment of the FA maps to a neonatal FA template, a mean FA image was created and thinned to create a mean FA skeleton, which represents the centres of all tracts common to the group. This skeleton was thresholded at a FA level of FA > 0.15, and voxelwise cross-subject statistics were used with randomise (v2.1) in FSL to test for differences in FA between infants treated with Epo and placebo using a general linear model, including the gestational age at birth and the corrected gestational age at the time of the scan as covariates. A statistical threshold of $p<0.05$ was applied after family-wise error (FWE) correction for multiple comparisons following threshold-free cluster enhancement (TFCE; (4)).
Result: Preterm infants treated with Epo demonstrated increased FA in the genu and splenium of the corpus callosum, the anterior and posterior limbs of the internal capsule, and the corticospinal tract bilaterally. Mean FA was significantly higher in preterm infants treated with Epo than in those treated with placebo ($p<0.015$). There were no voxels where FA was significantly higher in preterm infants treated with placebo.
Conclusions: Early Epo administration improves white matter development in preterm infants assessed by DTI and TBSS. Similar results have been shown in an immature animal model of neuroprotection through Epo. Neurodevelopmental follow-up of these infants is ongoing.
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MAGNESIUM SULFATE ANTENATAL EXPOSURE TO PROTECT BRAIN OF VERY PRETERM INFANTS: THE FIRST SCHOOL-AGE FOLLOW-UP (PREMAG RANDOMIZED CONTROLLED TRIAL)

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Background: Improvement of brain protection remains a challenge in infants born very-preterm in view of their increased rate of long-term neurosensory disabilities. Magnesium sulfate administered to mothers at risk of imminent very preterm birth has been shown to be decrease the rate of cerebral palsy at two years of age in meta-analysis of five randomised neuroprotective trials, including the french trial PREMAG. Multiple properties, some potentially beneficial and some deleterious, have been described and there is a lack of understanding of the neuroprotective effect of MgSO4. The aim of this study is to assess the school-age (11 years) developmental outcome of the French PREMAG cohort, to determine whether magnesium antenatal exposure has newly apparents harms which may counter-balenced the benefits observed in the two years follow-up. Patients and
Methods: Overall, 573 women with fetuses of gestational age < 33 weeks whose birth was planned or expected within 24 hours were enrolled in 13 french perinatals centers from, July 1997 to July 2003, with 286 and 278 women respectively assigned to receive a single 40-ml infusion of 0.1 g/mL of magnesium sulfate or isotonic 0.9% saline. 688 newborns were alive at randomization. 72 deaths were counted between 0 and 2 years, 606 were assessed at 2 years. A postal questionnaire was created from development scale and was sent to the families of surviving children. 185 patients were lost to follow-up (26.9%) at school-age (11 years) and 431 questionnaires were analyzed.
Result: No death was listed between 2 and 10 years. Motor dysfunction and behavioral disorders are reduced but differences are not significant (respectively 47.6% and 32.1% in the magnesium group and 51.7% and 37.1% in the placebo group) with no difference for cognitive difficulties (63.8% in the MgSO4 group versus 64.9% in the placebo group). Moreover, school retardation (4.2% versus 8.1%), home education services (3.4 % versus 8.7%) and bad health assessed by the parents (4% versus 8%) were reduced in the magnesium group, even none of the differences reached stastical significance between MgSO4 and Placebo groups.
Conclusions: These results do not show any long-term harmful effect of antenatal exposure to magnesium sulfate, in particular on cognitive development. There even exist a trend to a better schooling.
Results: should be nuanced, as this long-term follow-up study has some limitations, including statistical power. These results will be analyzed with long-term follow-up of the Australasian randomized trial (ACTOMgSO4) in order to increase the sample size. Given its beneficial effects and safety, the use of prenatal low-dose magnesium sulfate for preventing neurosensory disorders of very-preterm infants should be more widely used.

EFFECT OF THYROXINE SUPPLEMENTATION DURING THE FIRST FOUR WEEKS AFTER BIRTH FOR BABIES <28 WEEKS: DEVELOPMENT AT 42 MONTHS

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Background: Infants born at extreme prematurity are at high risk of developmental disability. Mild thyroid hormone deficiency affects brain development and behaviour. Hypothyroxinaemia of prematurity is common in extremely premature infants. This study investigated the hypothesis that early administration of thyroxine supplementation to very immature babies improves neurodevelopment.
Method: A multicentre double blind randomised placebo controlled trial. Infants <28 w gestation were recruited within 4 d of birth. Given levothyroxine (LT4), iv then po, or placebo until 32 w by postconceptional age. Infants had magnetic resonance imaging (MRI) scans at term-equivalence with diffusion tensor imaging. The following brain areas were studied: anterior and posterior corpus callosum internal capsule, frontal lobe, and occipital lobe. The following MRI variables were used: Apparent Diffusion Coefficient, Fractional Anisotropy, length and number of fibres. Neurodevelopment was assessed by Bayley-3 administered aged 42 m.
Results:. 75 infants (mean birthweight (sd) 821 (184) g) were randomised to receive LT4, 78 infants (mean birthweight (sd) 842 (200) g) received placebo. 38 infants were studied by MRI at term-equivalence. ADC was significantly higher (indicating less good myelination) in babies whose blood thyroxine concentration was in the lowest quartile during the first 4 w after birth in the right posterior limb internal capsule (p=0.03), left frontal lobe (p=0.04), posterior corpus callosum (p=0.02). The neurodevelopment of 30 infants who received LT4 and 29 who received placebo were assessed at median 42 m (range 40-45). Composite outcome scores (LT4-upplemented vs placebo) were as follows: Motor: 84 ±12 vs 77 ±13, mean difference (95% CI) 6.96 (0.55-13.38) (p=0.034) Language: 92 ±13 vs 83 ±20, mean difference (95% CI) 8.93 (0.16-17.70) (p=0.041) Cognitive: 91 ±10 vs 85 ±13, mean difference (95% CI) 6.35 (0.14-12.55) (p=0.045) Correlations between mean FT4 concentration during 1st 4 weeks and outcome were as follows: motor function (rho 0.25, p=0.084), language (rho 0.27, p=0.069), cognition (rho 0.35, p=0.016).
Conclusion: Supplementation for infants born <28 weeks' gestation with LT4 until 32 weeks by postconceptional age may be associated with improved outcome. These findings suggest that very immature infants may benefit from an early assessment of thyroid function and appropriate thyroid hormone therapy, if indicated.

NEUROPROTECTIVE EFFECT OF EXOGENOUS KETONE ADMINISTRATION IN THE NEONATAL RAT MODEL OF HYPOXIC ISCHEMIC ENCEPHALOPATHY

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Background: Several studies support the neuroprotective effect of ketosis in diverse experimental models of brain injury. The proportion of ketone bodies attributable to the brain energy metabolism is relatively higher in the developing brain especially during the suckling period. ß-hydroxybutyrate (BHB), a representative type of ketone body, is an alternative fuel to glucose and may have a potential role in the pathogenesis of neuronal damage by altering energy metabolism. However, few studies addressed the neuroprotective effect of induced-ketosis in the neonatal rat model of hypoxic ischemic encephalopathy (HIE). The aim of this study was to investigate the neuroprotective effect of pre- or post-ischemic BHB treatment in the neonatal rat model of HIE.
Methods: Three groups of 13d-old rats (pre-BHB, post-BHB and the control, n=18 in each group) were subjected to 8 % oxygen for 120 minutes following unilateral carotid artery ligation. BHB (5 mM/kg) or the same volume of 0.9% saline (the control) was intraperitoneally administered at 3 hr before (only in pre-BHB) and/or at 0, 2, 4 and 6 hr after HIE. The extent of brain damage (pathologic grade 0-4 in Cresyl-Violet staining) and the number of TUNEL-positive cells were evaluated at the cortex, the hippocampus and the striatum at 48 hours after HIE.
Result: From 1 h after the intervention, the mean plasma BHB levels were significantly higher in pre-BHB and post-BHB groups than the control group ($P<0.001$). The blood glucose levels did not differ between the 3 groups. The mortality rate did not differ between the groups: the control (n=2), pre-BHB (n=3) and post-BHB (n=2). The incidence of brain infarct did not differ between the 3 groups: the control (n=12), pre-BHB (n=6) and post-BHB (n=9). However, the rats with high pathologic score was significantly greater in the control group versus pre-BHB and post-BHB group in the cortex (n of grade 1/2/3/4, control vs pre-BHB and post-BHB : 1/1/2/7 vs 1/4/0/0 and 4/1/0/2, $P<0.05$) and the hippocampus (1/0/4/6 vs 1/3/1/0 and 0/3/3/1, $P<0.05$). Pathologic scores in the striatum did not differ between the 3 groups (0/2/4/1 vs 2/2/0/0 and 0/1/0/1, $P=0.10$). Compared with the control group (100%), rats treated with BHB demonstrated significantly decreased number of TUNEL positive cells in CA1 (pre-BHB and post-BHB: 47% and 53%, $P<0.05$), CA3 (15% and 42%, $P<0.01$) and dentate gyrus (11% and 20%, $P<0.01$) but not in the cortex (72% and 72%, $P=0.58$) and the striatum (60% and 53%, $P=0.07$). There were no differences in the pathologic scores or the number of TUNEL positive cells between the pre-BHB and post-BHB groups.
Conclusions: Induced ketosis by exogenous BHB administration, even as a post-treatment, reduced the extent of brain damage in the neonatal rat model of HIE.

SPHINGOSINE-1-PHOSPHATE RECEPTOR MODULATION REDUCES HYPEROXIA-MEDIATED BRAIN INJURY

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Background: Premature infants are highly susceptible to different environmental factors such as variable oxygen concentration and inflammation. As demonstrated previously, hyperoxia induces perinatal brain injury, particularly in the white matter due to cell death of premature oligodendrocytes (pOLN). However, up to now, effective therapies are still missing. The sphingosine 1-receptor (S1P) agonist FTY720 has been approved for the treatment of the neuroinflammatory, demyelinating disorder multiple sclerosis (MS). Experimentally and clinically it has been demonstrated that FTY720 treatment shows both anti-inflammatory and neuroprotective effects in MS. Since FTY720 can enter the brain and interact directly with S1P-receptors on neural cells, we were interested how FTY720 modulates pOLN cell death and differentiation using in vitro and in vivo models of hyperoxia.
Methods: In vitro: primary oligodendrocyte precursor cells (pOLN) were generated from mixed glia cultures, obtained from 0-2 days old Wistar rat brains. Cells were cultured for 3-5 days and treated with different concentrations of FTY720 (0, 10, 50, 100 and 1000 nM) prior to 24 hours of hyperoxia. Apoptosis was analyzed via LDH-release and flow cytometry for Annexin-V/7AAD on A2B5-positive pOLN. Furthermore, immunocytochemistry was applied to evaluate oligodendrocyte differentiation. Modulations of S1P receptor subtypes were analyzed with quantitative RT-PCR. In vivo: A single dose of FTY720 (1 mg/kg bodyweight) was administered to five days old Wistar rats prior to hyperoxia (24 h, 80% O2). Brain samples were collected at day 6 and 11, modulations of key protein expression was assessed by western blotting and immunohistochemistry.
Result: FTY720 attenuates hyperoxia induced cell death of pOLN in vitro as shown by a significant reduction of LDH release increased levels of annexin-V/7AAD negative cells. Immunohistochemistry further revealed a modulation of oligodendrocyte differentiation by administration of FTY720. Interestingly, hyperoxia induced S1P receptor expression was, at least in part, counterbalanced via FTY720 treatment. These in vitro results could be translated into the in vivo situation as we found decreased numbers of TUNEL positive cells and an increased MBP expression by FTY20 treatment in hyperoxic brains.
Conclusion/Outlook: As we demonstrate beneficial effects through S1P receptor modulation in the context of hyperoxia. Our data strongly suggest that FTY720 treatment might be a potential therapeutic strategy. In order to verify this hypothesis and to correlate the first in vivo findings to functional outcome, we plan to analyze the effect of FTY720 on motor and cognitive deficits after hyperoxia in a therapeutic in vivo setting.

COMPUTERIZED WORKING MEMORY TRAINING HAS LONG TERM POSITIVE EFFECTS IN VERY LOW BIRTH WEIGHT (VLBW) CHILDREN AT PRESCHOOL AGE

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Background During the past decades the medical treatment and survival of preterm born children have improved substantially. Despite the increased survival, the number of children with brain pathology and neuroimpairments is still high. Preterm born children perform poorer than term peers on tests of attention and executive functions including working memory (WM) tests. These skills are essential for a child's ability to learn, plan their actions, solve problems and to develop language and mathematical skills. Deficits in WM are associated with cognitive, behavioural and academic problems. The aim of this study was to evaluate if a computerized WM training program would have long term positive effects on verbal and visual WM, learning/memory as well as on behaviour in VLBW (birth weight < 1500 g) preschoolers.
Design/Methods: This was a prospective, randomized study that included 20 preterm VLBW children, born at the St. Olav University Hospital in Trondheim in 2005 and 2006. Mean birth weight was 1099g (SD 311) and mean gestational age 28.8 weeks (SD 2.8). Mean age at intervention was 5.8 years (SD 0.5). The children trained with the Cogmed JM computer program for 10-15 min. each day, 5 days a week over a 5-week period. The children were assessed before training, and 4 weeks and 8 months after completing the training program. Cognitive abilities were assessed with The Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III) before training. Non-trained WM were assessed with standard neuropsychological tests of verbal and visual WM and generalization effects were assessed by selected subtests from the NEPSY. The ADHD rating scale-IV was completed by one of the parents. To be able to evaluate any test retest effects due to repeated testing, a small group of children were tested 9 weeks before as well as immediately before they started to train. Any test with improvement in scores between the two test-points before training, were then excluded.
Results: Four weeks after training positive effects were seen on trained as well as non-trained WM tasks and a generalizing effect on auditory attention, phonological awareness and verbal and visual memory. At the 8 months follow-up the children had persistent positive effects and continued improvements on tasks regarding auditory attention, phonological awareness and visual as well as verbal memory. ADHD scores did not change significantly with time.
Conclusion: Computerized WM training in VLBW preschoolers seems to have lasting positive effects at 8 months follow-up. Our study indicates that preterm born children may benefit from early WM training and we speculate that this intervention may prevent or reduce cognitive problems that impact educational achievement. Larger studies are needed to confirm our findings.

EVOLUTIONS IN FETAL AND NEONATAL MORTALITY RATES IN EUROPEAN COUNTRIES: RESULTS FROM THE EURO-PERISTAT PROJECT

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Background: 2004 data from the Euro-Peristat project documented wide variations in fetal and neonatal mortality rates in Europe. Objectives We sought to evaluate whether mortality rates had declined in 2010 and whether these declines reduced inequalities between countries.
Methods: Aggregated data on live births, fetal and neonatal deaths by gestational age from 25 participating countries in 2004 and 2010 were used to compute fetal and neonatal mortality rates using inclusion thresholds of =28 weeks of gestation for fetal deaths and =24 weeks of gestation for neonatal deaths.
Results: In most countries, fetal and neonatal mortality rates declined, but decreases differed in magnitude. Neonatal mortality rates declined between 9% and 51% (average 29% in 21 countries) and fetal mortality rates between 1% and 39% (average 15% in 26 countries). Reductions tended to be more pronounced for countries with higher mortality rates in 2004, but some countries with lower mortality rates achieved significant continued improvements in outcomes. Wide variations in mortality rates persisted in 2010, with highest mortality rates being three times higher than lowest mortality rates (range 1.5 to 4.3 per 1000 total births for fetal deaths and 1.2 to 3.3 per 1000 live births for neonatal deaths).
Conclusions: Compared with 2004, fetal and neonatal mortality rates have declined in most European countries in 2010 but disparities have persisted. Investigation of health care policies and practices in high performing countries could provide insight into effective strategies for improving perinatal health outcomes.

NICU VOLUME AND EARLY MORTALITY: A POPULATION-BASED STUDY ON VLBW INFANTS IN A GERMAN COHORT

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Introduction/Background: There are contradictory results concerning the impact of NICU volume on mortality of VLBW infants. However, in several studies the number of infants treated in a single unit was an important, independent variable for risk-adjusted mortality apart from the level of care. We hypothesized that in a German VLBW cohort mortality until discharge after adjustment for disease severity by each of two severity scores (CRIB and PREM) would be higher in low-volume NICUs (LVN) than in high-volume NICUs (HVN). Patients and
Methods: Analysis of data from the compulsory German neonatal quality assurance program organised at the level of the federal states for all hospital admissions earlier than 11 days after birth. Birth cohorts of 6 consecutive years (2003-2008) from the Baden-Wuerttemberg registry. Inclusion criteria: GA <33 weeks and BW <1.500g. Variables considered: GA; BW; gender; FiO2max, FiO2min, base excess (each within 12 h after admission); classification of malformation; death before discharge. Calculation of CRIB/PREM scores for risk adjustment. CRIB/PREM scores were grouped into 4 categories: low (CRIB 0-5/PREM >2.5) (group 1); moderate (CRIB 6-10/PREM 2.5->0.5) (group 2); high (CRIB 11-15/PREM -1-0.5) (group 3); very high (CRIB >15/PREM <-1) (group 4). Definition of NICU volume: LVNs equivalent to < / = 50 cases/year, HVNs > 50 cases/year. Statistics: Wilcoxon/Mann-Whitney U-test, Fishers exact test, binary or multinomial logistic regression, as appropriate.
Result: Total of 5.340 cases (6.329 patients eligible, 25 excluded for lethal malformation, 964 excluded for missing parameter). 862 patients <750g. Decrease of raw mortality from 8.9% in 2003 to 5.7% in 2008. Descriptive statistics for LVNs vs. HVNs: total cases 2396 vs. 2944; GA (median) 29wks vs. 28wks*; BW 1155g vs. 1018g*; malformations 7.6% vs. 9.7%*; CRIB score (median) 2 vs. 3*; PREM score (median) 3.8 vs. 3.3* (*all significant for p<0.001), mortality 7.1% vs. 7.2% (n.s.). The proportion of high risk cases was significantly lower in LVNs vs. HVNs (p<0.001). After adjustment for disease severity mortality in LVNs was significantly higher for group 3 with the CRIB score (OR 1.70) and the PREM score (OR 3.44), and for group 2 with the CRIB score only (OR 1.49) (difference significant for p<0.05), whereas differences were not significant for groups 1 and 4 with both scores.
Conclusions: Irrespective of the allocated level NICUs with less than 50 VLBW cases per year in the specific regulatory condition in Germany have a higher adjusted mortality than NICUs with more cases. However, this impact might be limited by a ceiling effect when NICU volume increases above a certain number of cases. This effect and also the optimum number of cases per NICU with respect to low mortality could not be figured out from our data, because the upper range of cases in our series was only slightly above 100 cases/year. In extremely ill VLBW infants, who have an 'intrinsic' risk of mortality between 50% and 75% (group 4), the effect of NICU volume disappears, or the number of cases in our series may have been too small to prove an impact of NICU size.

ORGANIZATIONAL FEATURES IN ITALIAN NICUS

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Introduction Into Sonar research (Observational Study of Neonatal Assistance and caRe), a project aiming at assessing staffing and clinical results for 401-1,500 grams preemies, we defined an analysis of the organizational feature in Italian NICUs. We collected information about activities, organizational position into the hospital, staffing level and motivation, the last one through a survey regarding physicians' and nurses' perception about work arrangement. Aim of the research The research aims at describing the Italian NICUs' organizational features, regarding not only dimensions, but especially organizational position, staff's motivation, coordination methods in place. The mission is defining the various organizational arrangement in Italy. Methodology 60 Italian NICUs took part into Sonar research in 2010-2011; 54 provided data about organization. We analyzed activities performed by those Units and answers from the surveys; we focused particularly on NICUs' organizational position into hospitals, coordination and assessment tools, physicans' and nurses' motivation level. So we can define a specific description of each NICU regarding: - Unit complexity level (based on the number and kind of cases treated in one specific year); - Unit's organizational position in the hospital; - Presence of performance assessment systems; - Co-operation level among professionals; - Presence of clinical competence assessment systems; - Physicians' motivation; - Nurses' motivation; - Quality systems for nursing activities; - Nursing activities assessment systems.
Results: The table below shows the descriptive statistics of the variables identified. Mean Min Max Median SD Unit complexity level 1,97 0,30 6,65 1,78 1,31 Presence of performance assessment systems 2,70 0 10 2 2,32 Co-operation level among professionals 2,46 0,40 7,67 1,85 1,77 Presence of clinical competence assessment systems 2,55 1,25 4,00 2,65 0,60 Physicians' motivation 1,91 1,00 3,00 1,9 0,40 Nurses' motivation 2,42 1,80 2,92 2,41 0,22 Quality systems for nursing activities 2,37 1,50 3,03 2,33 0,33 Nursing activities assessment systems 2,47 1,41 3,16 2,52 0,36 These variables are used to define how the Italian NICUs organize, manage and provide neonatal care.
Conclusions: We could distinguish various organizational models, according to different communication and assessment systems. Some of them are principally based on advanced organizational systems; some other are more based on personal relationship. Further differences can be observed on geographic basis and according to different organizational developments during the years. We also investigated a possible connection between models and dimensions or activities; no significant correlation can be observed and this item will be further examine in depth. The NICUs organizational analysis can give the managers useful information about what strategies they could follow in order to produce more efficiency and make the staff more motivated. The SONAR study was sponsored by a non-restricted grant by Chiesi pharmaceuticals

OUTCOMES OF INFANTS <32 WEEKS' BORN IN NON-TERTIARY HOSPITALS: A POPULATION-BASED COHORT STUDY OVER 20 YEARS.

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Background: Preterm infants 'outborn' in non-tertiary hospitals before 32 weeks' gestation and particularly those born before 28 weeks' gestation have higher mortality rates compared with equivalent-gestation infants who are 'inborn' in a tertiary perinatal centre. The aim of this study was to determine if the proportion of outborn births before 32 weeks' gestation and outborn infant mortality rates had changed over a 20-year period. Patients and
Methods: We analysed data on all stillbirths and livebirths, 22+0 to 31+6 weeks' gestation, born in Victoria, Australia between 1990 and 2009. Births resulting from a termination of pregnancy were excluded. The relationships between 'outborn' status, birth status (stillborn or live born), gestational age, era and mortality before one year of age were analysed by logistic regression.
Result: 16,914 births were recorded. 3,605 (21%) were outborn, 13,309 (79%) were inborn. Stillborn infants were more likely to be outborn (OR 6.27, 95% CI: 5.76, 6.82, p <0.001). Data on the timing of stillbirth (before or during labour) were not available before 2009, so a risk ratio for intra-partum stillbirth comparing outborn with inborn infants could not be analysed. Over the 20-year period the proportion of infants who were outborn remained stable, however there was a significant increase in the proportion of outborn livebirths from 1999 onwards (p< 0.002). Of the 13,763 liveborn infants in the 20-year period, 1986 (14%) were outborn and 11,777 (86%) were inborn. Outborn livebirths were less mature than inborn livebirths: 27.7 weeks compared with 28.2 weeks (mean difference: 0.50 weeks, 95% CI, 0.38, 0.62, p<0.001). Mortality rates in all infants fell over time, and with increasing gestational age. The mortality rate by one year of age of the outborn livebirths was 28% compared with 14% of the inborn livebirths (OR 2.21, 95% CI 1.19, 2.55, p <0.001, adjusted for era and gestational age). The 24-27 week outborn livebirths had higher mortality rates compared with inborn livebirths (OR 2.44, 95% CI, 1.98, 3.02, p<0.001), whereas there was little difference in the mortality rates between outborn and inborn livebirths at 28-31 weeks' gestation (OR 1.22, 95% CI, 0.94, 1.60, p=0.14).
Conclusions: Despite a system of regionalised perinatal care designed to facilitate the birth of very preterm infants in a tertiary perinatal centre, the prevalence of birth of liveborn infants <32 weeks in non-tertiary hospitals in Victoria is increasing in recent years. Very preterm infants born in non-tertiary hospitals remain at greater risk of death in the first year of life compared with inborn equivalents. Identifying potentially preventable risk factors for outborn birth remains a priority.

ONTOGENY OF THE RECOGNITION OF THE MOTHER'S VOICE BY INFANTS BORN VERY PRETERM BEFORE TERM-CORRECTED GESTATIONNAL AGE: A HEART STORY...

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Background: Term newborn infants and near term fetuses exhibit an attraction for their mother's voice which can be identified by their behavioural and/or psychobiological responses (cardiac orienting reflex). The ontogeny of this specific sensitivity in very preterm infants (VPI) exposed to an atypical acoustic environment is unknown.
Methods: Longitudinal and prospective follow-up of 21 VPI of 29 [27-32] weeks of gestational age (GA) at 2 different post-menstrual ages (PMAs): 30-32 wks (period A) and 34-36 wks (period B). Evaluation of their physiological responsiveness (heart rate-HR, respiratory rate-RR, Oxygen Saturation-Sa02, regional cerebral oxygen saturation-rSO2 using NIRS) to 3 recorded female voices, telling, during 5 sec, the following sentence in French: « Mon petit bébé, il est l'heure de dormir maintenant, calmement, tranquillement » (English translation, 'My little baby, it is time to sleep now, quietly, peacefully'). The newborns were in active sleep state. The female voices were the following: mother's voice (MV), stranger mother's voice (SMV) and a female stranger's voice (FSV) emotionally neutral. The voices were randomly presented at a closely calibrated sound pressure level of + 10 (+/-3) dBA above background noise. We compared the mean variations of the parameters between baseline and per/post-stimulation periods by ANOVA (and post-hoc analysis when appropriate). The profiles of responses between the 3 voices and the 2 PMAs were also compared.
Result: In period A, we observed a significant reactivity only for MV: increases in HR ($p = 0.03$) and rSO2 ($p = 0.02$) of a mean amplitude of + 6.1 bpm, and +1.35% respectively. In period B, we noticed a significant responsiveness for nearly all voices for at least one parameter, mainly increased HR: MV (+9.2 bpm, $p = 0.03$) SMV (+ 9.9 bpm, $p = 0.04$) and FSV (+ 9.9 bpm, $p = 0.09$) with a decrease in rSO2 for the latter (-4.1%, $p = 0.04$). There was a slow initial HR decrease of -2.7 bpm (95% CI, -0.3 to -5.7) only for the MV. It was of - 5.2 (IC 95%, -1.8 to -8.5) in the 15 (71%) infants that presented this cardiac deceleration. This response pattern differed significantly from those observed for SMV and FSV.
Conclusions: In this study, VPIs have shown specific physiological responses for their mother's voice. They were able to detect it from 30-32 wks and to discriminate it between other female voices from 34 wks PMA as shown by a specific cardiac orienting reflex triggered only by their own mother's voice. Thus, they are capable to develop perceptual abilities similar to fetuses continuously exposed to the prosody of their own mother's voice. The determinants of this preference and its impact on the bonding processes, the development of language and emotions in VPI, should be evaluated further.

TO TOUCH MY CHILD: THE EXPERIENCE OF MOTHERS IN A NICU

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An early physical contact through touch between mother and son promotes adequate child development and constitutes the origin of bonding between the dyad. However, when the health condition of the new-born requires the admission in the Neonatal Intensive Care Unit (NICU), mother and child are separated and forced to interact in an adverse atmosphere, surrounded by a whole range of technology, essential to guarantee the new-born survival. The present research aims to understand the experiences of mothers when they touch their child in a NICU and thus to define guidelines that promote touching and the involvement of parents in caring for the child, with the purpose of encouraging mother-child interaction and stimulate autonomy in caring for one's child. Using a qualitative research methodology, of phenomenological inspiration, with a descriptive and exploratory design, semi-structured interviews were carried out to ten mothers of new-borns who were in a NICU, in Oporto. Data analysis was done with Bardin's content analysis technique and three themes emerged: "defining to touch", with the following identified categories: to touch is good, to touch is strange, to touch is to feel herself mother, to touch is to give and to touch is to receive; within the theme "understanding the complexity of touching", the following categories emerged: fears and benefits involving to touch and nurses as motivators for touching; finally, the theme "the contexts involving to touch", which includes two categories: obstacles and strengths. The results of this research constitutes an important contribution for the knowledge and understanding of the experience of mothers that touch their sons in a NICU, in identifying strategies to promote touch and the involvement of parents in the care of their child, with the purpose to allow the implementation of nursing interventions that promote the effective integration of the mother in the environment of the NICU.

WHAT IS THE IMPACT OF THE FREQUENCY OF ARTIFICIAL SOUNDS ON THE RESPONSIVENESS AND WELL BEING OF VERY PRETERM INFANTS?

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Introduction: Very Preterm Infants (VPI) are able to detect sound peaks emerging from background noise levels. They are exposed in the 'ecological niche' of their incubators to sounds, of variable and wide ranges of frequencies (F), but that are very often highly-pitched. In fetuses, the range of frequencies responded to, expands first downwards to lower F and second upwards to higher F. Little is known about the maturation of pitch perception in VPI exposed to an atypical auditory environment and about the impact of noise frequency on their physiological well-being.
Methods:: Longitudinal and prospective follow-up study of 21 VPI of 29 [27-32] weeks of GA at 2 post-menstrual ages (PMA): 30-32 wks (A) and 34-36 wks (B). Evaluation of their physiological responsiveness (heart rate-HR, respiratory rate-RR, Oxygen Saturation-Sa02, regional cerebral oxygen saturation-rSO2 using NIRS) to different pure tone auditory stimuli of variable pitches (100, 500, 2500 and 4500 Hz - duration 1 s) chosen for their 'naturalistic' relevance, and a recorded broad band sound (sterile bag opening - duration 5 s): F100, F500, F2500, F4500, SBO, respectively. The sounds were randomly presented, at a closely calibrated sound pressure level of + 10 (+/-3) dBA above background noise, when the infants were in active sleep state. We compared the mean variations of the parameters between baseline and per/post-stimulation periods by ANOVA (and post-hoc analysis when appropriate). The profiles of responses between the different acoustic stimuli and the 2 PMAs were also compared.
Result: In period A, we observed a significant responsiveness mainly for F500 with increased HR, Sa O2 and rSO2 ($p < 0.01$ for all of them) of a mean amplitude of + 7.9 bpm, +1.6 % and +2.6 %, respectively. Moreover, significant variations were noticed for F100 (decrease in rSO2 of a mean amplitude of -2.1 %), F2500 and SBO (decreases in RR of -14.6 breath/min and -13.2 breath/min, respectively) In period B, we noticed a significant responsiveness for F100 (increase in HR of a mean amplitude of 10.0 bpm, and decrease in rSO2 of a mean amplitude of -1.8%), SBO (increased HR of a mean amplitude of 11.7 bpm) but mostly F4500: increased HR, decreased RR, decreased SaO2 and rSO2 ($p<0.01$ for all) of a mean amplitude of + 13 bpm, -11.8 breath/min, -2.4% and -3.5%, respectively)
Conclusions: There exists, for sounds of equal intensity, a maturation of pitch perception in VPI from low to high frequency sounds. This pattern appears similar to the one observed in fetus that begin hearing sounds around 500 Hz of F. Our results are consistent with the known development of auditory evoked brainstem responses from VPI. This development of F perception allows them, from 34 weeks PMA, to respond to sounds ranging from 100 Hz to 4500 Hz. High frequency sounds can alter greatly their physiological well-being and cerebral oxygenation. As they are exposed to them in neonatal units at a similar sound pressure levels, medical equipment and monitoring devices should be adapted to avoid such a noxious exposure.

WEBCAMS IN THE NEONATAL INTENSIVE CARE UNIT: HERE'S LOOKING AT YOU KID!

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Introduction Approximately 10% of newborns require admission to the neonatal intensive care unit. Many tertiary neonatal units employ a restricted visiting policy whereby siblings, grandparents and extended family are generally not allowed or have very limited access to the neonatal intensive care unit. Webcams have previously been implemented in the neonatal intensive care unit setting in a number of countries and while they have presented many challenges, overall, they would seem to have had a positive impact. Objectives To determine the views from parents, physicians and nursing staff prior to the possible implementation of a webcam system into the NICU.
Methods: An anonymous 8-item likert-scale questionnaire was developed specifically to address parental views on the use of a webcam monitoring system within the neonatal intensive care unit. A second, 6-item, likert-scale questionnaire was created for medical and nursing staff. All questionnaires were answered anonymously. Opinions from parents were analyzed by means of a frequency test. Differences between the medical and nursing staff were investigated using the Mann Whitney U test. Statistical analysis was performed using IBM Statistics 20.0 (NY, USA). All tests were two sided and a p-value <0.05 was considered to be statistically significant.
Result: There were 99 responses in total (50 nurses, 26 physicians and 23 parents). Two sets of parents declined to participate. Parental computer usage was high overall, with 82.6% using a computer regularly. While many respondents currently do not use a webcam, almost three quarters (73.9%) said they would use the webcam system in the NICU regularly if it were implemented. Overall parents expressed a view that a webcam system would reduce the levels of stress that they might experience when they are away from the NICU. The nursing staff appeared to have far more concerns about the security behind the use of webcams in the NICU than the physicians. Members of the nursing staff were concerned about data protection and in general concerned about security risks. These differed significantly from physicians' views (p-value <0.001). There was a statistically significant difference between nurses and doctors in the area of stress levels experienced by staff with a webcam system in place (p-value<0.001). 72% of nurse felt strongly that a webcam system would increase the stress levels of staff compared to less than 20% of physicians.
Discussion: This study has shown that the majority of parents who completed the questionnaire have a positive attitude towards the implementation of a webcam system in the NICU and, as a result, are in favour of such a system being introduced. The sentiment that it would reduce stress levels for the parents is encouraging, but this can only be answered prospectively with objective assessments of parental stress levels when webcams are in use. Education of healthcare staff is required prior to webcam implementation.

DEVELOPMENT OF THE BEDSIDE ASSESSMENT, STABILISATION AND INITIAL CARDIORESPIRATORY SUPPORT (BASICS) TROLLEY

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Background: International guidelines for resuscitation at birth state that clamping of the umbilical cord should be deferred for one minute, but if a baby requires resuscitation then resuscitative measures take priority. With conventional resuscitation equipment it is difficult to provide resuscitation with the umbilical cord intact. When a baby requires assessment or resuscitation at birth it is normal practice for the baby to be taken to a resuscitation platform situated away from the delivery bed or operating table. This prevents the parents being able to see their baby or what is happening during the resuscitation, a factor that has been found to cause great anxiety. Research in other areas of emergency medicine has shown benefits when relatives are present at resuscitation. Whether these benefits are also associated with newborn resuscitation has not been assessed. The aim of this project was to design resuscitation equipment that would allow neonatal resuscitation to be performed at the maternal bedside or operating table, with the cord intact.
Method: Following discussions between a group of clinicians interested in this problem a series of draft drawings of the equipment was produced. A prototype was manufactured in the University of Liverpool Department of Engineering and refined in an iterative process of clinical review including testing in mock up clinical situations. The prototype was awarded a prize award for 'Best Redesign in Cardiovascular Medicine' at the Medical Futures Awards in 2011. An industrial partner, Inditherm Ltd, then joined the project. Continued improvements in the design were made by the same processes and the equipment was eventually manufactured in 2012.
Result: The resulting product is a small, highly manoeuvrable, height adjustable resuscitation trolley. Thermal care is provided by a Cosytherm heated mattress (Inditherm). Gas supply for suction and respiratory support requires is external. The trolley has two rails on which conventional neonatal resuscitation equipment can be mounted. In our evaluation this includes an air/oxygen blender, a gas powered suction device and a Tom Thumb Infant resuscitator (Viamed). The trolley was awarded a CE mark in September 2012 and is now manufactured by Inditherm Ltd with the name of 'Lifestart®'. An ongoing clinical evaluation of the use of the trolley is in progress as is a qualitative study of the views of parents of babies cared for on the trolley and clinicians using it.
Conclusion: Clinicians are able to identify clinical problems and to envisage technical solutions. It is necessary to work with other scientists and industrial partners to turn these solutions into reality to benefit patients.
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EXCESSIVE EXPOSURE OF THE PRETERM HEAD TO SHOCK AND VIBRATION DURING INTER-HOSPITAL TRANSPORT: A PRETERM MANIKIN STUDY

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Background Specialist neonatal intensive care has become increasingly centralised in large centres. In the UK, there are now over 10,000 neonatal inter-hospital transfers a year (Fenton and Leslie, 2012). Neonatal transport exposes the sick newborn to additional stressors including temperature instability, excess noise and mechanical vibration and shock (Mcnab 1995 and Campbell 1984). Whilst inter-hospital transport of premature babies improves survival, it is associated with an increased risk of intraventricular haemorrhage (IVH), an important risk factor for poor neurodevelopmental outcome (Mohamed 2010). Furthermore, transport results in a number of other adverse effects including cardiovascular and respiratory instability (Williams 2009). Aims We investigated whole body vibration (WBV, m/s2) during inter-hospital transport. We hypothesised that a gel mattress configuration would reduce WBV compared with the sponge mattress used in current clinical practice.
Methods:WBV during inter-hospital ambulance transport was measured using a realistic 25 week gestation size manikin weighing 800g. The manikin was nursed as in clinical practice with appropriate intensive care and safety equipment during ambulance journeys between hospitals in England. Two mattress configurations were studied: 1) sponge only which is current clinical practice in our transport service, 2) sponge with gel mattress (Squishon, Children's Medical Venture). As well as WBV we also calculated the A(8) ISO 2631:1997 International Standard for safe limits of WBV exposure. This advanced simulation system included three calibrated sensors, each with an accelerometer, gyroscope and magnetometer, which were sited on the forehead, body(nappy) and on the transport incubator frame. Each tri-axial accelerometer logged data at 100Hz. A synchronised GPS data logger was used to track distance and speed. Kruskall-Wallis and Mann-Whitney tests were used for statistical analysis with statistical significance at a $P<0.05$.
Results: There were ten journeys made giving a total journey time of 777 minutes. With the sponge mattress, WBV increased with increasing transfer speed. Median WBV (IQR) according to road speed was: urban roads=0.54m/s2 (0.28-0.85), suburban roads=0.76m/s2 (0.6-0.94) and rural roads=0.90m/s2 (0.78-1.02), ($P<0.01$). Addition of a gel mattress resulted in a significant attenuation of WBV at all speeds ($P<0.01$) by an average of 35%. When using the sponge mattress, the WBV could exceed ISO limits for healthy adults. Furthermore, the head of the manikin was exposed to acceleration forces similar to those seen on roller coasters (>2m/s2) and this appeared to be amplified through the transport system. Again, these effects were dampened with the use of a gel mattress.
Conclusions: Our study demonstrates that with increasing speed there is an increase in WBV exposure above recommended safe limits for healthy adults. Worryingly, head vibration and shocks are excessive and could be an important factor contributing to the increased risk of IVH observed with transported babies. Use of a sponge and gel mattress significantly attenuates WBV and this warrants further study.

OBESE WOMEN'S TWO-HOUR POSTPRANDIAL GLUCOSE LEVEL IS ASSOCIATED WITH OFFSPRING FAT MASS AND BIRTH WEIGHT, BUT NOT WITH LEAN MASS.

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Background Pre-pregnancy obesity and impaired glucose tolerance during pregnancy affect foetal body composition and increase the risk of delivering infants being large for gestational age. Short and long-term morbidity is affected and both the mother and infant have a high risk of developing metabolic disease. Reduction in gestational weight gain (GWG) may normalise newborn birth weight and body composition. We aimed to investigate the effect of maternal two-hour postprandial p-glucose (p-glucose 2h) level on neonatal body composition (fat and lean body mass) and birth weight in obese women, after adjusting for GWG. Patients and methods We consecutivly recruited obese (Body Mass Index (BMI) >30 kg/m^2) pregnant women in the Treatment of Obese Pregnant women study at Hvidovre Hospital. All infants were singletons born at term and were healthy. In order to minimize the weight gain during pregnancy (end-point: GWG < 5 kg), mothers were randomized (1:1:1) to: A: diet and exercise, B: exercise alone or C: control. P-glucose 2h level was assessed by oral glucose tolerance test (OGGT) during week 27-30. Pre-pregnancy weight was self reported, while all women were weighed during week 36-37; GWG was calculated as the difference between the two weights. Newborn recumbent weight (Seca digital scales) and length were measured according to anthropometric standards. Neonatal body composition was assessed within 72-hours after birth using dual-energy X-ray (DEXA) absorptiometry scanning (DXA, Hologic 4500, USA). Size for gestational age was calculated as birth weight adjusted for gestational age and sex according to Marsal et al.
Results: A total of 205 (83% of included) obese mother newborn dyads had a DEXA scan, which met predefined quality criteria and available p-glucose 2h measurement. Mean maternal p-glucose 2h level was 6.7 mmol/l (+/-SD 1.25) whereas GWG averaged 10.3 kg (+/-SD 6.39). Mean birth weight was 3697 g (+/-SD 521). Mean neonatal fat mass was 440 g (+/-SD 213). Mean normalized birth weight adjusted for gestational age and sex was 103 % (+/-SD 13.9). Linear regression analysis showed that neonatal fat mass was related to p-glucose 2h level, ß 23.7 g/mmol/l p-glucose 2h [95% CI 4.88,42.59]; (p=0.014), after adjusting for GWG, maternal age, education, smoking, prepregnant BMI, parity, gestational age, offspring sex and birth length. There was no association between neonatal lean mass and p-glucose 2h (p=0.78). Size for gestational age was related to p-glucose 2h level: ß 1.93 %/ mmol/l [95% CI 0.8, 3.02] (p=0.001) (after adjusting for GWG, maternal age, education, smoking, prepregnant BMI, parity and birth length). Maternal intervention did not affect p-glucose 2h level (p=0.64), fat (p=0.96) or lean mass (p=0.53) or size for gestational age (p=0.74).
Conclusion: Neonatal fat mass and size for gestational age are positively associated with p-glucose 2h level at 27-30 weeks of gestation after adjusting for maternal weight gain during gestation. Interventions targeting postprandial glucose levels might reduce neonatal adiposity, and thereby the risk of subsequent metabolic syndrome.

IDENTIFICATION OF CLUSTERS OF BODY COMPOSITION AND TIME CHANGES FROM 4 TO 7 YEARS IN CHILDREN FROM GENERATION XXI

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Background: Changes in single measures of obesity during childhood have been extensively addressed, but changes in clusters combining general and regional measures of fat location, could provide a new perspective to understand their effects on health outcomes. Objectives: To identify and compare clusters of body composition at 4 and 7 years.
Methods: Generation XXI is a prospective population-based birth cohort of 8647 children assembled during 2005-2006 at 5 public maternity units of Porto, Portugal. These analyses include children re-evaluated at 4-5 (86.2% of participation) and 7 years (ongoing since 2012), after excluding potential outliers (±3*interquartile range) in anthropometrics (n=2012, 48.4% girls). Body mass index (BMI), waist-to-hip ratio (WHR) and fat mass index (FMI=fat mass from tetra-polar bioelectric impedance/height2) were ascertained by trained personnel. Patterns were identified by model-based clustering. Measures were standardized separately at 4 and 7 years and z-scores were compared (Z4 vs. Z7) using paired samples T-test. Sex-stratification was not considered, since clusters were similar by sex.
Result: The Bayesian information criterion supported a model with 4 clusters: 26.8% of children were included in cluster 1, 25.4% in cluster 2, 15.7% in cluster 3 and 32.1% in cluster 4. In clusters 1, 2 and 4, children at 4 and 7 years were characterized by an adequate BMI, FMI and WHR (less than 1 SD above/below the population mean). However, from 4 to 7 years they embraced different changes: in cluster 1, children increased BMI (Z4=0.29, Z7=0.42; p<0.001) and FMI (Z4=0.27, Z7=0.36; p=0.01), but decreased WHR (Z4=0.10, Z7=-0.23; p<0.001); in cluster 2, children decreased BMI (Z4=-0.27, Z7=-0.32; p<0.001), but did not change their FMI (Z4=-0.52, Z7=-0.56; p=0.23) and WHR (Z4=-0.01, Z7=0.04; p=0.13); and in cluster 4, children decreased BMI (Z4=-0.65, Z7=-0.83; p<0.001), FMI (Z4=-0.44, Z7=-0.60; p<0.001) and WHR (Z4=-0.14, Z7=-0.35; p<0.001). In cluster 3, children at 4 years were characterized by a high BMI and FMI (more than 1 SD above the population mean) but by an adequate WHR. BMI (Z4=1.25, Z7=1.50; p<0.001), FMI (Z4=1.28, Z7=1.54; p<0.001) and WHR (Z4=0.13, Z7=1.04; p<0.001) increased from 4 to 7 years.
Conclusions: Although most children (clusters 1, 2 and 4) maintained their anthropometrics under normal ranges from 4 to 7 years, they experienced different changes, which can have different effects on cardio-metabolic health. An increase of BMI and FMI with time was observed in children already presenting values above normal ranges at 4 years, who also changed from an adequate to a high WHR (cluster 3).

BIRTH WEIGHT AND BODY MASS INDEX AT 4 YEARS OF AGE: THERE IS A MEDIATOR EFFECT OF UMBILICAL CORD ADIPOKINES?

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Background: Previous studies recognised the relation between birth weight and body composition in infancy. In addition, adipokines production during pregnancy seems to be associated with children's growth, although the underlying mechanisms are still unclear. This study pretended to evaluate the effect of umbilical cord levels of adipokines in the association between birth weight and body mass index (BMI) at 4 years of age. Patients and
Methods: This study included 847 single new-borns of the Portuguese population-based birth cohort Generation XXI, with data on birth weight, umbilical cord concentrations of adiponectin, leptin and resistin, BMI at 4 years of age and potential confounders. Birth weight was categorized as low birth weight (<2500g), adequate weight (2500-3999g) and macrosomia (>=4000g). At 4 years of age children's BMI was categorised according to the International Obesity Task Force criteria and further dichotomised as underweight/normal and overweight/obesity. Umbilical cord concentrations of adipokines were determined by ELISA. Medians and interquartile ranges (IQR) were compared using the Mann-Whitney test. The association between birth weight and BMI at 4 years of age was quantified as odds ratios (OR) and respective 95% confidence intervals (95%CI) fitting logistic regression models. Models were adjusted for new-born's sex and gestational age, maternal age, education and pre-pregnancy BMI. The final model was further adjusted for each adipokine and for the respective interaction terms.
Result: The prevalence of overweight/obesity was higher among macrosomic new-borns (39% vs. 18% in adequate weight vs. 6% in low birth weight; p=0.002). The umbilical levels of leptin, but not adiponectin and resistin, significantly increased with increasing birth weight (low birth weight: 6.8ng/ml (IQR=5.4ng/ml), adequate: 14.2ng/ml (IQR=13.4ng/ml); macrosomia: 22.7ng/ml (IQR=13.8ng/ml); p<0.001) and 4 years BMI (underweight/normal: 13.9ng/ml (IQR=13.1ng/ml) vs. overweight/obesity: 16.3ng/ml (IQR=14.8ng/ml); p=0.005). When compared to children with normal birth weight, macrosomic new-borns had higher risk of overweight/obesity at 4 years (OR=2.83, 95% CI = 1.28-6.27). No confounding or interaction effect of the umbilical cord adipokines was observed.
Conclusions: Birth weight is an important predictor of body mass index at 4 years of age and this relation was not explained by the birth concentration of adipokines.

THERAPEUTIC EDUCATION PROGRAM FOR CHILDREN AND ADOLESCENTS OBESITY. RESULTS OF A PILOT TRIAL.

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Introduction Obesity could be considered entirely a severe chronic disease, leading to comorbidities (like type 2 diabetes, hypertension, dyslipidemia, hepatic steatosis) since pediatric age. Despite the incidence of overweight seems to diminish in last years (as consequences of a great number of intervention programs aimed to preventing obesity), the prevalence of severe obesity (i.e. BMI = 4 DS) remains the same. Classical approach (i.e. dietary program, psychological intervention and coaching) has demonstrated limited effects. Therapeutic education, has been used in the management of several chronic diseases in aim to enable the patient suffering from a chronic diseases to manage his/her illness and treatment and to prevent avoidable complications, while keeping or improving his/her quality of life. We present « Obeduc (OBésité EDUCation Thérapeutique) », an ongoing original project which is showing some promising results.
Patients and Methods: We evaluate a pilot cohort, composed by 25 patients (12 M-13 F; mean age 10.8±5.1 ys; z-score BMI 3.49 ±0.54) included in Obeduc program and 20 sex, age and BMI matched patients followed by a classical approach (i.e. follow-up in our outpatient clinic every 3 months with medical and dietitian counseling). Our approach includes a day hospital after the first clinical management to permit a global evaluation of the status of the patient. Subjects underwent a complete physical examination and they respond to a medical interview focused on severity, duration and importance of the disease. The questionnaire OSA 18 was used to detect sleep problems and another one to explore social dimension. A second interview was made with a dietitian to investigate eating habits. A three-day dietary recall was made, allowing the evaluation of ingesta. A blood sample was obtained in order to evaluate carbohydrate and lipid metabolism. A 'hypercaloric standard meal',accounting for 6000 Kcal, was provided to evaluate alimentary behavior. After the entire work-up, the patient was seen in outpatient clinic after 1 month to discuss the entire results and after every three months.
Results: Our first results show that Obeduc program, for up to 1 year, is associated with a more significant weight loss compared with classical approach. (-0.75 vs -0.48 z-score BMI, with some percentage of loss at follow-up, 19.3 vs 19.0 %). No differences were observed according to sex and age.
Conclusion: This kind of multidisciplinary approach can be useful to cope with the disease in its complexities. A longer follow-up is needed to confirm these preliminary results.

EFFECT OF CHILDHOOD OBESITY INTERVENTION PROGRAMS ON INSULIN SENSITIVITY, LIPID PROFILE, ADIPOKINES AND LOW-GRADE INFLAMMATION IN 3- TO 5-YEAR-OLD CHILDREN.

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Background: Recent data show that the prevalence of childhood overweight and obesity in the Netherlands is still increasing. Childhood obesity is a risk factor for the development of insulin resistance (IR) and dyslipidemia. Increased concentrations for markers of low-grade systemic inflammation have been described in these children. Multidisciplinary lifestyle intervention programs for obese children have proven to be successful in reducing weight. Little is known about the effects of successful treatment programs for obesity on IR, lipid profile, adipokines and markers of low-grade inflammation in preschool-aged children. Objective: To assess the effects of a 16-week multidisciplinary intervention program, aimed at reducing BMI, on inflammatory parameters, lipid profile, IR and adipokines, in 3-year-old to 5-year-old overweight or obese children, and to compare the results with a group of overweight or obese children receiving a usual-care program. Method: Children and parents participated in a randomized controlled clinical trial, called 'Groningen Expert Center for Kids with Obesity (GECKO)-Outpatient Clinic'. Children and their parents were randomly assigned to a multidisciplinary intervention group or a usual-care group. The 16-week multidisciplinary intervention program consisted of dietary advice (6 sessions), 12 physical activity sessions and 6 psychological counselling sessions for parents. In the 16-week usual-care program, children and parents were seen 3 times by a resident in pediatrics who advised on healthy lifestyle. At the start and at the end of the treatment period, anthropometry and assessment of body composition were performed and blood was drawn after an overnight fast.
Result: 75 children were included. According to international cut-offs, 29 children were overweight and 46 children were obese. At the end of the treatment period, children in the multidisciplinary intervention group showed a larger decrease in BMI z-score (-0.5 (0.4) vs. -0.3 (0.4)) compared with children in the usual-care group (1). In the multidisciplinary intervention group, a statistically significant decrease in insulin (-2.2 (4.0) mU/L; p=.01), updated HOMA-IR (-0.3 (0.5); p=.02), HbA1c (-0.3 (0.5) %; p=.01) and TNFa (-2.5 (4.9) pg/mL; p=.01) was found. IL-6 showed a trend towards a statistically significant decrease (p=.09). In the usual-care group, decreases were found for insulin (-2.9 (4.8) mU/L; p=.01) and updated HOMA-IR (-0.4 (0.6); p=.01). Comparing both groups, changes over time were not significantly different apart for trends in the decrease in total cholesterol (p=.07) and TNFa (p=.06) which almost reached statistical significance in favor of the multidisciplinary intervention group. For both groups together, statistically significant correlations were found between decreases in BF% and decreases in insulin concentrations (r=.352; p=.02) and between decreases in BF% and improvement in updated HOMA-IR (r=.365; p=.02).
Conclusions: In 3- to 5-year-old children, both obesity intervention programs improved insulin sensitivity, in parallel with a reduced BF%. There were no statistical significant differences between both programs, although the multidisciplinary intervention group showed a trend towards a larger decrease in total cholesterol and TNFa, compared with the usual-care group. Reference: 1. Bocca G, Corpeleijn E, Stolk RP, Sauer PJ.
Results: of a multidisciplinary treatment program in 3-year-old to 5-year-old overweight or obese children. A randomized controlled clinical trial. Arch Pediatr Adolesc Med 2012;166:1109-15.

A MULTIDISCIPLINARY INTERVENTION PROGRAM IN 3- TO 5-YEAR-OLD OVERWEIGHT OR OBESE CHILDREN: EFFECTS ON HEALTH STATUS, EATING BEHAVIOR, AND QUALITY OF LIFE.

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Background: Worldwide, childhood obesity is still becoming more prevalent. Studies have shown associations between the grade of overweight and the children's eating style. Eating behaviors with a tendency to overeat emerge early in the developmental pathway and show individual continuity. Also, health-related quality of life (HRQoL) and childhood obesity seem to be associated. Obese children show lower scores for HRQoL, especially on scales for self-esteem and physical functioning. Multidisciplinary obesity treatment programs in school-aged children have demonstrated to improve HRQoL. Effects of multidisciplinary obesity treatment programs in preschool-aged children remain largely unknown. Objective: To evaluate the effect of a multidisciplinary intervention program in 3- to 5-year-old overweight and obese children on health perception and quality of life, and to assess the effects on eating behavior of both the children and their parents. Method: 75 children (29 overweight, 46 obese) aged 3 to 5 years were randomized to a multidisciplinary intervention program or to a usual-care program. During a 16-week period, children and parents in the multidisciplinary intervention group received dietary advice by a dietician, physical activity sessions guided by a physiotherapist and, for parents only, psychological counseling by a psychologist. During the same period, children and parents in the usual-care group visited a pediatrician 3 times, who advised on a healthy lifestyle. At baseline, after 16 weeks and 12 months, anthropometry was performed and parents completed the Dutch-Child-AZL-TNO-Quality-of-Life (DUX-25) questionnaire, the Child Health Questionnaire for Parents (CHQ-PF50) and the Dutch Eating Behavior Questionnaire (DEBQ).
Result: At 12 months follow-up, children in the multidisciplinary intervention group showed a greater decrease in body mass index (BMI) (p=.03) and a greater increase in the total quality of life (p=.04), especially for the physical domain (p=.025), compared to children in the usual-care group. For the total group, an inverse association between changes in BMI and changes in global health between baseline and 12 months was found (Spearman correlation -.357, p=.032). Children in the multidisciplinary intervention group showed a trend to increased restrained eating behavior (p=.069), children in the usual-care group a significant increase (p=.027).
Conclusions: A multidisciplinary intervention program in 3- to 5-year-old overweight and obese children has beneficial effects on BMI and health-related quality of life, present 12 months after the start of the intervention, compared with a usual-care program. A decrease in BMI is associated with an increase in global health perception. In addition, the multidisciplinary intervention program induced a change towards increased restrained eating behavior. However, a decrease in eating behavior associated with a tendency to overeat, was not found.

MICRO-METHOD WITH EDTA FOR THE DETERMINATION OF PLASMATIC LEVELS OF MICAFUNGIN IN NEONATES

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Objective: The micafungin pharmacokinetics differs in preterm infants from that of older children, for an enhanced clearance of the drug, inversely proportional to the birth-weight. As the dose to be administered in the infant is still uncertain, the possibility to easily assess micafungin plasma levels using a micro-method is important.
Methods: Whole blood samples were obtained from two neonates around the fourth day of therapy, immediately before the administration of micafungin and 30 minutes, 2 and 8 hours after the infusion. Blood samples, obtained by puncture of heel, were picked in a 0,2 ml capillary tube and transferred into micro-tubes, both containing sprayed EDTA. Plasma was separated by centrifugation at 3000g for 10 minutes and stored at -80°C until the analysis. Micafungin, and anidulafungin as internal standard (20 mcg/ml), were extracted using protein precipitation and chromatographic separation on a reversed phase column. The effluent was monitored at the two UV-wavelengths of 273 nm and 306 nm, which represent the absorption maxima of micafungin and anidulafungin
Result: The linear range for micafungin from plasma varied from 1 mcg/ml to 25 mcg/ml with a limit of 1 mcg/ml. The intra-daily coefficient of variation was 1.90% and that inter-days was 4.8%. The level of micafungin was about 25% lower in plasma than in serum in the same patient .
Conclusions: A micro-method with EDTA for the measurement of plasmatic micafungin in neonates may allow a complete pharmacokinetic study, withdrawing small amounts of blood. Now, extended data from neonates during micafungin treatment are needed.

LIPSTIC LIVERPOOL PHARMACOKINETIC/PHARMACODYNAMICS (PK/PD) STUDY OF TEICOPLANIN IN CHILDREN

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Introduction: Coagulase-negative Staphylococci (CONS) infection is the most common laboratory confirmed bloodstream infection (LCBSI) treated in neonatal and paediatric intensive care units and significantly impacts patient mortality and morbidity. There is a renewed interest in well-known antibiotics such as teicoplanin, a glycopeptide with a similar spectrum of activity to that of vancomycin but a better safety profile (less nephrotoxic). However, there are no sufficient pharmacokinetic (PK) studies of in children and current dosage recommendations do not account for patient variability, childhood developmental changes and current patterns of infection and microbial resistance. Aim: To assess the disposition characteristics of teicoplanin in children and neonates when used in hospital in the routine clinical context. Objectives: 1) To develop population PK data for teicoplanin in children. 2) To describe relevant PK/PD relationships. e.g AUC/MIC. 3) To assess the feasibility of PK sampling in the hospital routine setting.
Methods: Therapeutic clinical PK study in a routine hospital setting including 54 children (neonates from 24 weeks gestational age and children 1m to 16 years). Information on patient-specific factors which may affect teicoplanin PK profile is being captured including: postmenstrual age and post-natal age in pre-term babies, concomitant medication, medical history, weight, height and renal function. The study is divided in 3 stages being stage 1 for optimal sample strategy definition and interim analysis for accuracy of results. In parallel, a determination of the microorganism susceptibility to teicoplanin (MIC) will be done for clinical purposes and results collected for further PD analysis. Population PK/PD modelling will be undertaken using the non-linear mixed effect modeling software NONMEM. Regarding objective 3: Five intensive care patients (80% post-cardiac surgery), mean postmenstrual age(62 weeks, 2.2 days) have been recruited so far into the first stage of the trial with a total of 25 PK samples, mean of 5 samples per patient, which demonstrates the feasibility of the PK sampling in the intensive care routine setting. The study will be open in the Oncology Department, neonatal medical wards and neonatal intensive care unit in May 2013.
Scientific Impact: This study will provide a precise teicoplanin population PK model for children and neonates that will allow investigating further target PK/PD to define the optimal dosage recommendation.

EVALUATION OF DOSING GUIDELINES OF VANCOMYCIN IN NEONATES: ARE WE MOVING IN THE RIGHT DIRECTION?

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Background: Vancomycin is frequently used to treat neonatal late onset sepsis. Vancomycin trough levels are hereby suggested to be 10-15 mg/l. We aimed to identify covariates associated with suboptimal trough levels (<10 or >15 mg/l) in neonates and young infants. Second, we compared trough levels of our current dosing regimen based on postmenstrual age (PMA) and postnatal age (PNA) [1] with a dosing regimen based on PMA and creatinine [2].
Patients and Methods: Vancomycin therapeutic drug monitoring (TDM) trough levels of neonates and young infants collected after initiation of intravenous vancomycin therapy between June 2011 and December 2012 were retrospectively collected. Clinical covariates were extracted from patient files. The impact of continuous (Mann-Withney U test) and dichotomous variables (Chi-square test) on achieving a trough level between 10-15 mg/l or not was explored. During the study period two different vancomycin dosing regimens were used (A: based on PMA and PNA, B: based on PMA and creatinine). The same statistical analyses were performed on the observations of each dosing regimen separately.
Result: In total, 294 TDM observations [with median (range) birth weight (BW) 1575 (420 - 4680)g, current weight (CW) 1870 (420 - 4863)g, gestational age (GA) 32,29 (24,57 - 41,43) weeks and PMA 35,07 (25,14 - 56,00) weeks] were included. 78% of these trough levels were outside the predefined range. Lower age (GA and PMA) and weight (BW and CW) were associated with suboptimal TDM levels. Dosing regimen A (n=101 observations) resulted in a significantly lower median (range) trough concentration compared to regimen B (n= 193) [5,8 (1-20,1) vs 7,8 (1-37,8) mg/l]. Suboptimal TDM levels were associated with a significantly lower BW and CW in regimen A and with a significantly lower GA and PMA in regimen B.
Conclusions: In a large cohort of neonates and young infants, we documented that 78% of vancomycin trough levels were outside the range of 10-15 mg/l. Especially in the youngest (GA, PMA) and smallest (BW, CW) patients, suboptimal levels were documented. Since both dosing regimens evaluated, resulted in suboptimal trough levels, the search for optimal vancomycin dosing in neonates has to continue. 1. Neofax 2011, Thomson Reuters 2. Anderson BJ et al. Br J Clin Pharmacol. 2007; 63(1): 75-84.

EVALUATION OF FENTANYL DISPOSITION AND EFFECTS IN NEWBORN PIGLETS AS AN EXPERIMENTAL MODEL FOR HUMAN NEONATES.

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Background: Fentanyl is a potent synthetic opioid, widely used off-label in NICU. This study was aimed to investigate the pharmacokinetics (PK) as well as the cardiovascular, pulmonary and cerebral effects of fentanyl administered as the only narcotic agent in mechanically ventilated newborn piglets, a suitable animal model for human neonates.
Animals-Methods: Six mechanically ventilated newborn piglets (4d) were used. A thermodilution catheter was inserted into the femoral artery to monitor arterial blood pressure (MABP), heart rate (HR) and cardiac output (CO) as well as to obtain blood samples for gas analysis and determination of fentanyl plasma concentration by HPLC/MS-MS. Also, a catheter was inserted into the jugular vein to receive fentanyl infusion. Lung mechanics, oxygenation-index (OI) and ventilatory-efficiency-index (VEI) were measured. Change in cerebral perfusion-oxygenation was assessed using NIRS system. TOI, THI, fractional-tissue-oxygen-extraction (FTOE) and cerebral-intravascular-oxygenation (CIOËœcerebral blood flow) were monitored. Brain activity was monitored using an aEEG monitor. After surgical preparation, basal samples were obtained. Afterwards, animals received an i.v. fentanyl bolus dose (5 µg/kg), followed by a continuous infusion of 3 µg/kg/h for 90min. Dosing was established to achieve the target EC50 described for sedation (3 ng/ml), through a previously developed predictive PK model of fentanyl in humans neonates. All parameters were registered immediately after bolus administration, at T=1, 10, 30, 90, 95, 120 and 180 min after start of the infusion and then every 30min until the end of experiments. Values are expressed as mean±SD.
Result: The animals presented a 'reliable degree of sedation' up to T=210-240 min; only some agitation was noted at the end of experiment. VEI and OI were significantly altered within the first minute after bolus administration, due to a transient effect of fentanyl in pulmonary mechanics. Those parameters remained unchanged until initial awakening of the animals (T=210min). HR showed an increasing trend from T=180min to the end of the experiment without any significant changes in MABP and CO. THI and CIO tended to decrease over time, while FTOE was only partially increased. aEEG amplitude decreased almost 41±19% after fentanyl bolus administration. The pulmonary and brain effects of fentanyl were partially recovered from T=210min to the end of experiment. The average plasma concentration at the end of infusion was about 3ng/ml, thus providing evidence that the PK disposition of fentanyl in piglets is similar to that predicted in human neonates. Plasma fentanyl levels had been cleared to a high extent by the end of experiments (T=225-300min), which is consistent with animals showing initial signs of awakening from T=210-270 min.
Conclusions: Fentanyl PK was shown to be comparable between newborn piglets and human neonates, which served to confirm the adequacy of a previously developed predictive model for this age. The observed level of sedation in the tested animals was associated with some degree of chest wall rigidity and brain effects, which were only transient as they returned to basal values by the end of experiments. May lower fentanyl plasma concentrations be necessary in certain subpopulations, the model could equally aid in establishing the appropriate dosing.

REDUCTION OF SUFENTANIL DOSES AS CONTINUOUS ANALGESIA AFTER SURGICAL CLOSURE OF PATENT DUCTUS ARTERIOSUS (PDA) IN EXTREMELY PREMATURE INFANTS: A 10 YEARS RETROSPECTIVE SINGLE CENTRE STUDY

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Background: Pain management is mandatory in the NICU, especially in the post-operative period. Pharmakokinetic/pharmacodynamic studies in neonates have shown wide inter-individual variations for opioids. In 2007 we implemented low starting doses of sufentanil immediately after surgical PDA closure, following suggestions of reducing opioid doses in premature infants.
Methods: We retrospectively analysed efficacy and tolerance of the dosing regimens used for post-operative analgesia in our department between 2000 and 2010. Three different time periods were considered in accordance with practice changes implemented in our department: 2000-2004 ('high dose' sufentanil > 0.1 µg/kg/h); 2005-2007 ('high dose' > 0.1 µg/kg/h); 2008-2010 ('low dose' < 0.1 µg/kg/h). Those time periods were analyzed so as to distinguish effects of the general practice changes that occurred over time from the specific effects linked to sufentanil dose changes. The anaesthetic per-operative protocol remained unchanged throughout the study period. We collected data for all infants who underwent surgical closure of PDA between 2000 and 2010, focusing on the 72 post-operative hours. We assessed doses effectively used and EDIN pain scale scores at 0, 12, 24, 48 and 72 hours after surgery. We collected time to first extubation, urinary retention and time to enteral feeding after surgery. Comparison between time periods used Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables. Evolution of sufentanil doses and EDIN scores during the first 72 post-operative hours were modelled using linear mixed models, assessing the three time areas studied.
Result: 109 out of 120 infants who underwent surgical ductal closure in our unit were studied: 28 during epoch 1, 44 during epoch 2 and 37 during epoch 3. Mean gestational age and birth weight were similar between the 3 epochs (respectively 25.06 +/-1.09 weeks and 756+/-144 g for the whole population). Median age at surgery for epochs 1, 2 and 3 was respectively 19, 14 and 14.5 days (p=0.013). Median sufentanil doses ranged from 0.1 to 0.2 µg/kg/h during epochs 1 and 2 vs 0.02 to 0.05 during epoch 3 (p< 10-3 at 0, 12, 24 and 48 hours after surgery). More opportunities to collect EDIN scores were met during epoch 1. EDIN scores were similar at baseline for the 3 epochs. They were significantly higher during epochs 2 and 3 vs epoch 1 and the proportion of infants having at least one EDIN score = 4 during epochs 1, 2 and 3 was respectively 15%, 41% and 37% (p=0.06). Median time [IQR] to first extubation after surgery was 12 [6-16], 8 [6-11] and 12 [4.5-22] days for epochs 1, 2 and 3 respectively (p=0.21). The frequency of urinary retention was similar between 3 epochs. Time to enteral feeding start after surgery decreased with time.
Conclusions: Our study identified changes over time regarding EDIN scores that were not contemporaneous with the reduction in sufentanil doses used. Reduction of sufentanil doses for post-operative analgesia in extremely premature infants after surgical ductal closure provided satisfactory efficacy and tolerance, suggesting that the minimal effective dose of continuous intra-venous sufentanil might be < 0.1 µg/kg/h.

POSTOPERATIVE ANALGESIA VIA A SUBCUTANEOUS WOUND CATHETER AFTER DUCTUS LIGATION IN PRETERM INFANTS. PHARMACOKINETICS OF LEVOBUPIVACAIN.

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Key words: Preterm, pain, thoracic surgery, local anaesthesia.
Background: Various regional anaesthetic techniques have been shown to provide safe and effective postoperative analgesia with a reduced need for opioids in adults and older children. However, analgesic methods involving the use of local anaesthetics have hitherto been used only sparingly in association with surgical interventions in preterm infants. Administration of local anaesthetics through subcutaneous catheters placed in the surgical wound has been found effective in adults and older children . Aim:The aim of this study was to explore the pharmacokinetics following its use in extreme preterm infants after undergoing surgical ductus ligation.
Methods: Following Ethics committee approval and parental informed consent preterm infants scheduled for surgical ductus ligation were included in the study. All patients were anaesthetized according to a standardized protocol based on high-dose fentanyl (25-100mcg/kg) . Before skin closure the surgeon inserted a subcutaneous catheter into the surgical wound. By using a randomized double blind placebo controlled cross over study design the patients was randomized to either an infusion of levobupivacain 0,625mg/ml (2mg/kg/24h=3,2ml/kg/24h) or placebo (NaCl 9mg/ml). Every eighth hour the infusion was switched between levobupivacain and saline. Blood samples for determination of plasma levobupivacain concentrations were taken at 10,13,16,19,22 and 24 hours after start of the infusion regimen. Postoperative analgesia was assessed by EDIN pain scale and the postoperative opioid administration was adjusted in relation to the assessed pain scores. Patients were also closely monitored for any signs of systemic local anaesthetic toxicity. This pharmacokinetic study is a part of a lager study that focused also on pharmacodynamics, pain assessment and cerebral heamodynamics during potoperative local anaesthesia in extremely preterm infants.
Result: 20 extremely preterm infants 23-27 gw (mean weight :721g) were included in the study. Plasma levobupivacaine ranged 100 to 450 mcg/l(toxicity level approx.2000mcg/l). There were no signs of 'wash out' of levobupivacain during the periods of placebo saline administration. No side effects were noted.
Conclusions: Infusion of levobupivacain through a wound catheter following surgical ductus ligation in preterm infants was found to be associated with plasma levels well within the safety range.

TIME OF BIRTH AND RISK OF RESPIRATORY ILLNESS IN PRETERM INFANTS <30 WEEKS GESTATION (GA): A RETROSPECTIVE MATCHED-PAIR COHORT STUDY

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Background: There is conflicting data on whether the day and time of birth has an independent effect on the risk of perinatal death and morbidity. At term, the risk of neonatal death ascribed to anoxia is increased outside the hours of the normal working week. Few studies have explored the effects of timing of birth on the mortality risk of very-low-birth-weight (VLBW) infants. Even less is known about the impact of timing of birth on morbidity among surviving VLBW infants. Aim: To evaluate the impact of timing of birth on the respiratory morbidity of infants <30 GA.
Methods: Retrospective matched-pair cohort analysis of surviving preterm infants <30 GA born in a single tertiary centre between 2006 and 2012. Patients with congenital anomalies were excluded. Patients included were grouped according to whether they were born between 8:00AM and 8:00PM (day) or between 8:00PM and 8:00 AM (night) on any day of the week. Groups were matched for antenatal steroid courses (AS), GA, birth weight in grams (BW), 5 minute APGAR (APGAR-5). Outcome measures were intubation and surfactant at birth (SURF), length of first ventilation episode (MVfirst), total length of ventilation (MVtotal), length of non-invasive respiratory support (NIRSup), pneumothorax (PNEU), and oxygen at 36 weeks corrected gestational age (BPD). Qualitative data were analyzed using the Chi-Square test and quantitative data using Mann-Whitney-test. $P<0.05$ was considered significant. Data is displayed as median and 25th-75th quartile range (IQR) or ratio (n/N) and percentage (%).
Result: 326 patients were included (178 day, 148 night). No significant differences in the baseline characteristics of both groups were identified (day vs. night): AS 159/178 (89%) vs. 136/148 (92%), p=0.46; GA 27 (25-28) vs. 27 (25-28), p=0.06; BW 960 (786-1163) vs. 900 (672-1153), p=0.15; APGAR-5 8 (7-9) vs. 8 (7-9), p=0.6. With regard to outcome measures a significant difference in the rate of intubation and surfactant, total length of ventilation and BPD was noted. Patients born in the day were intubated/received surfactant less frequently (124/178 [70%] vs. 124/148 [84%], p=0.004), were ventilated for a shorter period of time (3[1-10] vs. 6 [1-23], p=0.02) and had a lower BPD rate (53/178 [30%] vs. 68/148 [46%], p=0.003). No significant difference was found with regard to NIRSup (18 [6-45] vs. 19 [6-50], p=0.49) and PNEU (10/178 [6%] vs. 7/148 [5%], p=0.81).
Conclusions: After adjusting for the most important risk factors for respiratory illness preterm infants born at night seem to be at higher risk for intubation and surfactant than during daytime with an increased risk for developing BPD subsequently. This could suggest potentially modifiable factors, such as staffing levels and experience as well as education and training in current best practice delivery room management that could be addressed with the goal of improving outcomes.

MATHEMATICAL DIFFICULTIES IN VERY PRETERM CHILDREN: A DIFFERENT AETIOLOGY THAN CHILDREN WITH DEVELOPMENTAL DYSCALCULIA

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Background: Children born very preterm (VP; <32 weeks) have poorer academic attainment across all school subjects than their term-born peers. Particular difficulties with mathematics have been observed that are out of proportion to difficulties in other subjects and persist even after controlling for IQ. Previous studies have failed to identify the nature of VP children's mathematics difficulties due to a reliance on general standardised tests. However, it has been suggested that VP children's poor mathematical attainment may have similar causes to individuals with Developmental Dyscalculia, such as weak number sense skills. Therefore we aimed to assess VP children's mathematics skills in fine detail to identify specific areas of difficulty and to determine whether these are similar to children with Developmental Dyscalculia.
Design: 117 VP children aged 8-10 years in mainstream schools were recruited with a control group of 79 term-born classmates. Children completed two half-day assessment sessions comprising a variety of standardised and experimental tasks. Experimental measures were used to assess specific mathematics processes including number sense (magnitude comparison and number line representations), number naming, counting, access to number facts, strategy use and conceptual knowledge. Standardised measures assessed mathematical attainment and non-verbal IQ. Effect sizes (Cohen's d) were computed for comparison across tasks.
Results:. VP children had significantly lower standardised scores for non-verbal IQ (mean difference -7.2; 95%CI -13.0 to -1.3; d=0.4) and mathematics attainment (-12.27; -18.0 to -6.6; d=0.6). For experimental measures, VP children had significantly poorer performance on tests of number line representations (d=-0.3, p=0.036), number recognition (d=-0.4; p=0.008), counting (d=0.5; p=0.002), and access to number facts (d=0.4; p=0.011). VP children also used more immature strategies when completing simple maths problems than controls (d=0.3; p=0.026). However, there were no group differences on tests of magnitude comparison and conceptual knowledge. After adjustment for IQ, significant group differences remained only in number naming (p= .036), counting (p= .025) and access to number facts (p=0.001).
Conclusions: This is the first study to identify specific areas of mathematical difficulties in VP children. These results suggest that the nature of VP children's difficulties with mathematics is different from individuals with Developmental Dyscalculia as they do not have specific problems with number sense. In contrast, they appear to have problems with basic procedural and factual aspects of mathematics, which may be explained by their well-documented deficits in general cognitive skills. Improving VP children's attainment in mathematics may thus require the development of population-specific interventions.

PULMONARY EFFECTS OF TRANSITION FROM INVASIVE TO NON-INVASIVE RESPIRATORY SUPPORT AND POSITIONAL CHANGE IN PRETERM INFANTS

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Introduction: In an attempt to minimize ventilatory induced lung injury, preterm infants on invasive mechanical ventilation are usually extubated as soon as possible once lung function has improved. To maximize extubation success, patients are usually placed in prone position. The effect of transitioning preterm infants from invasive to non-invasive respiratory support and from supine to prone position on lung volume, respiration and ventilation distribution is currently unknown. We hypothesized that extubation would result in a drop in end-expiratory lung volume (EELV) and ventilation, and that changing to prone position would improve these parameters.
Patients and Methods: 20 preterm infants (gestational age: 28.7±1.6 wk; birth weight: 1124±387 g) with respiratory distress syndrome (RDS) were enrolled in the study. Infants were placed in supine position and changes in EELV, tidal volume and its distribution were monitored by electrical impedance tomography before and after extubation from high frequency ventilation (HFV) to nasal continuous positive airway pressure. To eliminate the effect of high-frequency oscillations on lung volume and to allow for spontaneous breathing, oscillations were stopped for two minutes prior to extubation. Ten minutes after extubation, infants were placed in prone position. Data on invasive and non-invasive continuous distending pressure (CDP), oxygen need (FiO2), transcutaneous carbon dioxide levels (TCPCO2¬) and oxygen saturations (S¬pO2) were also recorded. Comparative analysis was performed with Wilcoxon signed rank test for skewed data and the student t-test for normally distributed data.
Result: Before and after extubation the CDP and FiO2 were, respectively, 7.9±0.5 vs 6.0±0.2 cmH2O and 0.27±0.02 vs 0.23±0.04. EIT showed a significant increase in both EELV (median 3.8 AU/kg, interquartile range (IQR) -0.8 - 28.3, $p<0.05$). Minute volume increased after extubation due to larger tidal volume (median 2.2 AU/kg, IQR 0.4 - 5.3, $p<0.05$) and unchanged respiratory rate. Ventilation distribution was unaffected. Changing from supine to prone position further increased EELV (median 34.1, IQR 9.9 - 60.8 AU/kg, $p<0.01$) with a decreased respiratory rate (mean difference -4.9 ± 9.6 breaths/min) and stable tidal volume, distributed more homogeneously over ventral and dorsal lung regions than in supine position.
Conclusions: Following extubation, preterm infants with RDS are able to maintain and even improve their lung function (EELV, tidal volume) on non-invasive support and this effect is augmented by placing infants in prone position. These results suggest that infants should preferably be placed in prone position following extubation.

PILOT RANDOMISED, BLIND PLACEBO-CONTROLLED TRIAL OF DOBUTAMINE FOR LOW SUPERIOR VENA CAVA FLOW (SVCF) IN THE LOW BIRTH WEIGHT INFANTS (LBWI)

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Background and aims: Echocardiography-derived low SVCF is a relevant biomarker of circulatory impairment shortly after birth in the LBWI as associates adverse neurodevelopmental outcome and death. Dobutamine (DB) has been suggested as the best therapeutic option for this condition. However, the efficacy and safety of DB vs placebo (PL) in either hypotension or low SVCF has never been tested in this population. This exploratory trial aims to gather information in the face of a therapeutic confirmatory trial.
Methods: One hundred and twenty-seven LBWI who reached illness score below threshold were serially scanned from birth up to 96h. Infants were randomly assigned to receive DB [step-wise dose increase: 5-10-15-20 µg/k/min] or PL [equal volume] if SVCF <41 ml/k/min within 1st 24h (low SVCF). Volume expansion prior to intervention was not administered per protocol. Primary outcome: SVCF is normalized (SVCF>41 ml/k/min) and maintained (SVCF>41 ml/k/min at 60 min). Secondary outcomes: short-term (96h) evolution of the routine clinical and biochemical parameters indicating circulatory impairment, near-infrared spectroscopy parameter, and cranial Doppler-ultrasound measurements; and the main neonatal clinical diagnoses at term equivalence. Statistics:T-student, X2 and mixed model analysis.
Result: SVCF showed increasing trends throughout the first 96h in the whole cohort. The prevalence of low SVCF was 22% and associated immaturity [low SVCF 26.7 (2) wks of GA; controls 27.7 (2) wks of GA; p=0.02] and need for advanced resuscitation at birth [low SVCF 57.1%; controls 31.6%; p=0.02]. In infants who showed low SVCF [DB=16; PL=12], the intervention started at 7.8 (1.1) h from birth without differences between both groups. Groups were comparable with respect to perinatal data. SVCF increased independently of group allocation. However, infants on DB showed higher heart rate (p=0.001), serum glucose (p=0.008) and bicarbonate (p=0.04) concentration, and the base excess was less negative (p=0.059) than those on PL. No other differences were found either in the short-term or term equivalence outcomes between the intervention groups. Low SVCF significantly increased the risk of ischemic events (spontaneous bowel perforation or severe vascular spasm) [OR 13; 2.4-69.2; p<0.01].
Conclusions: Low SVCF is a strong biomarker of abnormal blood flow distribution early after birth in the LBWI. In this exploratory trial, there is a trend towards better short-term outcome of biochemical perfusion parameters in the DB-treated infants. Speculation: Potential role for systematic volume expansion prior to intervention to decrease DB side effects. Disclaimer: The authors have no potential conflict of interest. The study was supported by the Spanish Health Ministry, SAS/2481/2009 and the SAMID network (RD08/0072/0018).

TITLE SCAVENGING OF FREE HEMOGLOBIN PROTECTS CHOROID PLEXUS EPITHELIUM FROM APOPTOSIS AND CELL DAMAGE FOLLOWING IVH

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Introduction: Intraventricular hemorrhage (IVH) is a major cause of severe neurodevelopmental impairment in preterm infants. To date, no therapy is available that prevents infants from developing serious neurological disability. Following hemorrhage, cell-free hemoglobin (Hb) and its metabolites are released into the intraventricular space and formation of methemoglobin has been shown to be a causal initiator of inflammation. Thus, extracellular Hb might be the culprit in the development of brain damage following preterm IVH. Accordingly, removal, scavenging, or neutralization of extracellular Hb and its down-stream metabolites might present a plausible approach towards protection of the immature brain following preterm IVH.
Objective: To investigate the structural and functional damage and characterize the inflammatory response in the choroid plexus following IVH and to evaluate the protective effects following treatment with scavengers of Hb, heme and free radical.
Methods: Using a rabbit pup model of IVH we characterized the inflammatory gene and protein expression at 24 and 72 hours in the choroid plexus. Structural and functional integrity of choroid plexus, at 72 hours following IVH, was examined using electron microscopy (EM) in animals treated with intraventricular injection of the heme- and radical scavenger a-1-microglobulin (A1M) and in sham controls. In order to further characterize cellular and molecular mechanisms, primary human choroideus plexus epithelial cells were exposed to different Hb-metabolites with or without the addition of the Hb scavenger haptoglobin (Hp) or the heme- and radical scavenger A1M.
Results: Following IVH, TNFa, IL1ß, and HO-1 mRNA expression in the choroid plexus were highly upregulated at 24 and 72 hours ($p<0.01$) with a concomitant increase in TNFa protein levels. Following IVH, EM displayed disintegrated choroid plexus epithelium with fragmented microvilli, apoptotic bodies, swollen mitochondria and increased epithelial staining of TNFa. However, rabbit pups treated with intraventricular A1M displayed an intact structural integrity of the choroid plexus epithelium and a reduced or total inhibition of TNFa, IL-1ß and HO-1 mRNA expression. In vitro studies showed an increased necrosis (LDH), apoptosis (Caspase activation) and expression of MMP-9 in epithelial cells exposed to metHb and heme but not in cells exposed to oxyHb. Treatment with Hp or A1M displayed a very protective effect towards the metHb- and heme-induced effects and thereby reversed or reduced necrosis, apoptosis and pro-inflammatory response.
Conclusion: Following IVH there is a distinct upregulation of inflammatory cytokines in the choroid plexus at 24 and 72 hours. This is associated with disintegration and severe damage to the choroid plexus epithelium. Treatment in vivo, using the heme- and radical scavenger A1M almost completely inhibited these effects. Furthermore, in vitro exposure of choroid plexus epithelial cells to Hb-metabolites revealed that mainly metHb induces inflammation and apoptosis. Co-incubation with the Hb-scavenger Hp or A1M reversed or reduced these effects. In conclusion, our studies present a therapeutic opportunity and a means of decreasing the damage in the choroid plexus following IVH.

PHARMACOKINETICS AND DOSING OF CEFAZOLIN IN NEONATES BASED ON TOTAL AND UNBOUND DRUG CONCENTRATIONS

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Introduction: Cefazolin (CFZ), a time-dependent and highly protein bound cephalosporin, is frequently administered in neonates for antimicrobial prophylaxis or therapy. In early life, CFZ pharmacokinetic (PK) observations are limited and CFZ dosing regimens are variable. Therefore, we aimed to explore CFZ PK and its covariates in (pre)term neonates based on total and unbound concentrations and to optimize neonatal CFZ dosing.
Methods: Neonates, receiving CFZ intravenously as routine surgical prophylaxis, were included. Blood samples were collected at 0.5, 2, 4, and 8 h after the first (50 mg/kg) and before subsequent CFZ doses (50 mg/kg/8h). A population PK analysis, based on total and unbound CFZ concentrations was conducted using non-linear mixed effect modeling. The impact of clinical covariates on CFZ volume of distribution (Vd), clearance (Cl), and protein binding parameters was explored. Monte Carlo simulations were used to evaluate CFZ dosing regimens. We hereby aimed to reach 60% of time above the minimal inhibitory concentration for susceptibility of staphylococcal species (8 mg/L).
Results: In 36 neonates, with median (range) gestational age of 37 (24-40) weeks, postnatal age (PNA) 9 (1-30) days, birth weight (BW) 2720 (540-4200) g and current weight (CW) 2755 (830-4200) g, 119 plasma samples were collected. A one-compartment PK model was developed. CW was identified as covariate on Vd, hereby reducing inter-individual variability of Vd with 50%. BW and PNA were found as covariates on Cl, explaining 58% of Cl variability. Median Vd for a neonate with a current weight of 2755 g was 0.863 (3.55) L and median Cl (CV%) for a neonate with a birth weight of 2720 g and postnatal age of 9 days was 0.185 (12.8) L/h. For neonates with CW = 2000 g a reduced CFZ dose (25 mg/kg) each 12h (PNA = 7days) or 8h (PNA >7 days) could be suggested.
Conclusions: In a large neonatal cohort, inter-individual variability in Vd (50%) and Cl (58%) was explained by CW and BW+PNA respectively. This is the first report on CFZ PK in neonates taking into account both total and unbound drug concentrations. This is important since only the unbound drug is pharmacologically active. Based on an integrated pharmacokinetic / pharmacodynamic approach, an optimized CFZ dosing regimen could be derived. Dose reduction can hereby result in extra albumin binding places available for other endogenous or exogenous compounds.

EFFECT OF NUTRITION IN EARLY POSTNATAL LIFE ON BRAIN VOLUMES IN PRETERM INFANT

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Preterm newborns are at risk of postnatal growth failure and impaired long-term neurocognitive development. Inadequate nutrition in early postnatal life might be partially responsible for growth failure and might result in alteration in brain structure, growth and cognitive function. Aim of the study was to investigate the relationship between cumulative protein, fat and energy intake, protein and energy deficit during the 1st 4 weeks after birth, with weight gain and cerebral volumes at term equivalent age (TEA).
Patients and Methods: 131 infants (GA 27.0±1.5; BW 934±193 g; PMA 41.4±0.8 weeks) admitted to NICU, who had an MRI at TEA, were studied. Protein, fat and energy cumulative intakes, protein and energy deficit, weight gain over the first 4 weeks were collected from the patients' computerized database. An automatic segmentation technique was used to quantify total brain volume (TBV), cerebellum (CB), cortical grey matter (GM), unmyelinated white matter (UWM), and basal ganglia (BG). Multiple linear regression analysis was applied to determine association between nutrition intake, postnatal growth and brain volumes, corrected for GA, postmenstrual age (PMA), BW Z-score, white matter injury (WMI) and neonatal morbidity (BPD, PDA, NEC, IVH and sepsis).
Result: Cumulative total protein, fat and energy intake did correlate with weight gain ($R=0.61$, $p=0.002$; $R=0.66$, $p<0.001$; $R=0.65$, $p<0.001$), that was also associated with TBV, CB, BG and GM. After correction for GA, BW Z-score, PMA, WMI, cumulative fat and energy intake were positively associated with TBV, CB and GM. Enteral protein, fat and energy intake did positively correlate with TBV, CB and GM. After correcting for illness and days of parenteral nutrition (PN) correlation did only persist for CB ($R=0.51$, $R=0.41$, $R=0.50$, $R=0.51$, $R=0.51$; $p<0.005$). Energy deficit did correlate with days of PN and was negatively associated with TBV, CB and GM ($R=-0.61$, $R=-0.66$, $R=-0.64$; $p<0.005$). Babies who were at full enteral feeding by 15 days after birth showed significantly higher TBV, CB, GM and BG at TEA, compared to the others. No correlations were found between protein deficit and brain volumes. No significant correlation was observed between macronutrients and UWM.
Conclusions: Weight gain during the first 4 weeks after birth was positively influenced by total protein, fat and energy intake and was associated with brain volume at TEA. Energy deficit, due to prolonged PN and related to illnesses, was responsible for reduced brain volume. After correction for several neonatal complications, (BPD, PDA, NEC, IVH and sepsis), cerebellar growth at TEA appeared sensitive to nutrition during the first month after birth.

CEACAM1 AND ITS IMPACT ON MYELINATION

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Background and aims: Preterm birth is defined as birth before 37 weeks of gestational age. About 7-10% of all neonates are preterms, and each year, about 12-13 million preterms are born. Although there was huge progress in the treatment of these babies, they are still at high risk to develop multiple morbidities such as neurocognitive disorders (encephalopathy of prematurity) which are a huge burden for the children and their families. Multiple factors are causal for encephalopathy of prematurity, such as hyperoxia and maternal or neonatal inflammation, but the mechanisms are poorly understood. To develop new pharmaceutical approaches for treatment, a better understanding of the underlying molecular mechanisms is needed. CEACAM1, a member of the carcinoembryonic antigen-related cell adhesion molecules (CEACAM) which has complex functions in cell proliferation and differentiation and also is involved in inflammatory processes, seems to be a promising target protein.
Material and Methods: Ontogenetic CEACAM1 expression was analyzed in untreated Wistar rats from postnatal day 1 (P1) to P28. Modulation of CEACAM1 expression in a model of encephalopathy of prematurity (Wistar rats, inflammation at P3, hyperoxia at P5) was detected at P6 and P11. In vitro experiments were performed in rat primary oligodendrocyte cell cultures. IHC, aquisition of protein and RNA, Western Blot, PCR and qRT-PCR were perfomed according to standard protocols.
Result: CEACAM1 is expressed in oligodendrocytes of the developing rat brain with a close spatio-temporal correlation to myelination. Additionally, in a rat in-vivo model of inflammation- and hyperoxia-induced encephalopathy of prematurity, CEACAM1 expression is altered. In vitro, stimulation of CEACAM1 on primary oligodendrocytes increases myelination.
Conclusions: Due to its ontogenetic expression profile and its ability to increase myelination in vitro, CEACAM1 is a target protein for therapeutical approaches with regard to myelination disorders.

EFFECTS OF LEVETIRACETAM IN A MODEL OF OXYGEN-GLUCOSE DEPRIVATION IN PRIMARY HIPPOCAMPAL NEURONS

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Background: Hypoxic-ischaemic encephalopathy (HIE) resulting from perinatal asphyxia often leads to severe neurologic impairments or even death. HIE is frequently accompanied by epileptic seizure activity aggravating brain injury. Levetiracetam (LEV) being a new anticonvulsant is approved for clinical application to infants older than four weeks of age and is already used off-label in neonates already. Of interest LEV does not show an adverse effect on developmental apoptosis in the newborn brain. Previously, the administration of LEV in high concentration showed beneficial effects in an adult rodent model of ischaemic brain injury and in neuronal cultures exposed to hypoxia-induced injury. In one of our previous studies we could not confirm these results in a neonatal animal model of hypoxic-ischemic brain injury. The aim of the present study was to investigate whether treatment of primary hippocampal neuronal cultures with high dose concentrations of LEV is able to prevent neurotoxicity following oxygen-glucose deprivation (OGD).
Methods: Cultured primary hippocampal neurons (10 DIV) prepared from 16.5 day old embryonic mice were treated with OGD serving as model for HIE. Neurons were randomly assigned to one of the following treatment groups: i) control ii) OGD iii) OGD+LEV. LEV (100µM) was applied to the cultures 30 min prior to OGD. As outcome parameter cell death was evaluated using calcein-AM and propidium iodide (PI).
Result: Application of LEV did not reduce the number of dead cells assessed by the PI/Calcein ratio in the OGD group treated with 100 µM LEV (47%) compared to the untreated OGD group (46%).
Conclusions: Our preliminary data show that administration of LEV has no neuroprotective effects against OGD in primary hippocampal neurons. Ongoing studies investigate different concentrations of LEV and underlying mechanisms.

EFFECTS OF HYPOTHERMIA AND LEVETIRACETAM ON NEUROPROTECTIVE PATHWAYS AFTER HYPOXIA-ISCHEMIA IN THE NEONATAL MOUSE BRAIN

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Background: Hypoxic-ischemic injury (HI) to the developing brain remains a major cause of morbidity. Hypothermia is currently the only established neuroprotective treatment available for term borns with hypoxic-ischemic encephalopathy, saving one in eight infants from developing severe neurological deficits. Therefore, additional treatments with clinically applicable drugs are indispensable. Furthermore, the pathophysiological mechanisms of hypothermia-induced recovery are not clearly understood. Objective: This study examines a potential additive neuroprotective effect of hypothermia combined with levetiracetam in neonatal mouse HI.
Methods: 9-days-old C57BL/6-mice were subjected either to a sham-operation or to HI (modified Rice-Vannucci-model). After HI, the pups were randomized into six groups: 1) no treatment, 2) hypothermia (whole body-cooling, 4 hours, 30°C), 3) high-dose levetiracetam intraperitoneal (70 mg/kg body weight), 4) hypothermia combined with high-dose levetiracetam intraperitoneal, 5) low-dose levetiracetam intraperitoneal (7 mg/kg body weight), 6) hypothermia combined with low-dose levetiracetam intraperitoneal. Hemispheres were analyzed 24 and 96 hours after HI by protein analysis and immunhistochemistry. From P28 to P59, sensorimotor function was assessed via different tests.
Result: Hypothermia only and combined with low-dose levetiracetam was associated with a decrease of apoptosis and an increase of neuroprotective hypoxia-triggered parameters, but without additive effects. Intraperitoneal treatment with high-dose levetiracetam caused an increase of apoptotic factors. Behavioural testing demonstrated improved sensorimotor outcome after treatment with hypothermia.
Conclusions: Whole-body cooling provides neuroprotection in the neonatal mouse brain by reducing apoptosis and activation of neuroprotective hypoxia-triggered parameters. However, treatment with levetiracetam after hypoxic-ischemic injury has no additive effects.

LONG-TERM FOLLOW-UP OF CHILDREN BORN WITH EXTREMELY LOW BIRTH WEIGHT: STANDARDIZED PARENTAL ASSESSMENT OF DEVELOPMENTAL AND BEHAVIORAL PROBLEMS AT 11-12 YEARS OF AGE

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Background and Aim: Extreme prematurity, as well as intrauterine growth restriction carry risks for long-term sequelae. The increasing survival rate of low gestational age infants has not been accompanied by an increase in early detectable sequelae such as cerebral palsy (CP). However, neurocognitive dysfunction and disadvantaged school achievements are common in children born very preterm. Improvements in perinatal care influence outcome, thus comprehensive long-term studies are needed on geographically defined birth cohorts. In this national study, we assessed the developmental profiles in children born with extremely low birth weight (ELBW) during a two-year period.
Methods: The study group consisted of all surviving children born in Finland 1996-1997 with a birth weight less than 1000 g. A control group of randomly selected children born full-term were included. A standardized questionnaire, the Five to Fifteen (FTF), was sent to the parents. The questionnaire assesses motor skills, executive functions, perception, memory, language, learning, social skills, and emotional/behavioral problems. The assessment was performed at a mean (±SD) age of 11.6 (0.72) and 11.8 (0.79) years, in ELBW and control children, respectively. A profile analysis was carried out using mixed ANOVA with the group (ELBW vs. control group) as the independent variable and the 22 FTF subdomains as dependent variables, adjusted for mothers' education.
Result: Of all 206 surviving ELBW children, 144 (71%) participated and 29 control children were included in the study. Of the non-participating ELBW children, 4 had CP, 7 mental retardation, 6 both CP and mental retardation, 20 were lost to follow-up, 10 declined , 13 local follow-up and 2 forms disappeared. The gestational age of ELBW group was 27.2 weeks (2.1) and birth weight 800.3 grams (141). Background factors between the groups were similar, except mothers' education level. On the FTF, a significant between-subjects effect of group emerged, $F(1,168) = 11.21$, $p = 0.001$, $?p2 = 0.063$. A significant within-subjects effect indicated that the effect of group was not similar for all subdomains, $F(9.6,1619) = 2.65$, $p = 0.004$, $?p2 = 0.016$. Compared to the control group, the ELBW group had significantly more problems in gross motor skills ($p < 0.001$), fine motor skills ($p = 0.005$), attention ($p = 0.010$), hypoactivity ($p = 0.008$), planning and organizing ($p = 0.004$), perception of relation in space ($p = 0.005$), time concepts ($p = 0.009$), body perception ($p = 0.004$), visual perception ($p = 0.015$), memory ($p = 0.019$), receptive language ($p = 0.007$), communication ($p = 0.037$), math ($p = 0.001$), general learning ($p = 0.003$), coping in learning ($p = 0.002$) and social skills ($p = 0.016$). However, no group differences were found in hyperactivity/impulsivity, expressive language, reading/writing or emotional/behavioral problems (all $p > 0.05$).
Conclusions: Even at prepuberty, ELBW children have significantly more difficulties in the majority of developmental domains than children born full-term. The results will be compared to neuropsychological test results to reveal the possibility to use this parental questionnaire to screen subgroups in need of further assessments. Extended developmental follow-up and support are prerequisite for evaluating outcome of perinatal care.

LASTING IMPACT OF MAJOR NEONATAL MORBIDITIES ON THE OUTCOME OF 10 TO 16-YEAR OLD CHILDREN WHO WERE BORN AT 23-25 WEEKS GESTATION AFTER ACTIVE PERINATAL CARE: A REGIONAL SWEDISH FOLLOW UP STUDY FROM 2 TERTIARY PERINATAL LEVEL CARE CENTERS.

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Background: Active perinatal care (APC) has improved the survival of extremely preterm infants (EPT) born at or < 25 weeks of gestation. Concern remains on the high rates of neonatal morbidities in these EPT infants and uncertainty prevails over the extent to which these morbidities predict poor long-term outcomes in EPT infants. Objective: To determine the individual and combined prognostic effects of bronchopulmonary dysplasia (BPD), intraventricular hemorrhage grade 3-4 (IVH) or periventricular leukomalacia (PVL), and severe retinopathy of prematurity (ROP) in 10-16 year old EPT children born at 2 tertiary care centers in Sweden (Uppsala and Umeå University Hospitals) who have been adhering to a policy of APC that included universal resuscitation of all EPT infants born alive. These EPT children are well characterized in their neonatal period in published reports.
Design/Methods: 213 EPT children were born alive from 1992 through 1998 and 140 (66 %) survived to a postmenstrual age (PMA) of 36 weeks. 132 (98% of all EPT survivors) were analyzed at 10-16 yrs of age. Poor outcome was defined as combined end point of death or survival to 10-16 years with one or more of major disability, i.e., disabling cerebral palsy, shunt for hydrocephalus, severe hearing loss/deafness, blindness and severe cognitive delay with FSIQ =55 = = -3SD WISC-IV).
Result: Thirty-three (25%) EPT children had poor outcome; 6 (4%) died in the first year of life and 19% had one or more major disability. In children who were free of BPD, IVH/PVL, and severe ROP the rate of poor long-term outcome was 13% (95% CI, 5%-22%). Corresponding rates with any 1, any 2, and all 3 neonatal morbidities were 23% (95% CI, 11%-36%), 50% (95% CI, 26%-74%), and 75% (95% CI, 50%-94%), respectively. Multivariate logistic regression analyses revealed that morbidity count strongly predicted poor outcome [OR 2.5 (95% CI, 1.5-4.1)] and IVH/PVL was associated with poor outcome [OR 4.7 (95% CI, 1.2-18.7)].
Conclusions: In infants born at or < 25 weeks of gestation who survive to a PMA of 36 weeks, a simple count of 3 common neonatal morbidities strongly predicts the risk of poor outcome at 10-16 yrs of age. This study also reports that rates of poor outcome are similar to the centers with more conservative policies of care despite high survival rates after APC.

YOUNG ADULTS BORN PRETERM WITH VERY LOW BIRTH WEIGHT DISPLAYS DIFFERENT LATENCY IN EVENT RELATED CUE-P3 POTENTIAL THAN CONTROLS.

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Background: Preterm birth with very low birth weight (VLBW) can impact on the individual's cognitive performance. Lower scores on cognitive tasks including general intelligence and specific neuropsychological functions have been reported in VLBW subjects. The underlying electrophysiological basis of such reduced performance in VLBW subjects has not been studied and remains undetermined. Objective: In our study, event related potentials (ERPs) from a visual two stimuli cued GoNoGo task were obtained to identify the consequences of VLBW on electrophysiological activity in young adulthood. This GoNoGo paradigm has been shown to evoke some well-known event related potentials, like the Cue-P3 and P3Go in parietal leads, and the P3NoGo in frontal leads. Behaviorally reaction times, variability of reaction time, omissions and commissions errors were also assessed. Design/
Methods: All participants were part of a long-term prospective cohort study. Twenty-seven VLBW young adults (19 females), with mean age 23 (range 21-23), birth weight 1242g±224g; gestational age at birth 29±3 weeks, and 27 matched controls (13 female) participated. ERPs were recorded with 19 electrodes in the standardized 10-20 system during a visual GoNoGo. ERP data was analyzed with Win-EEGv2.82. Amplitude and latency was measured with fractional area approach.
Result: Behaviorally there were no significant differences between groups in reaction time, variability in reaction time or commission errors, but the VLBW subjects had significantly more omissions ($p<.05$). Latency of P3Go was for both groups about 320ms, with no difference in amplitude. For Cue-P3 we found a significant difference for latency between groups (VLBW mean=357ms±45ms, controls' mean=450±62ms, $p=.0001$, Cohen's $d=1.73$). The Cue-P3 amplitude was not significantly different between groups.
Conclusions: The Cue-P3 wave is generally regarded as the neural correlate of processing information relevant for preparation of the Go response. In the VLBW group the cue was processed almost at the same latency as for the Go stimuli, while the controls processed the cue much later than the P3Go. The difference in speed of processing of cue can be related to increased omission errors in the VLBW group. If so, the VLBW group had an undifferentiated neuronal activation pattern for the two stimuli that can explain some of the inattentiveness reflected in increased number of omissions.

HEMODYNAMIC CHANGES IN NEONATAL SEPTIC SHOCK- VASOMOTOR FAILURE OR MYOCADIAL DYSFUNCTION: A PROSPECTIVE OBSERVATIONAL STUDY

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Background: The hemodynamic changes in neonatal septic shock are not understood completely. As a result, the treatment of neonatal septic shock is empirical and is largely based on data from pediatric and adult studies. We planned this study to evaluate hemodynamic changes in neonatal septic shock utilizing functional echocardiography and to study the effects of vasoactive drugs on hemodynamic parameters.
Patients and Methods: We conducted this prospective observational study in a level III neonatal intensive care unit of a referral teaching hospital over a period of 2 years and 6 months from March 2010 to August 2012. The study was registered (CTRI/2011/091/000012). Neonates with septic shock (Shock-group; diagnosed according to the modified International Pediatric Consensus Conference statement on sepsis and organ dysfunction in Pediatrics) and an equal number of gestation and postnatal age matched healthy neonates (Control- group) were enrolled. Functional hemodynamic parameters [left & right ventricular output (LVO, RVO), ejection fraction (EF), isovolumetric relaxation time, early passive to late active peak velocity ratio] and celiac & middle cerebral artery flows were measured in shock-group prior to initiation of vasoactive drugs, while the baby was receiving fluid bolus(s). Repeat assessment was performed after 30 to 40 min of vasoactive drug infusion. Control-group underwent a single assessment after enrollment. We compared the various hemodynamic variables between shock-group and control-group using paired-t test or Wilcoxon Signed rank test. We also compared the hemodynamic variables in shock group before and after vasoactive drugs using paired-t test or Wilcoxon Signed rank test.
Result: We enrolled 56 neonates with septic shock and 56 controls. At baseline, median (IQR) LVO was significantly higher in neonates with septic shock as compared to controls [304 (204 to 389) vs 233 (206 to 303) mL/kg/min, $p<0.001$], but EF was similar between the two groups (56±12 % vs 55±5%, $p=0.25$). We were able to record 'post-vasoactive drugs' hemodynamic variables in 43 out of 56 neonates with septic shock. Out of 43 neonates, 28 received dopamine, 12 received dobutamine and 3 received both dobutamine and dopamine as initial vasoactive drugs. After infusion of vasoactive drugs, there was a significant increase in heart rate and RVO compared to baseline in the shock-group but LVO and EF did not change significantly. Of cases, 42 died (Non-survivors), 12 survived (Survivors); and final outcome of two neonates was not available. The non-survivors were significantly lighter [median (IQR)-1562 (1390, 1805) vs 1199 (973, 1483), $p=0.02$; had lower EF [mean (SD)- 52 (13) vs 61 (7)%, $p=0.04$] and had shorter IVRT [median (IQR)- 28 (20, 51) vs 50 (34, 59); $p=0.04$] as compared to survivors.
Conclusions: We found an elevated LVO but normal EF in neonates with septic shock. This suggests that neonatal septic shock is predominantly due to vasoregulatory failure. Vasoactive drugs significantly increased RVO which was predominantly due to increase in heart rate.

TOTAL LEFT AND RIGHT VENTRICULAR SYSTOLIC SHORTENING IN PREMATURE AND TERM BORN INFANTS. INFLUENCE OF HEART SIZE AND POSTNATAL MATURATION

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Introduction: The role of echocardiography in neonatology has changed over the past few years and is a valuable tool in assessing the myocardial function of neonates. Mitral annulus systolic excursion (MAE) is a measure of left ventricular longitudinal function. Tricuspid annulus peak systolic excursion (TAPSE) reflects longitudinal right ventricular systolic function.
Patients and Methods: Echocardiographic examinations were conducted at day three after birth in 53 premature infants (gestational age 30-35 weeks) and at expected term (+/- 14 days). 48 term infants were also examined day three after birth and at three months of age. MAE and TAPSE were measured at day three and after maturation in both groups. The parameters were normalized for heart size.
Result: MAE and TAPSE were higher in the term group than in the preterm group both at day three and after postnatal maturation ($p<0.001$). However, there was no difference between the groups after normalizing the results by the length of the septum (table). Comparing the term infants at day three and the preterm infants at expected term, the left and right ventricular excursion were higher in the preterm group, also when normalized for heart size ($p<0.001$). Table. Preterm Day 3 Term Day 3 Preterm Expected term Term3 months LVEDL(mm) 28.4 (27.6, 28.2) 34.8 (33.8, 35,8)** 36.2 (35.4, 37.0) 42.4 (41.2, 43.6)** TAPSE(mm) 6.75 (6.41, 7.09) 8.20 (7.77, 8.63)** 11.11 (10.62, 11.60) 13.60 (12.99, 14.21)** MAE left lat.(mm) 4.41 (4.16, 4.66) 5.23 (4.88, 5.58)** 6.78 (6.51, 7.05) 7.29 (6.88, 7.70)* MAE septum(mm) 3.54 (3.38, 3.70) 4.11 (3.89, 4.33)** 5.19 (4.95, 5.44) 7.15 (6.74, 7.56)** MAEAv/LVEDL 0.139 (0.133, 0.146) 0.136 (0.127, 0.145) 0.166 (0.160, 0.172) 0.172 (0.162, 0.181) TAPSE/LVEDL 0.237 (0.225, 0.249) 0.238 (0.223, 0.254) 0.308 (0.295, 0.321) 0.322 (0.307, 0.337) Mean(CI), LVEDL, left ventricular end diastolic length; Av, average left lateral and septum; *$p<0.05$, **$p<0.001$ (compared with previous column)
Conclusions: Higher MAE and TAPSE in the preterm group at expected term compared to the term group at day three, also when normalized for heart size, may indicate compensatory effects in the preterm infants. Both ventricular size and postnatal maturation influenced global ventricular systolic function.

SUPERIOR VENA CAVA FLOW FOR ASSESSMENT OF CEREBRAL CIRCULATION IN ASPHYXIATED NEONATES DURING AND AFTER THERAPEUTIC HYPOTHERMIA

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Background: Hypothermia has become standard treatment of perinatal hypoxic-ischemic-encephalopathy (HIE). Blood pressure (BP) is commonly used for assessment of circulation in the neonatal intensive care unit. Doppler ultrasound can be used to measure blood flow velocity in the anterior cerebral artery (ACA). Measure of superior vena cava (SVC) flow may provide an indicator of cerebral perfusion, as approximately 80% of SVC flow has been estimated to return from the brain. Aim: To assess the relationship between circulatory parameters of the ACA, SVC and BP in asphyxiated newborns during and after hypothermia. Hypothesis: The cerebral circulation is better reflected by SVC flow or SVC velocity time integral (VTI) than BP during therapeutic hypothermia.
Methods: Forty-four asphyxiated newborns eligible for therapeutic hypothermia were investigated with ultrasound within 12 hours of body temperature of 33.5ºC (T1), on the third day of hypothermia (T2) and within 12 hours after rewarming (T3). We measured peak systolic, end-diastolic and mean velocities in the ACA. SVC flow was calculated on the basis of SVC diameter and SVC-VTI measurements. Arterial BP was monitored continuously through indwelling umbilical arterial catheters. Dopamine infusion was given to 10, 15 and 8 infants at T1, T2 and T3. Two neonates were treated with additional dobutamine and adrenaline. All patients received continuous morphine infusion for reduction of pain and discomfort.
Result: Mean velocity in the ACA, SVC flow and VTI increased from T1 to T3 ($p<0.001$). There was a significant correlation between SVC flow and ACA mean velocity at T1 ($r=0.4$; $p<0.02$), and between SVC-VTI and ACA mean velocity at T2 ($r=0.507$, $p=0.001$). The correlation found between SVC-VTI and ACA mean velocity was weak at T1 ($r= 0.303$, $p=0.08$) and T3 ($r=0.306$, $p=0.06$). Mean BP at T1, T2, T3 was stable (44, 43, 45 mmHg) and did not correlate with SVC or ACA parameters.
Conclusions: We found a significant correlation between SVC flow/SVC-VTI and cerebral circulation during hypothermia, but no correlation with BP. This supports the need for supplemental monitoring of cerebral circulation during hypothermia. SVC flow and SVC-VTI could be an option.

MYOCARDIAL PERFORMANCE IN NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) DURING WHOLE BODY HYPOTHERMIA AND AFTER ACTIVE REWARMING.

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Background: Therapeutic hypothermia improves the neurological outcome in infants with hypoxic ischemic encephalopathy (HIE) and is now standard of care. The impact of this intervention on hemodynamics has been studied, but the impact of rewarming is unknown. Changes in myocardial performance and regional blood flow may further impact on the injurious process and are the subject of this prospective observational study. Objective: To evaluate changes in cardiac function and systemic blood flow in newborns with HIE during whole body therapeutic hypothermia and after rewarming.
Design/Methods: Serial echocardiography was performed at the following time points: [Hypothermia I] within 24 hours after commencement of cooling; [Hypothermia II] between 48-72 hours of hypothermia [Rewarming I] within 24 hours of rewarming at normothermia; [Rewarming II] after starting feeds. Evaluation of myocardial systolic [ejection fraction (EF)] and diastolic [isovolumic relaxation time (IVRT)] performance, right (RVO) and left (LVO) ventricular output and pulmonary vascular resistance (PVRI) index [right ventricular ejection time: pulmonary artery acceleration time] was performed. Clinical hemodynamic variables (e.g. heart rate, arterial pressure) were collected at these time-points. Comparison between the hypothermia and rewarming periods was conducted using related samples Wilcoxon Signed Rank Test.
Result: Twelve neonates were studied at a mean gestational age and birth weight of 40 ± 1.0 weeks and 3435 ± 787g respectively. Therapeutic hypothermia was commenced at a median of 1.5 hours [range 0-4.5hours]. An increase in LVO (108 to 162 ml/kg/min, $p<0.001$) and RVO (187 to 257 ml/kg/min, $p=0.001$), reduction in IVRT (59 to 39, <0.001) and PVRI (3.81 to 3.12,$p= 0.03$) were seen after rewarming. No differences in mitral E/A ratio(1.1 to 1.0,$p=0.3$) or LVEF (66% to 66.5%,$p=0.5$) were seen. Five patients exhibited bidirectional or right-to-left shunting across atrial or ductus level during hypothermia. This was associated with prolonged mechanical ventilation (6 vs. 1 day; $p=0.003$). Only one infant had bidirectional shunting which persisted beyond 24 hours after rewarming.
Conclusions: Rewarming was followed by an increase in systemic and pulmonary blood flow, lower PVR and altered diastolic performance. The relationship of these physiologic changes to neonatal outcomes needs further evaluation. Presence of supra-systemic pulmonary pressure during the hypothermia stage may be associated with adverse clinical outcomes.

ASSESSMENT OF SUPERIOR VENA CAVA FLOW IN EXTREMELY PRETERM INFANTS BORN LESS 28 WEEKS GESTATIONAL AGE ON FIRST DAY OF LIFE

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Background: Assessment of superior vena cava flow (SVCF) on echocardiography is used to indirectly estimate cerebral perfusion in preterm infants. Impaired cerebral perfusion is thought to be a major contributor in the pathogenesis of intraventricular haemorrhage (IVH). Aims: Aim of the study was to estimate SVCF on echocardiography at < 24h of age in a cohort of patients at highest risk of developing intraventricular haemorrhage stratified by GA less 28 weeks and to assess clinical factors that contribute to the development of IVH. Patients/Study design: Single centre retrospective cohort study. A total of 247 infants (23 0/7- 27 6/7 weeks GA) admitted to Southmead Hospital tertiary NICU between 03/2008 and 01/2012 were enrolled in the study. 109 patients were eligible for SVCF analysis.
Methods: Retrospective clinical data collection and evaluation of medical history and independent re-assessment of digitalised stored cranial ultrasound (CrUS) examinations. Calculation of SVCF was performed as described by Kluckow M. et al. (Arch Dis Child 2000; 82: F182-F187). Statistical analysis was performed using SPSS 17.0 (Student t-test; MWU test, multivariable logistic regression; ROC).
Result: The GA of the study group was 25 4/7 weeks in median (23 2/7-27 5/7 range). 46/109 (42%) infants developed IVH defined on cranial CrUS at day 7 postnatal age. SVCF measured at 8.5 h of life in median (1-23h range). SVCF was significant lower (71ml/kg/min median, 30-140 ml/kg/min range) in infants diagnosed with IVH compared to infants with no IVH (84 ml/kg/min median, 27-200 ml/kg/min range, p= 0.049; 95%CI:0.04-25.5). SVCF was irreversibly correlated to PDA size (r= -0.21: p=0.03). Infants with IVH were born with lower GA (24 5/7 versus 25 6/7 median; p= 0.01), less antenatal steroids (p=0.02), higher incidence of spontaneous vaginal delivery (p=0.003), elevated INR at delivery (p=0.02) and lower platelet count at 24h of age (p=0.001). Multivariable logistic regression analysis (gender, GA, antenatal steroids, SVCF, CRP at 24h) did not confirm independent association of SVCF at < 24h of age with development of IVH.
Conclusions: Our study results confirm low SVCF at < 24h of life contributing to the pathophysiology of IVH in extremely preterm infants. Early postnatal echocardiographic assessment estimating PDA shunt and SVCF is prerequisite to balance cerebral perfusion in infants at risk of developing IVH.

EARLY DETECTION OF CARDIAC DYSFUNCTION AFTER PRETERM BIRTH BY SPECKLE-TRACKING ECHOCARDIOGRAPHY

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Background: Preterm birth is associated with adverse cardiovascular events later in life. The underlying mechanisms are unknown. We undertook a sequential analysis of cardiac function after preterm birth by speckle-tracking echocardiography (STE) and compared the results to a healthy control group.
Methods: Evaluation of cardiac function of 25 very preterm infants (GA 26-30 weeks) at birth, at term-equivalent age and at 3 months of corrected age and comparison to the findings in 30 healthy term children (1st investigation intrauterine). We measured longitudinal strain (%), strain rate (1/sec) and tissue velocities (cm/s) in both ventricles in systole and diastole to characterize myocardial performance and compared the results to conventional echocardiography.
Results: At 3 months of corrected age, very preterm infants exhibit significantly lower left ventricular (LV) strain values (19.9 vs 22.0%, $p<0.001$), systolic (5.8 vs 6.4 cm/s, $p=0.01$) and diastolic (7.8 vs 10.6 cm/s, $p<0.001$) tissue velocities and early diastolic strain-rate values (3.9/s vs 4.7/s, $p<0.001$) compared to healthy control infants born at term. There was a trend to lower values even in the right ventricle- though not statistically significant.
Conclusion: Left ventricular systolic and diastolic dysfunction emerges already 6 months after very preterm birth and can be identified by STE while conventional echocardiography is not able to detect abnormal myocardial performance at this age. LV dysfunction might occur because of premature adaption towards higher systemic afterload and incomplete re-modelling of the LV early in life.

NEONATAL ONLINE TRAINING AND EDUCATION (NOTE) - WHERE ARE WE NOW?

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Introduction: Following positive evaluations of previous neonatal online educational projects funded by the Leonardo da Vinci fund of the European Commission the NOTE programme has been introduced to provide the opportunity for standardised education and training in neonatology for both trainees and qualified specialists. The first two modules have been awarded academic credit (10 European Credit Transfer and Accumulation System) at Master's level by the University of Southampton. The modules are funded from fees paid by participants and from pump-priming funds from the European Society for Paediatric Research (ESPR). This report presents data from the first phase of the collaboration between the NOTE Faculty, the ESPR and the University of Southampton. Recruitment The recruitment process was primarily via 'flyers' sent to members of the European Society for Neonatology (ESN) and to previous 'Leonardo' participants. Details concerning the first module - Neonatal Neurology - were also posted on the NOTE web-site. 60 online applications were received; of these applicants eight did not subsequently register and two registered but did not participate. The main reasons for application included the 'desire to improve, enhance and upgrade knowledge and skills', the opportunity to 'give solid foundation to support clinical practice', 'to gain a unique insight into international differences and standards' and to discuss practice. Demographics of Participants Of the 50 participants 26 (52%) were male and 24 (48%) female. The mean age was 38 years (range 28-60). 32 were doctors in training, 14 were qualified paediatricians or neonatologists and 4 were advanced neonatal nurse practitioners (ANNPs). 16 were working in the UK, 7 in Sweden, 6 in Denmark, 3 in Spain, 2 in Norway, 1 in Holland, 1 in Austria and 14 outside Europe. 18 (36%) of the participants reported that English was their first language. Module Structure The neurology module was developed by a subject specialist in collaboration with the NOTE Faculty. It was delivered in English over 16 weeks; the total study time required was 200 hours. Participants were divided into 3 groups: 2 comprised training clinicians and one qualified specialists group. Each group was supported by at least 2 neonatologists with experience as online tutors. Learning outcomes were defined using Bloom's taxonomy and the summative assessment comprised evaluation of online participation, development of a written clinical guideline and an online examination. Evaluation 50% of participants completed an evaluation questionnaire. On average participants spent 8 hours studying per week (2-20). Most highly rated aspects were the supportive learning environment, the quality of the materials, tutor support and the sharing of experience. The need for increased feedback and greater use of video was suggested to enhance the learning experience.
Conclusion: This evidence suggests there is continuing demand for structured neonatal online education from trainees, ANNPs and experienced clinicians seeking continuing medical education. This approach offers a unique opportunity both to acquire and to share knowledge and experience which may lead to an improvement in the quality and standard of neonatal care provision.

ASSESSMENT STRATEGY AND OUTCOMES FOR THE FIRST MODULE OF AN ONLINE EDUCATIONAL PROGRAMME IN NEONATOLOGY

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Background The first module, Neonatal Neurology, of the Neonatal Online Training and Education Education and Training (NOTE) programme ran for 16 weeks from October 2012 until February 2013. The module had been awarded 10 credits at Masters Level under the European Credit Transfer and Accumulation System by the University of Southampton. The module was funded by fees paid by participants and supported by a grant from the European Society for Paediatric Research (ESPR). Participants Of the 50 participants from 17 countries, 14 were qualified paediatricians or neonatologists, 32 were doctors in training and 4 were advanced neonatal nurse practitioners (ANNPs). Participants were assigned to one of 3 groups for asynchronous and real-time online discussions. Group A (n=14) comprised the qualified paediatricians/neonatologists, who were participating as part of continuing medical education (CME), Group B (n = 18) comprised experienced trainees and Group C (n=18) included less-experienced trainees. The ANNPs were included in Groups B and C. Each group was supported by two tutors, who were neonatologists with experience of online tutoring. Assessment Methodology Summative assessment comprised:tutor evaluation of the quality of the contributions to asynchronous group discussions using a structured assessment tool (20% of the total mark);the development by individuals of a clinical guideline (20%) and an online multiple-choice (MCQ) examination ('best of five') aimed at assessing both knowledge and application (60%). The MCQs were presented in a random order and a local invigilator ensured participants did not have access to textbooks, lecture notes or online resources. The performance of each question was analysed using the Moodle 'item analysis' indices and poorly performing question options were excluded from the final score. Group discussions and clinical guidelines were subjected to double-blind marking and a sample of the assessments was reviewed by an external examiner. To be eligible for the award of academic credit all three components of the assessment must be completed.
Results: 35 (70%) participants completed all of the assessments. 33 (94%) achieved passes. 50% of the CME group elected not to undertake the written assessments. Scores for the MCQ exam showed a positive correlation with scores for the clinical guidelines ($r=0.58$, $p=<0.01$) but there was no statistically significant correlation between the MCQ and the clinical guidelines scores and only a weak correlation between the scores for the group discussion and the guidelines ($r=0.37$; $p=<0.05$). There was no significant difference in scores between the three groups for the MCQ and clinical guidelines but the mean scores for contributions in group discussions were different for the two trainee groups (64.4% for Group C vs. 85% for Group B; $p=0.016$). There was no significant correlation between overall assessment outcomes and the duration of neonatal experience.
Conclusion: An assessment strategy for an online module has been developed which aims to assess the analysis, synthesis and application of knowledge. The outcomes for this module have shown a correlation between two of the three arms of the assessment strategy. Further development of the evaluation of the group discussions may be required.

E-LEARNING & COMPETENCIES -WHAT'S IN IT FOR THE PAEDIATRIC TRAINEE

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Introduction E Learning and a competency based education system has several advantages. It can be used as a method of training and assessing junior doctors. RCPCH has currently advocated several E learning resources on its website. An SHO Learning passport was devised to support trainees new to General Paediatrics which incorporated online & workplace competency assessments
Methods: Specific competencies were outlined, mapped to training curricula [RCPCH and RCGP] and used to produce a Blended Learning package and commenced in 2011. Each trainee completed specific E-learning modules; consultants assessed competencies by case based discussions (CBD's) and prescribing. A survey was carried out to assess its efficacy, applicability and areas of improvement.
Results: 35 Trainees were contacted.17 completed the survey.80% of respondents felt the learning package increased confidence & competence in assessment of sick children, discharging patients, safe prescribing practice and increased awareness of child protection concerns. 88% opined the learning package was relevant to their career pathway and Cbd's with consultants were helpful. 94% recommended the package for future trainees. 88% of the trainees gained new knowledge by completing the package. 52%of the trainees apply the knowledge/skills gained everyday in their current roles.
Conclusions: Trainees experience can be variable and non uniform depending upon exposure, strengthening the need for learning resources and formative assessments. This survey amongst our former trainees shows that appropriate E Learning resources & targeted competency based assessments can meet this learning need. Similar models of Blended Learning may benefit Paediatric trainees across Europe.

HIGH FIDELITY SIMULATION TEAM TRAINING IMPROVES MEDICAL TEAM PERFORMANCE FOR NEONATAL RESUSCITATION IN THE DELIVERY ROOM. A CLUSTER RANDOMIZED CONTROLLED TRIAL (ARPEGES STUDY)

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Background: High Fidelity Simulation (HFS) is efficient to teach neonatal (NN) resuscitation skills to individuals. However delivery room resuscitation is a team work. In the AURORE Perinatal Network (28 maternity units (MU), 45 000 births/year), we showed that an in situ training program based on HFS is feasible. Objectives: We aimed to determine whether in situ HFS training of 80% the perinatal staff of a MU is able to improve the overall team performance for NN delivery room resuscitation.
Methods: We performed a cluster randomized controlled trial in 12 Maternity Units (MU), which were assigned to receive either HFS training or no training. Our HFS training consisted of 4-hour sessions for multidisciplinary groups of 6 professionals. Sessions were delivered in situ by experienced neonatologists and midwife. A baseline evaluation of the 12 MU was performed from Jan. to Feb. 2012. A random sample of 10 professionals in each MU was faced with 2 standardized programmed scenarios run on a NN HF-simulator. The medical procedures were video recorded for later assessment. The 12 MU were then randomly designed to receive or not the HFS training from Mar. to Jun 2012. All the MU were again evaluated 3 months later using the same 2 scenarios. The evaluation was based on analysis of the videos by two neonatologists blind to the pre/post and training/non training arms. Compliance with 2010 ILCOR Guidelines and skills were evaluated using a score sheet based on different published scores and the teamwork performance using the TEAM score (Cooper 2010). To compare the differences in team performance between the training group and control group, the total median and median scores of each of the items is calculated and compared using the Mann-Whitney U test
Result: There was no statistical difference between the 2 groups characteristics and performances before training. 34 HFS training sessions were necessary for the training of at least 80% of perinatal staff of the 6 MU of the training group. A total of 230 videos were analysed from Jan. and Feb. 2013. The total technical score improved of 40.63% in the training group for the scenario 1 ($p=0.01$) and 29.7% for the scenario 2 ($p=0.004$). The team performance for the 2 scenarios improved of 60.8% ($p=0.001$).
Conclusions: Our trial shows the efficacy of an in situ training program, dedicated to team rather than to individuals, in improving NN resuscitation performance in MU.

NEST: NEONATAL EDUCATION SIMULATION TRAINING IN A TERTIARY NEONATAL UNIT

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Introduction: 'Point of care' simulation is a novel approach in medical education allowing multidisciplinary teams to train together in clinical environments. There is wide recognition that multidisciplinary simulation in intensive care can help reduce medical errors.
Methods: A team trained in medical simulation piloted neonatal education simulation training(NEST) over 18 months from September 2010. 13 sessions were run from September 2010 to April 2012. Feedback collated from initial sessions was used to produce a business case which enabled funding of high fidelity simulation mannequins and equipment. Suggestions included practising simulation on the NNU with individuals in their original roles rather than actors. Feedback from doctors and nurses in the initial pilot was used to design a 'Modular Programme' based on 25 curriculum based scenarios run 'Point of Care' on the NNU. This was implemented in April 2012 and evaluated in January 2013. 3 areas of significant concern (ET tube fixation, ET tube slippage and umbilical catheter extravasation) have been simulated. The impact on these critical incidents was evaluated prospectively from October 2012.
Results: Since December 2010, 27 sessions of neonatal simulation have been delivered. The number of multidisciplinary sessions has gone up from 2 over an 18 month period before April 2012 to 10 in the last 6 months. 97 feedback forms evaluated in the last 6 months show 97% of participants agreed the sessions were relevant to their training and 99% agreed it was important to their clinical practise. 96% of participants agreed that post scenario multidisciplinary feedback was useful and 100% agreed the sessions were of a high educational quality. Fewer nurses (58%) strongly agreed with the sessions being relevant to their clinical practice as compared to doctors (92%). Nurses have been incorporated into faculty and empowered to take sessions. Since October 2012 we have had only 1 case of umbilical extravasation (7 episodes in preceding 6 months). ET tube slippage has been eradicated. Accidental extubations however remain an issue.
Conclusion: We present data showing planning and implementation of a multidisciplinary simulation programme over a 3 year period which complements other methods of neonatal education. NEST is unique in that the participants have directed its evolution through their feedback. This has resulted in better multidisciplinary participation allowing simulated team training of critical incidents. A reduction in certain critical events simulated in these sessions has occurred. There is recognition through the feedback that some sessions are rated better by doctors than nurses. Sessions led by doctors using scenarios based on the RCPCH curriculum might not necessarily meet the needs of nursing and midwifery colleagues. As educators, we must not presume learning objectives for colleagues in other fields. The focus should be on how existing curriculum can be adapted to meet competencies and learning objectives for all participating individuals. Involving senior educators from both of these teams is an essential aspect of the process. Nurse educators are being encouraged to lead sessions and curriculum map. NEST is reproducible, and shows how existing curriculum's can be integrated to train different multidisciplinary groups together.

TEACHING AND TRAINING ASSESSMENT OF PAEDIATRIC PATIENTS USING VIDEO BASED TEACHING MATERIAL

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Introduction/ background: The clinical assessment of the pediatric patients is difficult. If a student is able to assess a patient shown at a video he/she is possibly also able to assess a patient in a clinical setting. As part of developing and introducing video based teaching in Pediatrics we evaluated the impact of access to pediatric video material, formal teaching sessions and the knowledge that a video was included in the exam on student performance in assessing pediatric patients presented as video cases.
Method: Medical students, who attended the pediatric course at University of Copenhagen during the fall 2011 and the spring 2012, assessed 8 video cases, presenting different common pediatric patients. The videos lasted 30-90 seconds. Each video was shown twice, before the students recorded their assessments on pre-printed forms. The test was done one week before the exam. Students were not allowed to discuss the videos during the test. We developed a Rubric score of the records of students' assessments including 4 domains: General Condition of the Child, Principal Symptoms, Suggested Diagnoses, and Coherence of Answers. Each domain was scored 0-4. To evaluate the intra- and inter-observer interclass correlation a total of 25 records, made by students during the fall 2011, were scored by two independent observers (MM) and (GG). In the beginning of the spring semester 2012 a pediatric video library was established at a university server available to students at all times, and the pediatric departments were asked to offer video based tutorials to students. Furthermore, a video case was included in the Pediatric exam. To evaluate the effect of the intervention the records of another sample (n=95) of students before and after this intervention were scored by MM. Students were matched according to gender, time and location for attending the pediatric course. Included were the students who were present the days MM presented video cases. No students were excluded. Records were blinded before scoring. Data were normally distributed and analysed using interclass correlation and paired t-test.
Results: The intra-observer interclass correlation coefficient (n=25) was 0.94 and inter-observer interclass correlation (n=25) was 0.71. A total of 95 students participated in the test to evaluate the effect of the intervention: fall 2011, n=37 and spring 2012, n=58. The students score after the intervention in spring 2012 (mean 7.0±2.3, n=58) was significantly higher ($p<0.001$) than the students score in fall 2011 before the intervention (mean 4.7±2.0, n=37). The effect size (Cohen's d) was 1.1 (95% CI 0.6-1.7).
Conclusion: The availability of a library of short videos presenting paediatric patients, formal tutorial sessions using video and the knowledge that videos were a part of the examination were very effective in improving student ability to assess such videos. It remains to be established if this intervention also improves the ability to assess patients in real life situations.

THE UNBORN SIBLINGS OF PRETERM INFANTS - A FOLLOW UP REGISTER-LINKAGE STUDY OF THE 1987-1990 FINNISH BIRTH COHORT

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Background: Families of newborn preterm infants may encounter crisis or at least suffer from decreased quality of life which may lead to longer interbirth intervals, i.e. time between two subsequent births. We investigated this in comprehensive Finnish nationwide registers.
Aim: The purpose of this register-linkage study was to describe interbirth interval after a preterm singleton birth.
Method: We obtained data from Finnish Medical Birth Register (MBR) that encompasses detailed pregnancy and newborn data (available from 1987 onwards) for each infant born in Finland. We included all the children born between Jan 1, 1987 and Sep 30, 1990 (n=235 624). Sibling data (from Jan 1, 1987 to May 31, 2012) came from the National Population Register Centre (PRC). We linked the data by unique personal identification numbers allocated for every resident of Finland. The number of singleton births was 230 378, 9983 (4.3%) where preterm. Interbirth interval was defined as the time between an index child's birth during 1987-1990 and the subsequent birth to a same mother. The effect of gestational age was analyzed by Cox-regression for proportional hazards. In addition, index child sex, maternal age and the number of mother's previous children were taken account as covariates. We excluded births of 1178 infants (555 preterm, 5.5%) who died before 1st birthday and 2210 because of stillbirth. Data on gestational age was missing for 2916 (1.3%).
Result: There was 56.8% probability that a subsequent sibling was born to an index child, the average interbirth interval being 3.7 years. The number of subjects in five subgroups according to gestation weeks - breakpoints at 28, 32, 37 and 42 weeks - were 225, 769, 8211,205 218 and 9648. Survival without a sibling was dependent on gestational age. At age 2, percentages of index children with a sibling in these subgroups were 10.7%, 12.5%, 14.9%, 15,9%, 18.8% and 16.0%. At the age 3 these percentages were 20.8%, 23.3%, 29.4%, 31.0%, 35.9% and 31.1%. At the end of follow-up, number of those with a sibling, in the preterm groups pooled, was 39 per thousand less than expected. We compared interbirth intervals to those born at 37-42 weeks of gestation first with an unadjusted Cox model. In the three respective preterm child subgroups, the hazard ratios for having a sibling were 0.64 (0.52 to 0.78), 0.71 (0.62 to 0.80) and 0.92 (0.89 to 0.95). For nulliparous (N=91004). these hazard ratios were 0.48 (0.37 to 0.63), 0.57 (0.50 to 0.65) and 0.82 (0.79 to 0.85). In models adjusted with maternal age, index child sex and number of previous deliveries (if appropriate), the hazard ratios were approximately the same.
Conclusions: Preterm birth has a double legacy on the population: of each thousand children born alive preterm, 55 die during infancy; for the remaining, 39 siblings remain unborn.

DISCHARGE HOME OF VERY LOW BIRTH WEIGHT INFANTS (VLBW): HOW MUCH AMBITIOUS SHOULD BE THE NEONATOLOGIST?

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Introduction/Background: Neonatal care of VLBW has worldwide improved, leading to a reduction of their mortality rate. In the delivery rooms and in the NICUs the intensive care has shift to a less invasive approach, with better short and long-term outcomes. The time of discharge home is one of the main indicator of preterm infant wellbeing, quality of neonatal cares and rational use of health resources. Nowadays standards to judge the length of stay (LOS) of VLBW have not been yet described. AIM: To analyse the main factors influencing the LOS and consequently the timing of discharge home of VLBW infants admitted to our NICU during the last ten years and to compare our data with Vermont Oxford Network (VON).
Patients And Methods: In this retrospective hospital-based study we enrolled 1053 VLBW infants, admitted to our NICU from 2002 to 2011. For these babies we analysed the mean LOS, comparing with VON data also considering the different birth weight (BW) classes (Group1: 501-750g, Group2: 751-1000g, Group3: 1001-1250g, Group4: 1251-1500g). Furthermore we evaluated the clinical characteristics influencing the timing of discharge home (reach of full oral feeding, non-invasive respiratory support and shift from incubator to crib) of 120 VLBW, admitted to our NICU in 2012.
Results: Mean LOS rose from 2002 to 2011, both in our NICU (from 64.2 to 69.9 days) and in VON (62.1 to 63.9 days). According to different BW, babies of G1, G2, G3, G4 had a mean LOS respectively of 120, 86, 61, 44 days in our NICU versus 108, 82, 57, 40 days in VON. Mean LOS of different BW groups of VLBW infants increased from 2002 to 2011, but the critical increase was for group 1 (from 115 days to 174 in our NICU and from 105 to 110 days during the same decade in VON). Furthermore the analysis of the clinical characteristics of Groups 2 (17/120 pts; 14.2%), 3 (31/120 pts; 25.8%) and 4 (61/120 pts; 50.8%), born in 2012, showed no significant difference in post-menstrual age (PMA) to reach full oral feeding (37.4, 36.9, 36.6 wks respectively), to stop non invasive respiratory support (34.2, 33.1, 33.2 wks respectively) and to shift from incubator to crib (35.6, 35.4, 35.5 wks). The infants of Group 1 (11/120 pts; 9.2%) reached these steps of maturation and stability at a significant higher PMA (full oral feeding 41.6 wks, non invasive respiratory support 37.7 wks, shift from incubator to crib 39 wks) ($p< 0,001$).
Conclusions: Improvements in neonatal cares correspond to an increasing survival of youngest infants (BW <750g) and consequently in a raising in their LOS. Significant differences exist in term of days of respiratory support, nutritional approach and thermostability for this group of patients compared to the rest of VLBW. Efforts to improve respiratory and nutritional autonomy of this selected and so fragile group of patients will probably help to change the trend of LOS.

HEALTH ECONOMIC IMPACT OF LATE AND MODERATE PRETERM BIRTH

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Background: Preterm birth rates are rising, with babies born at moderate (32-33 weeks) and late (34-36 weeks) preterm gestations contributing substantially to this increase. However, although very preterm birth has been extensively researched, little is known about the economic impact of birth between 32 and 36 weeks of gestation. Objective: Within the setting of a prospective population based study, we sought to determine the economic costs associated with moderate and late preterm birth.
Patients and Methods: We present preliminary analysis of data from an economic study nested within a prospective population-based cohort study of infants born between 32+0 and 36+6 weeks in Leicestershire and Nottinghamshire in the East Midlands region of England between September 2009 and December 2010 (the Late And Moderate preterm Birth Study (LAMBS)). A comprehensive profile of resource use, encompassing length of stay by intensity of care, surgery, investigations, procedures, drugs, consumables, transfers and post mortem examinations was collected between birth and hospital discharge and valued using a combination of primary and secondary costs (GB£, 2011 prices).
Result: Of 1350 moderate and late preterm infants eligible for inclusion in the LAMBS study, 1140 (84%) were recruited; A randomly selected sample of 1247 infants born at =37 weeks of gestation (79% of those eligible) were also recruited as a term control group. Mean (SD) total costs were estimated at £11,735 (£7666) for infants born moderately preterm, £4647 (£13,265) for infants born late preterm (£5649 (£12,862) for the combined moderate and late preterm group) and £2032 (£1375) for children born at = 37 weeks of gestation. The mean cost difference (preterm v term) was £3617 (bootstrap 95% CI £3028, £4444; P<.0001). Separate multivariate regressions revealed that, even after controlling for clinical and sociodemographic confounders, moderate and late preterm birth increased costs by an average of £7524 (SE £509; P<.0001) and £1847 (SE £264; P<.0001), respectively, in comparison to the term reference group.
Conclusions: Compared to birth at =37 weeks of gestation, both moderate and late preterm birth are associated with significant incremental initial hospitalisation costs to discharge. Given the rising prevalence of preterm birth such data are important to inform service planning and provision.

HEALTH-RELATED QUALITY OF LIFE OF YOUNG ADOLESCENTS BORN VERY PRETERM: A NATIONAL COHORT STUDY.

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Background: While the survival rate of very preterm infants has improved over the last decades, the rates of motor, learning and behavioural morbidities have not and may affect the child's quality of life. A better knowledge on the impact of prematurity on long-term health-related quality of life (HrQoL) is therefore important for clinical and parent guidance. We aimed to assess HrQoL in a national cohort of young adolescents born very preterm, and to identify predictors for poorer HrQoL.
Patients and Methods: All children born below 30 weeks of gestation in Switzerland in the year 2000 and survived, i.e. 290 (70%) of 416 subjects, were contacted at age 12 years, together with their parents. Subjects' HrQoL was assessed by both the Kidscreen-27 (KS-27) child- and parent forms. Neonatal data of the cohort were obtained from the prospectively collected dataset of the Swiss Neonatal Network. Information on sociodemographic characteristics was assessed by a generic parental questionnaire.
Result: Of 262 contacted families, 170 returned the complete set of questionnaires for 188 adolescents [65% of the survivors cohort, 97 females, mean (range) gestational age 27.8 (24.1-29.9) weeks and birth weight 1015 (420-1730) grams, mean age at assessment: 12 (11-13)]. Included children had similar neonatal and sociodemographic characteristics as those who did not participate (all p>.05). Average self-rated HrQoL of former preterms was similar to Swiss KS-27 norms except for the dimensions ‘Psychological well-being', ‘Peers & Social Support' and ‘School Environment', which were higher than the Swiss KS-27 norms (all p<.005). No difference between parent-reported HrQoL and Swiss KS-27 norms was present. Multivariate analysis showed that ‘single family status', ‘surgical closure of ductus arteriosus', and ‘neonatal sepsis' were independently associated with poorer self-rated HrQoL, while lower ‘socioeconomic status', ‘surgical closure of ductus arteriosus', and ‘cerebral palsy' were associated with poorer parent-reported HrQoL. No gender-, gestational age- or birth weight effect on HrQoL was observed.
Conclusions: HrQoL in this population-based cohort of adolescents born very preterm is satisfactory and in some psychosocial aspects better than contemporary Swiss norms. Both socio-demographic as well as neonatal factors play a role in the prediction of long term outcome of these children.

CAN A CHANGE IN INSTITUTIONAL PRACTICE BY AVOIDING ELECTIVE C-SECTION BEFORE 39-WEEKS GESTATION DECREASE NICU ADMISSIONS AND HOSPITAL COSTS?

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Introduction: Several reports associate elective C-sections before 39 weeks gestation (EC-S<39W) with increased Neonatal Intensive Care Unit (NICU) admissions. ACOG recommends against EC-S<39W gestation. In 2010 we began strongly discouraging elective C-section deliveries before 39 weeks (soft stop) and stopped allowing them in 2011 (hard stop). There are no reports of decreasing NICU admissions and hospital costs by avoiding EC-S<39W.
Objective: To determine if an institutional practice change will decrease NICU admissions and hospital cost for infants born by elective C-section before 39 weeks. **Design/Methods:** We reviewed the data from electronic records of all deliveries at Joe Di Maggio Children's Hospital performed from January 2009 to August 2012. We compared the number and mode of all deliveries as well the rate of admissions to the NICU of infants born by EC-S<39W. Hospital costs of EC-S<39W infants admitted to the NICU were estimated. Appropriate statistical tests were used.
Results: The data is summarized in Table1. A total of 14,644 deliveries were performed during the study period, 40.9% of which were by C-section. There were no significant differences in the yearly variation of total deliveries or the percentage of C-sections. There was a significant decline in the number of EC-S<39W (from 303 to 0 $p < 0.01$), with an initial decrease during the 'soft stop' period and a further decrease in the 'hard period'. The number of infants admitted to the NICU born by EC-S<39W also decreased significantly from 62 to 0 ($p < 0.01$); the correlation between these variables was 0.7. The estimated NICU cost for this population was substantially reduced.
Conclusion: Delaying EC-S<39W resulted in a significant reduction in admissions to the NICU of late preterm or early term infants. This practice was cost effective. While physician education and encouragement resulted in some decline in elective deliveries before 39 weeks, a 'hard stop' was necessary for a major change in practice.

IMPACT OF RATIONALISING ANTIBIOTIC PRACTICE ON THE PREVALENCE OF COLONISATION AND BLOOD STREAM INFECTION WITH HOSPITAL ACQUIRED ORGANISMS

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Background: Sick neonates nursed in NICU are highly susceptible to colonisation and infection with hospital acquired organisms. These organisms may be extremely pathogenic and more importantly resistant to conventional antibiotic therapy. Rationalising the use of antibiotics can reduce colonisation and infection with these hospital acquired organisms(HAO). Based on the local research and audit, local antibiotic therapy practise was rationalised over the last decade (antibiotics discontinued in non-infected babies at 36 hours instead of 48 hours, real time availability of blood culture results from laboratory 24 hours per day, change in antibiotic regimen). Aims: To measure the rate of colonisation & infection with HAO in babies on the neonatal unit before and after the introduction of the new policies. To analyse the antibiotic usage pattern in these two periods.
Methods: Retrospective collection of data before(1997) and after(2010) the changes in policy. Routinely collected weekly swab results and blood culture data for all babies during the periods were retrieved from the microbiology database. Colonisation and infection rates for the two periods were compared. The following organisms were classified as HAO: Pseudomanas aeruginosa, Serratia Marcesans, Acinetobacter,Sternotrophomonas,staphylococcus aureus (both MSSA and MRSA) and gentamicin resistant E Coli.
Result: Total number of admissions was 1197 in 2010 and 797 in 1997. Mean gestational age,[wks (range)] in 1997 was 33.6(22-42) and 2010 was 35.3 (23-42), mean birth weight [grams (range)] was 2212(440-5600) in 1997 and 2555(470-5430) in 2010, median length of stay [days (range)] was 7(0-240) in 1997 and 5(0-147) in 2010. Antibiotics usage: (percentage of total number of antibiotic doses) Augmentin(43.1%), Gentamicin(23.6%), Vancomycin(13.7%) were predominantly used in 1997. Benzyl penicillin(12.5%), Gentamicin(12%), ciprofloxacin(14%), Teicoplanin(6.5%), Metronidazole(11.8%) were predominantly used in 2010. Based on the change in policy of blood culture reporting, we have achieved an estimated reduction in antibiotics usage by 39% (4690 doses in 1997/2853 doses in 2010) in true negative infections. For the following organisms colonisation rate(per 1000 admissions) were reduced in 2010 compared to 1997 - Pseudomonas aeruginosa 86.8(2010), 190.7(1997), Sternotrophomonas 28.4(2010), 63.9(1997). For the following organisms colonisation rate were increased in 2010 compared to 1997 - Serratia marcesans 86.8(2010),58.9(1997), Acinetobacter 35.9(2010), 7.5(1997), Methicillin sensitive staphylococcus aureus 342.5(2010), 111.6(1997), Gent resistant E. coli 88.5(2010), 10(1997). Blood stream infections with the following organisms (per 1000 admission) were reduced in 2010 compared to 1997 - Serratia marcesans 1.6(2010), 6.2(1997), Methicillin sensitive staphylococcus aureus 5.8(2010), 7.5(1997), Gent resistant E. coli 7.5(2010), 11.2(1997). Blood stream infections with the following organisms were increased in 2010 compared to 1997 - Pseudomonas Aeruginosa 2.5(2010), 0(1997), Acinetobacter 0.8(2010), 0(1997). There were no documented bacteraemias with Sternotrophomonas and MRSA in either period.
Conclusions: The rationalisation of antibiotic therapy in our unit has led to a significant reduction in antibiotic pressure. A consequence of this is change in the pattern of colonisation with an overall reduction in blood stream infection rate with HAO. This highlights the importance of promptly discontinuing antibiotics in non-infected babies and making an appropriate choice of antibiotics depending upon local colonisation and infection pattern.

FEEDING PATTERNS AND INTESTINAL PATHOLOGY IN EXTREMELY PRETERM INFANTS BORN AFTER ABNORMAL ANTENATAL DOPPLER BLOOD FLOW

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Background Growth-restricted preterm infants are at increased risk of necrotising enterocolitis (NEC) particularly if absent or reversed end-diastolic flow velocities (AREDFV) are detected on antenatal Doppler ultrasound. The Abnormal Doppler Enteral Prescription Trial (ADEPT) randomised 404 preterm, with gestational age below 35 weeks and birth weight below 10th centile, born after AREDFV, to commence enteral feeding ‘early', on the second day after birth, or ‘late' on the 6th day. Subsequent feed advancement followed a regimen, which should have achieved full feeds by day 14 in the early and day 18 in the late group. Infants who started feeds ‘early' reached full, sustained enteral feeding significantly sooner that those starting feeds late with no difference in rate of NEC between groups (1) The ADEPT protocol contained a minimisation algorithm at <29 weeks gestation and 86 infants recruited were within this sub-group. Extreme prematurity is an additional risk factor for NEC and feed intolerance. The aim of this secondary analysis was to describe feeding and gastrointestinal outcomes in growth restricted infants <29 weeks gestation and to determine the rate of feed advancement which they tolerate. Method: Sub-group analysis of prospectively collected data from 404 infants born within 54 hospitals in the UK and Ireland who were recruited to a randomized feeding trial (ADEPT).
Participants: 404 preterm, growth restricted infants with abnormal antenatal Doppler studies recruited to ADEPT. 83 infants <29 weeks (mean birth weight 688 grams) and 312 infants >/=29 weeks gestation (mean birth weight 1126 grams) who survived until commencement of feeds and in whom full feeding records were available were included in this analysis. Main outcome measures: Full feeds were achieved later in infants <29 weeks; median age 28 days (IQR 22-40) compared with 19 days (IQR 17-23) in infants >/=29 weeks (Hazard Ratio (95% CI): 0.35 (0.3 to 0.5). The incidence of NEC was higher in this group; 32/83 (39%) compared to 32/312 (10%) in those >/=29 weeks (RR (95% CI): 3.7 (2.4 to 5.7). Infants <29 weeks tolerated very little milk for the first 10 days of life and reached full feeds 11 days later than predicted from the trial regimen. 90% of infants <29 weeks had at least one episode of feed intolerance compared to 58% of infants >/=29 weeks (RR (95% CI) 1.6 (1.4 to 1.8). Receiving >50% breast milk prior to reaching full feeds significantly reduced the risk of NEC (Effect measure (95% CI) 0.46 (0.27-0.78).
Conclusions: Growth restricted infants born <29 weeks gestation with abnormal antenatal Dopplers are extremely vulnerable to NEC and to feed intolerance and failed to tolerate even the careful feeding regimen of the ADEPT trial. A slower advancement of feeds and exclusive use of breast milk may be indicated for these infants.
1. Leaf A, Dorling J, Kempley S, McCormick K, Mannix P, Linsell L, et al. Early or Delayed Enteral Feeding for Preterm Growth-Restricted Infants: A Randomized Trial. Pediatrics. 2012 May;129(5):e1260-e8.

NEONATAL MODULATION OF SERUM CYTOKINE PROFILES BY A SPECIFIC MIXTURE OF NEUTRAL AND ACIDIC OLIGOSACCHARIDES IN PRETERM INFANTS

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Introduction: Infections are common in preterm infants and cause differences in cytokine levels. The combination of neutral oligosaccharides and acidic oligosaccharides (scGOS/lcFOS/pAOS) decreases the incidence of infections in preterm infants. Aim of this study was to measure cytokine levels in preterm infants during the first year of life and to determine the effect of supplementation of neutral and acidic oligosaccharides (scGOS/lcFOS/pAOS) to either human milk or preterm formula. Furthermore, other perinatal factors (breastfeeding, infections, GA and BW) in relation to these cytokine levels were analysed.
Patients and Methods: In a randomized controlled trial, preterm infants (GA <32 weeks and/or birth weight <1500 g) received a scGOS/lcFOS/pAOS mixture or a placebo (maltodextrin) between days 3 and 30 of life. Cytokine levels (IL-1ß, IL-2, IL-4, IL-6, IL-8, IL-10, IL-17, IFN-?, TNF-a) were analysed at 5 time points during the study: before start of the study, at day 7, at day 14 and at 5 and 12 months after the start of the intervention.
Result: In total, 55 preterm infants in the scGOS/lcFOS/pAOS group and 58 in the placebo group were included. During the neonatal period all measured cytokine levels increased at day 7 ($p < 0,05$ except for IL-8) and returned to the level at birth at day 14 ($p>0.05$, except for Il-1ß and IL-10, who remained at higher level). After the neonatal period IL-6, IL-8, IL-10, IL-17 and TNF-a decreased at 5 months and remains at low level at 12 months (al $p<0.05$). IL-1 ß decreased at 12 months ($p<0.05$). Preterm infants who received scGOS/lcFOS/pAOS showed lower cytokine levels of IL-1 ß, IFN? and TNFa ($p< 0.05$) and a trend towards lower levels of IL-4, IL-6, IL-8 and IL-17 ($p<0.10$) at day 7 compared to non-supplemented preterm infants. This effect disappeared at day 14. In the neonatal period, only serious infection before sampling increased all cytokine levels (p<. There was no effect of BW, GA or breastfeeding on the cytokine levels.
Conclusions: Cytokine levels increase during the neonatal period, followed by a decrease at 5 months and 12 months for most cytokines. Enteral supplementation of neutral and acidic oligosaccharides (scGOS/lcFOS/pAOS) decreased cytokine levels in preterm infants at day 7 of life. Thereafter, this effect disappeared suggesting a temporary anti-inflammatory effect.

BOLUS VERSUS CONTINOUS FEEDING: EFFECTS ON BREATHING PATTERNS AND CARDIORESPIRATORY EVENTS

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Background and aims: Tube feeding, both continuously or through boluses, is a common practice in NICUs, due to the preterm infants' inability to coordinate sucking, swallowing and breathing. Although continuous feeding may be preferable in case of delayed intestinal transit, this technique implies the permanence of a nasogastric tube for the whole feeding period, potentially affecting the breathing patterns. Conversely, bolus feeding might enhance the abdominal distension, which has been hypothesized to influence the respiratory features. This study aimed to evaluate and compare the incidence of apnoeas and hypoxic episodes between bolus and continuous tube-feeding.
Methods: Thirty healthy preterm infants (median gestational age: 30+4 weeks [IQR: 28+5 weeks - 32 weeks]; median birth weight: 1275 g [IQR: 1111 g -1529 g]) underwent a 6-hours polysomnographic recording of hypoxic episodes, defined as SatO2 <80%, and total (TA), obstructive (OA), central (CA) and mixed (MA) apnoeas. During the monitoring, each baby was fed twice through a nasogastric tube; one meal was given continuously over 3 hours, while the other was administered as a 10-minutes bolus. The tube was removed after bolus administration. The number of hypoxic episodes and TA, CA, OA and MA was compared between the two techniques by means of the Wilcoxon Signed Rank Test.
Result: Overall, 212 apnoeic episodes occurred after bolus feeding (150 CA, 29 OA, 33 MA), while 242 apnoeic episodes were recorded during continuous feeding (188 CA, 23 OA, 31 MA). A total of 55 hypoxic episodes were detected: 22 occurred after bolus administration whereas 33 happened during continuous feeding. Although the incidence of apnoeas and hypoxic episodes was higher during continuous feeding, the differences between the two techniques were not statistically significant ($p>0.05$).
Conclusions: A trend towards an higher number of both hypoxic and apnoeic episodes was observed during continuous feeding. Nevertheless, since the differences between the two techniques were not statistically significant, on the basis of these preliminary data it is not possible to establish which feeding technique may have a minor impact on breathing patterns.

POTENTIAL ROLE OF NITRIC OXIDE IN INTESTINAL INFLAMMATION IN THE IMMATURE HUMAN INTESTINE.

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Background and Aim: Among the mediators associated with necrotizing enterocolitis in preterm infants, nitric oxide (NO) is an ubiquitous signalling molecule that is involved in several important physiological and pathological processes in the gastrointestinal system including motility, vascular regulation and cellular inflammation. NO synthase 2 (NOS2) is the NOS isoform most widely implicated in the processes of epithelial cell injury/apoptosis, host immune defence and perpetuation of the inflammatory response. However, the specific role of NOS2-mediated NO in the intestinal inflammation of the immature human intestinal mucosa remains unclear. We have previously reported genomic studies and bioinformatic analysis demonstrating that EGF attenuates the inflammatory response in the mid-gestation human small intestine using serum-free organ culture (Physiol Genomics 2012, 44(4):268-80). Recently, we also reported that the non-steroidal anti-inflammatory drug, indomethacin (INDO), exerts multiple detrimental metabolic effects on the immature human intestine (Genomics 2013, 101(3):171-7). In this study we investigate the potential role of NOS2 in modulating the gut inflammatory response in organ cultures under protective and stressful conditions by looking at the expression profile of NOS2 itself and the metabolic pathways that it is known to influence.
Methods: Gene expression profiles of cultured human fetal intestinal explants (mid-gestation) were investigated in the absence or presence of a physiological concentration of EGF (50 ng/ml) or 1μM INDO for 48 h using Illumina whole genome microarrays. Ingenuity Pathway Analysis (IPA) software identified several NOS2-related genes and their expression patterns were confirmed by qPCR.
Result: By comparing gene expression profiles induced by EGF to that of INDO on the immature ileum, IPA identified two canonical pathways where NOS2 is known to play an important role: 'free radical scavenging/oxidoreductase activity' and 'glycolysis/gluconeogenesis'. For instance, we noted that the gene expression of several antioxidant enzymes such as DUOX2, DUOXA2, GPX2, SOD2, TXNRD1 and, especially NOS2, were significantly up-regulated by EGF while INDO induced the opposite effect. In addition, we observed that certain mitochondrial functions ('glycolysis/gluconeogenesis') were highly repressed by INDO in the immature intestine, unlike EGF, which increased expression of several genes involved in this pathway such as ALDOA, FBP1, HK2, LDHA and PGK1.
Conclusions: The differential gene expressions suggest that the protective effect of EGF against oxidative damage could be mediated by increased expression of NOS2 whereas INDO may contribute to intestinal damage by depleting antioxidants. The potential importance of antioxidant pathways is underscored by our observation of relative differences in mitochondrial function. Thus we show that NOS2 is a likely regulator of inflammatory response and may provide a mechanistic basis for the protective effect of EGF and the deleterious effects of indomethacin on the immature gut.

PONDERAL INDEKS AND OTHER RISK FACTORS IN NEWBORN INFANTS WHO DEVELOP GASTROINTESTINAL PERFORATION - MATCHED CASE CONTROL STUDY

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Background. Gastrointestinal perforations (GIP) in newborns are mainly related with necrotizing enterocolitis. Congenital anomalies with obstruction can also be a cause of GIP. Early recognition all infants at high risk for GIP is essential in reducing morbidity and mortality. Little is known about perinatal risk factors, and ponderal index in infants with gastrointestinal perforation has not been reported. According to PI, newborn infants are divided into obese, malnourished, and normal. Ponderal index is used for discrimination between symmetric and asymmetric growth restriction. Neonatal hypotrophy with normal PI is usually fetal origin and genetically determined low growth potential, whereas its association with low PI is associated with prenatal malnutrition.
Objective. Our objective was to examine relative importance of ponderal index and other perinatal and postnatal risk factors that contribute to the appearance of gastrointestinal perforations. This study also determined the incidence of neonatal GIP and mortality after GIP. Patients and methods. Retrospective matched case - control study was conducted between January 1990. and December 2011. The medical records, surgical records and hystopathologic examinations of all newborn infants with GIP were reviewed (n= 35). For the comparison of perinatal and postnatal risk factors, a control group of infants was matched to the study group. The infants admitted immediately before and after the study infant and being ± 1 week of gestational age of the study infant were included (n= 70). Any twin of a study patient was also included in the control group (n= 6).
Results: During the 22 - year period 35 neonates with gastrointestinal perforation were treated in the University hospital Split, Croatia. Incidence of GIP was 0,88/1000 admissions to Clinical department of neonatology and 0,34/1000 live births. Study and control infants were well matched for gestational age. Infants with GIP were more likely than control subjects to have very low birth weight (BW<1500 g). Ponderal index was no different between infants with gastrointestinal perforation and control subjects. Study infants were more likely to have birth weight below 10th percentiles for gestational age, week and sex (hypotrophy, 'small for gestational age'-SGA). Among SGA infants in study group 63,6% of them had low PI and asymmetrical constitution, 36,4% infants had normal PI and symmetrical constitution. PI was no different between SGA patients with gastrointestinal perforation and SGA control subjects. Infants with GIP were more likely than control subjects to have anemia. The predominant cause of perforation was necrotizing enterocolitis (51,4%). The site most commonly perforated in our series was the large bowel (45,7%). The overall mortality rate was 31,4%.
Conclusions: Gastrointestinal perforations occurred more frequently in very low birth weight infants. The most significant risk factors for GIP were anemia and hypotrophy. We did not find significant associations between ponderal index and GIP.

EXPOSURE TO HYDROCORTISONE INDUCES A BIPHASIC RESPONSE IN IMMATURE HUMAN INTESTINAL EPITHELIAL CELLS AND SIGNIFICANTLY ATTENUATES INFLAMMATORY CHEMOKINE SECRETION IN THE IMMATURE HUMAN GUT

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Introduction: The immature human gut has a propensity to exaggerated inflammatory responses which are thought to play a role in the pathogenesis of necrotizing enterocolitis (NEC). Prenatal short-term exposure to corticosteroids has been reported to reduce the risk of NEC while longer-term postnatal dexamethasone treatment is associated with gastrointestinal hemorrhage and perforation, as well as adverse neurodevelopmental outcomes in preterm infants. We investigated the time-dependent impact of hydrocortisone on gene expression patterns and inflammatory responses in immature human gut models.
Methods: Time-dependent effects of hydrocortisone on gene expression patterns were investigated in the nontransformed primary human fetal intestinal epithelial cell line H4 by cDNA microarray. The functional effects of hydrocortisone on inflammatory responses were assessed using human fetal intestinal organ culture prepared from tissue obtained from therapeutic abortions as well as H4 cells. Inflammatory responses were induced by stimulation with IL-1beta (1 ng/mL), TNF-alpha (10 ng/mL) or poly I:C (50 ng/mL) with and without 1 μM hydrocortisone. IL-8 secretion was measured by ELISA as functional read-out.
Result: Principal Component Analysis (PCA) and Gene enrichment analysis of microarray data exhibited a biphasic pattern. Short term hydrocortisone exposure demonstrated stronger effect in many of the networks and canonical pathways involved in innate immune and inflammatory responses including the IL-1beta pathway. Stimulation with IL-1beta increased IL-8 secretion in the fetal ileum from 1276 +/- 190 pg/mL to 3836 +/-701 pg/mL ($p=0.02$). This response was reduced to 152 +/-28 pg/mL by hydrocortisone ($p=0.006$). In H4 cells, IL-1beta increased IL-8 secretion from 0 +/-0 ng/mg protein to 3784 +/-41 ng/mg protein ($p<0.0001$) and this response was significantly reduced by hydrocortisone to 1546 +/-89 ng/mg protein ($p<0.0001$). In H4 cells exposed to hydrocortisone for 48 hours, IL-1beta-induced IL-8 secretion was reduced less to 1974 +/-96 ng/mg protein ($p<0.0001$). A relatively constant but modest reduction in IL-1beta-induced IL-8 secretion was detected after 2-48 hours of exposure to hydrocortisone and this effect was not dependent on the presence of hydrocortisone at the time of stimulation. Moreover, the immunomodulatory effect of hydrocortisone conditioning remained unaltered after a 6-hour washout period with medium alone. Hydrocortisone inhibited IL-8 secretion in response to TNF-alpha and poly I:C in H4 cells when administered simultaneously with the proinflammatory insult. In contrast, TNF-alpha or poly I:C-induced IL-8 secretion was not reduced in cells treated with hydrocortisone for 48 hours prior to stimulation.
Conclusions: Hydrocortisone significantly attenuated inflammatory responses in the immature human gut when administered at the time of the proinflammatory insult. Interestingly, exposure to hydrocortisone before inflammatory stimulation resulted in a more specific and less pronounced anti-inflammatory effect. These functional differences in anti-inflammatory potential of hydrocortisone resulting from timing of exposure were reflected in time-dependent hydrocortisone-induced changes in gene expression patterns detected by cDNA microarray. Our observations provide a physiologic basis for understanding the different clinical effects of corticosteroids in the immature human gut depending on the timing of treatment.

INTRAVENOUS LIPID EMULSIONS CONTAINING FISH OIL (FO-LE) ARE NOT ASSOCIATED WITH IMPAIRED GROWTH IN PRETERM INFANTS (PI) ON PARENTERAL NUTRITION (PN).

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Background And Aims: Long chain n-3 fatty acids (n-3 LCPUFA) play a pivotal role during CNS development and the provision of docosahexaenoic acid (DHA) is recommended for the PI. However there is a concern that oral FO, rich in DHA, may adversely affect growth of PI (Carlson et al. Lipids 1992) as it decreases arachidonic acid (ARA). Over the past 2 decades no new data became available to confirm or refute this finding as FO is often used in association with a source of ARA. In very recent years FO was added to the fat blend of intravenous lipid emulsions (LE) for the PN of the PI and information on growth is lacking. We studied the effect of FO-LE on the growth of PI on PN.
Methods: We retrospectively reviewed the growth data of 235 PI (BW<1250g) consecutively admitted to our NICU between 2008 and 2012 who received routine PN starting within 1h of life, according to a well-defined PN scheme. As part of several clinical trials, study patients received one of 5 LE. LE were 1=FMS (10% FO, 40:50 MCT:Soybean oil), 2=MOSF (15% FO, 30:30:25 MCT:Soybean oil:Olive oil), 3=S (100% Soybean oil), 4=MS (50% MCT and 50% Soybean oil) and 5=OS (80% Olive oil and 20% Soybean oil). In this study we grouped the patients who received the FO containing LE, FMS and MOSF (FISH) (n=101, GA 199±15 d, BW 960±176 g) and those without FO, S MS and OS (CONTR) (n=134, GA 198±15 d, BW 961±192 g). We compared macronutrient and energy intakes during PN and enteral feeding (EF), anthropometry at birth and at 36 weeks post-menstrual age (36w-PMA) and growth velocity.

	FISH (n=101)	CONTR (n=134)	p
PN-Non-Protein Energy (Kcal/kg)	893±396	946±582	0.4
PN-Amino Acid (g/kg)	41±18	44±26	0.4
EF-Non-Protein Energy (Kcal/kg)	4530±1713	4510±1577	0.9
EF-Protein (g/kg)	153±54	154±54	0.9
MM (ml/kg)	3723±3197	3402±2960	0.4
IMF (ml/kg)	3081±2640	2871±2559	0.5

Results: Anthropometry at birth was similar between groups. No differences were found between the two study groups in PN and EF macronutrient and energy intakes from birth to 36w-PMA, as well as in mother's milk (MM) and infant milk formula (IMF) volumes (Table 1). Anthropometry at 36w-PMA and weight gain from birth to 36w-PMA are shown in the Table 2. There were no significant differences in the main complications of prematurity (not shown).

Table 1. Cumulative Nutritional Intakes from birth to 36w-PMA FISH (n=101) CONTR (n=134) p PN-Non-Protein Energy (Kcal/kg) 893±396 946±582 0.4 PN-Amino Acid (g/kg) 41±18 44±26 0.4 EF-Non-Protein Energy (Kcal/kg) 4530±1713 4510±1577 0.9 EF-Protein (g/kg) 153±54 154±54 0.9 MM (ml/kg) 3723±3197 3402±2960 0.4 IMF (ml/kg) 3081±2640 2871±2559 0.5 Table 2. Anthropometry at 36w-PMA and growth FISH (n=101) CONTR (n=134) p Weight (g) 1941±326 1899±320 0.3 Total Length (cm) 42.9±2.3 42.9±2.3 0.8 Head Circumference (cm) 30.8±1.5 30.6±1.4 0.2 Weight-SDS variation [Birth-36w-PMA] -1.1±0.6 -1.2±0.6 0.03 Weight gain [Regained-BW-36w-PMA] (g/kg/d) 17.1±2.5 16.5±2.6 0.06 Weight gain [Regained-BW-1800 g] (g/kg/d) 17.5±2.8 16.8±2.8 0.04

Conclusions: In this large cohort of PI on PN the use of FO-LE was not associated with impaired growth. Further work is needed to investigate other safety aspects of FO-LE in PI and their impact on long term neurodevelopment.

OIL (FO): A RANDOMIZED CLINICAL TRIAL

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Background: New intravenous lipid emulsions (LE) containing FO, as source of n-3 fatty acids (FA), have recently became available for infants. Limited data exists on tolerance and efficacy in Extremely Low Birth Weight Infants (ELBWI).
Patients and Methods: ELBWI (BW 500 to 1249 g), who according to local guideline received routine PN starting within 1 h of life, were randomized to two LE: MOSF (15% FO, 30:30:25 MCT:Soybean oil:Olive oil) and S (100% Soybean oil). Each LE was studied at two fat intakes: 2.5 (2.5F) and 3.5 g/kg/d (3.5F). Serum triglycerides (sTG) were measured by routine biochemistry on day 3, 5 and 7. Plasma lipid classes and their FA composition on day 7 and 14 by gas chromatography. Whole blood routine biochemistry was also obtained several times a day in conjunction with blood gas analyses.
Result: Eighty infants were randomized: 21 to MOSF-2.5FF, 18 to MOFS-3.5F, 22 to -S-2.5F and 19 to S-3.5F. Demographics and clinical characteristics were similar at birth. MOFS infants had significantly higher plasma phospholipid Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) and lower Arachidonic acid (ARA) (table 1).

Table 1. PL FA on day 7

	MOSF-2.5F	MOSF-3.5F	S-2.5F	S-3.5F	p[1]
C18:1n-9	15.82 ± 1.45^{a}	16.49 ± 1.58^{a}	$14.42 \pm 1.76^{a,b}$	13.14 ± 0.89^{c}	0.00
C18:2n-6	15.67 ± 2.15^{a}	15.69 ± 1.71^{a}	18.78 ± 2.38^{c}	19.99 ± 1.15^{c}	0.00
C18:3n-3	0.13 ± 0.05^{a}	0.13 ± 0.05^{a}	0.17 ± 0.08^{a}	0.21 ± 0.07^{c}	0.01
C20:4n-6	9.71 ± 1.12^{a}	9.41 ± 1.06^{a}	11.18 ± 1.51^{c}	10.71 ± 0.72^{a}	0.00
C20:5n-3	1.58 ± 0.50^{a}	1.67 ± 0.27^{a}	0.27 ± 0.13^{c}	0.21 ± 0.06^{c}	0.00
C22:6n-3	3.06 ± 0.44^{a}	3.18 ± 0.51^{a}	2.19 ± 0.42^{c}	2.14 ± 020^{c}	0.00

[1] by one way Anova test, different superscripts indicate Bonferroni test, $p<0.05$

Plasma PL, TG and Free Cholesterol were significantly higher in MOFS-3.5F group compared with the other study groups, while Cholesterol Esters were lower in MOFS (2.5F+3.5F) than S (2.5F+3.5F) infants (table 2). HyperTG (sTG > 250 mg/dl) was 9%, 18%, 9% and 3% in the four group (MOFS-3.5F, MOFS-3.5F, S-2.5F and S-3.5F respectively, p= 0.214). MOFS infants had a significantly lower total plasma bilirubin (area under the curve) than S patients (43.3 ± 6.5 vs. 46.5 ± 7.8, $p<0.05$). No differences were found in other safety parameters.
Conclusions: A LE with 15% FO resulted in higher plasma phospholipid DHA and EPA, but lower ARA than a soy-based emulsion. Total bilirubin was lower with MOFS then with S. Reduced lipid tolerance was found with MOFS at 3.5 g/kg/d Lipid intake. Clinical implications of these important changes should be addressed in future studies.

HYPERALIMENTATION USING CURRENT UK PARENTERAL AMINO ACID FORMULATIONS DOES NOT PREVENT LOW PLASMA ARGININE LEVELS IN VERY PRETERM INFANTS.

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Background: Although arginine is not an essential amino acid (AA), arginine deficiency is well recognised in very preterm infants (VPI) receiving parenteral nutrition (PN) and is associated with major complications of prematurity. VPI may require plasma arginine levels above the reference range (RR; 53-71micromol/l) typically used for newborn populations. Our recent telephone survey revealed tertiary UK neonatal services use PN containing AA from 2 licensed formulations : 14% use AA-P (arginine 8.4g/100gAA); 83% use AA-V (arginine 6.3g/100gAA). Human milk contains 4g/100gAA arginine. We hypothesised that hyperalimentation (optimising protein/energy intake) in PN-dependent VPI would prevent arginine deficiency irrespective of AA formulation. Aim: To compare the plasma arginine levels in VPI randomised to receive control PN (CPN) or hyperalimentation PN (HPN) regimens in two randomised controlled trials (RCT).
Methods: Both studies were single centre (Liverpool Women's Hospital) RCT with HPN containing 30% more protein/energy than CPN. RCT1 (PN contains AA-P) and RCT2 (PN contains AA-V) recruited infants <29weeks gestation and <1200g birthweight in 2004-6 and 2009-12 respectively. Actual daily protein and arginine intake was calculated using the recorded PN and enteral intake data from the second week of life. Plasma AA levels (secondary outcome in both studies) were measured in the second week of life if receiving >35% nutrients from PN.
Result: Plasma AA levels were obtained at median (IQR) postnatal age 9 (8-10) days in both RCTs. In all 4 groups, median plasma essential AA levels were within/above their RR. There were no differences in gestation between the HPN and CPN groups in either study. RCT1 outcomes (AA-P) Mean (SD) birthweight (g) was 870 (167) in CPN group (n=50) versus 858 (166) in HPN group (n=52). Mean (SD) protein intake (g/kg/day) was 2.6 (0.4) in CPN group versus 3.0 (0.5) in HPN group. Mean (SD) arginine intake (mg/kg/day) was 201 (44) in CPN group versus 230 (55) in HPN group. Median (IQR) plasma arginine levels (micromol/l) were 42 (26-61) in CPN group versus 47 (29-75) in HPN group (p=0.19). RCT2 outcomes (AA-V) Mean (SD) birthweight (g) was 868 (174) in CPN group (n=62) versus 917 (157) in HPN group (n=45). Mean (SD) protein intake (g/kg/day) was 3.0 (0.2) in CPN group versus 3.6 (0.5) in HPN group. Mean (SD) arginine intake (mg/kg/day) was 175 (14) in CPN group versus 215 (32) in HPN group. Median (IQR) plasma arginine levels (micromol/l) were 34 (21-45) in CPN group versus 40 (25-53) in HPN group (p=0.21).
Results summary: Both RCT achieved significantly higher actual daily protein and arginine intakes in HPN compared to CPN infants (all comparisons p<0.01). While there was a trend towards higher median plasma arginine levels with HPN regimens, these remained below RR. Lower PN arginine content (AA-V) in RCT2 resulted in lower arginine intake in RCT2 compared to RCT1 despite higher protein intakes.
Conclusions: These study data demonstrate hyperalimentation does not prevent low plasma arginine levels in VPI. The data indicate that the proportion of arginine in current UK neonatal PN AA formulations is too low.

EFFECT OF CONCENTRATED AQUEOUS PARENTERAL NUTRITION SOLUTIONS ON CENTRAL VENOUS CATHETER COMPLICATIONS IN VERY PRETERM INFANTS: THE RANDOMISED CONTROLLED SCAMP NUTRITION STUDY

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Background: Early postnatal growth failure is well recognised in very preterm infants (VPI) and is associated with early nutritional deficits. We have shown suboptimal nutrition can be prevented by standardising and concentrating parenteral nutrition (PN). There are few data from the preterm population describing central venous catheter (CVC) complication rates with concentrated PN. Our original (control) standardised, concentrated neonatal parenteral nutrition (PN) regimen (10% glucose, 2.8g/kg/day protein/lipid) was modified. This Standardised, Concentrated, Added Macronutrients Parenteral (SCAMP) nutrition regimen (12% glucose, 3.8g/kg/day protein/lipid) was evaluated in a randomised controlled trial powered to evaluate early head growth (primary outcome). It is not known whether increasing osmolality and lipid/glucose content to SCAMP regimen levels has the potential to increase risk of CVC occlusion, thrombophlebitis and infection, so reducing line life and increasing sepsis rates.
Aim: To compare line life and infection rates during first 28 days of life in VPI randomised to receive SCAMP nutrition or the original standardised, concentrated PN regimen (control).
Methods: The study (ISRCTN: 76597892) received ethical approval. Control PN was started within 6 hours birth. Following parental consent, VPI (birthweight <1200g; gestation <29 weeks) were randomised (day 2-5) to either start SCAMP or remain on the control regimen. The study intervention ceased after 28 days. Daily nutritional intake and estimated mean daily osmolality from PN infusion data were collected for day1-28 along with blood culture and inflammatory marker data. CVC type, location, duration and reason for removal were recorded. Data analysis was performed in 28 day survivors.
Result: 150 infants were randomised at mean age 73.5 hours. Mean (SD) birthweight (g) and gestation (weeks) was: 900(158) versus 884(183) and 26.8(1.3) versus 26.6(1.4) in SCAMP (n=74) and control (n=76) groups respectively. All CVC types The estimated PN infusion osmolality had a range of 1025-1270 and 855-1120mosmol/l.water in SCAMP and control groups respectively. There were no statistically significant differences in CVC use between the groups. Median (IQR) line life was 8.5 (7-11) and 9 (7-12.5) days for all CVC types in SCAMP (n=66) and control (n=69) respectively. The corresponding rates for at least one positive blood culture during the 28 day intervention period were 32% and 38% respectively (p=0.48). No differences between the groups were identified following subanalysis for organism type or changes in inflammatory markers. Umbilical venous catheters (UVC): In the SCAMP group, 89% underwent UVC insertion at birth, with 14% removed for positive blood culture and a median (IQR) line life of 10 (2-13) days. 84% of control infants underwent UVC insertion, with 21% (p=0.34) removed for positive blood culture and a median (IQR) line life of 10 (7-13) days. Percutaneous central venous catheter (PCVC) In the SCAMP infants 88% required at least one PCVC with 14% removed for positive blood culture and a median (IQR) line life of 8 (5-11.5) days. 81% control infants required a PCVC, with 15% (p=0.80) removed for positive blood culture and a median (IQR) line life of 7 (6-12) days.
Conclusions: Increasing PN osmolality and nutrient content does not increase CVC complication rates.

BREAST FED HYPOGLYCAEMIC BABIES DO NOT HAVE HIGH BLOOD CONCENTRATIONS OF ALTERNATIVE FUELS IN THE FIRST 48 HOURS

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Background: It has been suggested that breast fed babies are at low risk of the neurological damage due to hypoglycaemia because of the availability of alternative cerebral fuels. However, there is a paucity of evidence about availability of alternative cerebral fuels in the first 48 hours after birth. We sought to determine blood concentrations of alternative cerebral fuels during hypoglycaemia in the first 48 hours.
Method: All babies were =35 weeks, =48 hours old, at risk of hypoglycaemia and enrolled in the Sugar Babies Study. Blood glucose concentrations were measured using the glucose oxidase method. Hypoglycaemia was defined as a blood glucose concentration < 2.6 mM. Babies with persistent hypoglycaemia (blood glucose concentration <2.6 mM on two occasions >30 min apart) had a blood sample taken for measurement of alternative cerebral fuels and insulin. Normally distributed data were compared using t-tests, otherwise the Wilcoxon test was applied. Data are median (range).
Result: Blood samples were taken from 35 hypoglycaemic babies at 3.9 (1.8-39.8) hours after birth. Concentrations of lactate, beta-hydroxbutyrate, and glycerol were low in all babies and did not differ between babies who were and were not breast fed (table).
Table: Concentrations of cerebral fuels (mM) and insulin (uU/ml) Breast fed babies (n=15) Not breast fed (n=20) Glucose 2.1 (0.1-2.5) 1.8 (0.2-2.4) Lactate 3.0 (0.0-7.9) 3.0 (0.0-6.7) Beta-hydroxbutyrate 0.07 (0.00-0.42) 0.04 (0.00-1.20) Glycerol 0.28 (0.00-1.03) 0.22 (0.00-0.62) Insulin 1.4 (0.0-4.8) 0.8 (0.0-7.2)
Conclusions: Alternative cerebral fuels are unlikely to provide neuroprotection to breast-fed hypoglycaemic babies in the first 48 hours after birth.

ABNORMAL GLUCOSE LEVELS AT DISCHARGE TIME IN VERY PREMATURE BABIES

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Abnormal glucose homeostasis is a well-described disorder in very preterm (VPT) infants (<32 weeks) during the first weeks of life. Some studies suggest that metabolic immaturity and/or lack of energy stores might contribute to persistence of these disturbances well into term-equivalent age. We hypothesized that this population is still at risk of presenting abnormally low and/or high glucose values at the time of discharge home.
Patients and Methods: We investigated glucose levels during 48 hours with a continuous monitoring device in a cohort of 60 VPT infants that were near hospital discharge. The lower and upper limits of detection are 40 and 400 mg/dl; the data are not displayed in real-time, but downloaded onto a computer at the end of the monitoring period. Hypoglycemia was defined as a glucose value =45mg/dl and hyperglycemia as =140mg/dl (severe if =180mg/dl). Episodes were considered relevant only if abnormal values persisted for longer than 30 consecutive minutes. For each baby, perinatal data, information about clinical course and complications was extracted from the clinical chart. Feeding regimes were in accordance with current practice (breast feeding on demand or 20-25 ml/kg feedings of breast milk or formula every 3 hours). All data were analyzed with SPSS 17.0. Possible differences between normoglycaemic patients and the ones with abnormal glucose values were assessed by uni and multivariate analysis. Differences with p-values lower than 0,05 were considered statistically significant and those between 0,1 and 0,05 were considered as trends.
Result: 60 patients were included in the study, 34 of them (34, 56,7%) boys. Twelve babies (20%) had a prenatal diagnosis of Intrauterine Growth Restriction (IUGR). Gestational age and weight at birth were 28,4±2,2 weeks and 1.100±289 g, and postmenstrual age and weight at the time of study were 37,9±1,5 weeks and 2.240±327g. We obtained a total of 37.435 glucose readings from the continuous monitors and 407 paired capillary samples. Intermittent sampling did not detect any hypoglycaemia and 3 values in 3 different babies were abnormally high. In the continuous registers, and according to our definitions of relevance, 5 babies (8.3%) had isolated hypoglycaemia =45 mg/dl (3 of them reaching 40 mg/dl), 14 (23.3%) had isolated hyperglycaemia and 8 (13,3%) had episodes of both. The mean duration of hypoglycaemia lower than 45 mg/dl was 2.8 ±2.9 hours/ affected patient and 4.68 ± 4.35 hours/ affected patient in the case of hyperglycaemia =140 mg/dl, with 12 infants becoming severely hyperglycaemic (=180mg/dl) for an average period of 1,8 ± 1,1 hours/ patient. Of the twelve severely hyperglycaemic patients, five also developed severe hypoglycaemia. No specific characteristics identified the hypoglycaemic babies, except for a trend to a shorter course of parenteral nutrition (<14 days, p 0,07). In a logistic regression model, history of IUGR (p 0,037) and female gender (p 0,063) seemed to increase the risk of severe hyperglycemia.
Conclusions: Very preterm babies continue to present abnormal glucose values, especially hyperglycaemia, by the time of hospital discharge. We could not identify risk factors for hypoglycaemia, while IUGR and female gender seemed to predispose to hyperglycaemia.

NEURODEVELOPMENT OF VERY AND LATE PRETERM INFANTS AND CORRELATION WITH MATERNAL STRESS AT 12 MONTHS OF CORRECTED AGE

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Background. 'Late preterm" newborns (34-36 weeks of gestation) represent more than 70% of all preterm labors. Despite the high prevalence and increased medical risk, little is known on early and long-term neurodevelopmental outcome of these children and data are controversial. To our knowledge there are no studies on the parental stress of late preterm infants (LPI) compared with parents of very preterm infants (VPI). This study aimed to asses the outcomes of VPI and LPI at 1 years of corrected age (CA) and to examine correlation with maternal stress.
Methods. Seventy-three subjects, LPI (N=34) and VPI (N=39) born from January 2010 to December 2011 admitted to our NICU of the Children's Hospital Bambino Gesù of Rome, Italy, and their mothers, took part in the study. Congenital malformation, genetic syndrome, severe neurological and sensorial deficits were excluded. Children were evaluated at 12 months CA with the Bayley Scales of Infant and Toddler Development-Third Edition (Bayley III). Their mothers (mean age=35.8±5.9) completed a questionnaire on parenting stress (Italian version of Parenting Stress Index-short form, PSI-SF) during the same session. Neonatal and socio-demographic data were collected.
Results:. 63 preterm infants (25 LPI and 38 VPI) completed the Cognitive, Language and Motor Scales of Bayley III. Mean Cognitive composite Score (Cog; 104±10; $p<.001$) was significantly higher than Language (Lang; 97±10) and Motor composite score (Mot; 91±10). Mean Bayley scores were in the normal range in LPI e VPI without significant differences between groups. The mean Total Parenting Stress score (N=26 of LPI mothers and N=36 of VPI mothers) was significantly higher ($p<.05$) in VPI (68.89±20.3) than LPI mothers (59.23±12.2), accounted primarily for the Difficult Child subscale (mean was 23.83±8.8 and 19±4.8 respectively; $p<.05$). Bivariate correlations showed that for both LPI and VPI, Language score at Bayley III was significantly related to gestational age ($r=.44$, $p<.05$ and $r=.43$, $p<.01$ respectively); while for VPI only, the Parent-Child Difficult Interaction score of PSI-SF was negatively related to Language score of Bayley III ($r=-.33$, $p<.05$).
Conclusion. Our study showed that the mean neurodevelopment outcome of VPI and LPI groups at 12 months of corrected age corresponded to the normative and that language development and motor skills were weaker than cognitive domain. Mothers of VPI exhibited greater psychological fragility compared to the others in daily management and understanding of child's behavior. These data, although preliminary, suggest the need of specialized and individualized multidisciplinary follow-up which includes a systematic assessment of parental concerns and of mother/child interaction.

EARLY EXPRESSION OF BREAST MILK IS ASSOCIATED WITH A REDUCTION IN THE LENGTH OF STAY FOR THE VERY PRETERM INFANT?

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Background: Breast milk confers nutritional and immunological benefits to the very preterm infant. Expression rates and timing of expression can vary significantly in the first number of days and can contribute to a delay the initiation of oral feeds. ?OBJECTIVE: To develop a multimodal approach to enhancing early expression and administration of breast milk in mothers of very preterm infants and assess the subsequent neonatal outcomes, including initiation of feeding, establishment of full feeds and feeds at discharge.
Design/Methods: A multimodal approach including a lactation consultant, dietician, medical, midwifery and neonatal nursing staff resulted in the development of a protocol focussing on enhancing the expression of breast milk for the very preterm infant. This consisted of mechanisms to encourage and support the expression of breast milk within the first 24 hours. A checklist detailing the antenatal consultation, provision of equipment, ongoing support and education of the mother and medical staff. A prospective chart review was performed and was compared to a historic cohort of infants from 2010. Statistical analyses were carried out using SPSS 18.?
Results: 80 infants (39 prospective; 41 retrospective) were included. Infants in both groups had comparable birth weight (1.13 vs 1.08kg), gestation (28.8 vs 28.4 weeks), indication for delivery and mode of delivery (vaginal 40% vs 32%). Initiation of oral feeding with EBM (median 2 vs 3 days), earlier regain of birth weight (mean 8.9 days vs 12.5 days, p=0.04), achievement of full feeds (12.7 vs 14.7) and a reduced length of stay in the prospective cohort (mean 50 days vs 60 days p = 0.02). There was no difference in the incidence of NEC, BPD or sepsis. There was no difference in the choice of feeding at discharge, with 46% on breast milk at discharge.?
Conclusions: This multidisciplinary initiative has resulted in a number of positive outcomes including an earlier initiation of feeding, earlier achievement of full feeds and a significant reduction in the duration of hospitalisation for very preterm infants. Despite these interventions, only less than half are being fed breastmilk at discharge.?

PARENTAL PERCEPTION OF THERAPEUTIC HYPOTHERMIA FOR HYPOXIC ISCHEMIC ENCEPHALOPATHY

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Introduction/Background: It is recognised that having a newborn in an intensive care environment is a very stressful experience for parents and can influence future parenting as well as outcomes. Little is known regarding parental experience and perceptions of therapeutic hypothermia (TH) for hypoxic ischemic encephalopathy (HIE) and communication and discharge needs of families whose infants have been cooled is unexplored. This knowledge is also critical for planning and development of services. The aim of our study was to explore parental perceptions of this relatively new treatment modality.
Patients and Methods: A postal questionnaire survey of all parents whose babies received TH at Princess Anne Hospital (PAH) from September 2009 - August 2012 (n=51) was carried out. The questionnaire was developed in consultation with the neonatal medical, nursing and family liaison support teams. There were 23 questions covering aspects such as communication, clinical management, follow-up and care in general. Each question had several tick box options and space for free-text comments. A reminder was sent at 4 weeks to families who did not respond to the initial questionnaire. The responses were anonymised and we performed descriptive statistical analysis and exploration of free text comments. The project received local R&D approval.
Result: Thirty one families responded (60%) of which 58% were inborn and 42% outborn. Of the nine babies who died only one family completed and returned the questionnaire. Almost all parents felt that the treatment and its benefits were explained to them in sufficient detail but only 61.3% felt that they had a good understanding of the therapy before it was started. Overall 50% recall having had sufficient opportunities to speak to staff before start of the treatment. Seventy percent of parents felt that bonding between them and their baby was affected by TH, but almost all of them commented that it was only temporary and they bonded well with their baby later. Ninety seven percent of the newborns had an MRI of the brain; 72% of parents recall having results explained along with potential long term implications of findings. Some families (10%) felt that follow up was not timely and appropriate and these were all outborns transferred to PAH for TH. They commented on being 'lost in the system to follow-up'. There were also comments on differences in understanding and perception within families, and parents attributed this to circumstances at or after birth and lack of communication opportunities with the neonatal team as a result. Although 61.3% felt that they did not have good understanding of what TH involved prior to commencing treatment the majority of parents were happy that this was initiated without delay and they trusted the judgement and clinical decisions made by involved teams.
Conclusions: The survey revealed parental perceptions of this relatively new treatment. Of note were the perceived lack of understanding of TH and issues around communication and delivery of information to parents and between hospital teams. The survey also highlighted albeit temporarily, the effect of TH on bonding between parents and their newborn baby.

PARENTS' EXPERIENCES OF FOLLOW-UP FOR THEIR VERY PRETERM CHILD

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Background: UK neonatal services offer follow-up to two years corrected age for children born very preterm (VP; =31 weeks). The development of these services has been largely audit-driven and parents' views have not been formally explored. As part of a clinical service evaluation, we used qualitative methods to explore parents' experiences of follow-up for their VP child.
Methods: Eleven mothers of VP children attending a 2-year follow-up consultation participated in a semi-structured telephone interview. Interviews followed a topic guide with open questions followed by probing questions to explore parents' views of their child's consultation and of the general accessibility and organisation of follow-up provision. Responses were transcribed verbatim and analysed using Thematic Analysis.
Result: Theme analysis revealed seven themes. Mothers highly valued seeing the same consultant throughout their child's follow-up because 'they know the children and their journey better than anyone else'. Their satisfaction and feelings about the length of follow-up was associated with their perception of their child's outcomes, with longer-term follow-up preferred by those whose children had on-going problems. Generally mothers thought their children were doing well and did not anticipate future problems which might necessitate further follow-up. Of concern was the finding that mothers felt that other healthcare professionals had a paucity of knowledge about preterm birth and that there was a lack of communication between neonatal and other healthcare services leaving them to integrate their child's care. Follow-up in general was viewed positively as mothers perceived this as providing a valued link back to the security offered by the neonatal intensive care unit (NICU).
Conclusions: Mothers value neonatal follow-up for their very preterm child and the continuity of care this affords. There is concern that other healthcare professionals are less well informed about their child's needs and that a more integrated approach to long-term care is needed. Further research in this area may aid in developing services that meet the needs of families with VP children and help them in their transition from the NICU.

THE MOTHERS OF BABIES ENROLLED IN A RANDOMISED CONTROLLED TRIAL REPORT A POSITIVE EXPERIENCE

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Background: Randomised controlled trials are an essential part of improving outcomes for babies and their families. Researchers can be hesitant about undertaking clinical trials involving babies soon after birth due to the vulnerability of the baby, and potential risk of increasing anxiety for parents. There is a paucity of evidence about the parental experience of having a newborn baby in a clinical trial. We sought to determine the mothers' experience of having their newborn baby participate in a randomised double-blind placebo-controlled trial soon after birth.
Method: Eligible mothers had consented to their baby's participation in the Sugar Babies Study, which sought to determine if 40% dextrose gel was an effective treatment for hypoglycaemia. Mothers of potentially eligible babies were identified and invited to join the study antenatally where possible, but others were approached postnatally. Babies were enrolled in the study as soon after birth as possible and remained in the study for 48 hours. Two weeks after the birth mothers were interviewed by phone about their experience of the trial.
Result: Four hundred and eighty one mothers were enrolled, of whom 313 (65%) gave consent antenatally. All mothers were contacted and 462 (96%) were interviewed at 2 weeks. Most mothers (447, 93%) reported they would consent to participating again if they had another eligible baby, and 440 mothers (91%) reported they would recommend participation to family and friends. The best things reported about the study were the support provided by researchers and the opportunity to participate in research that may improve the care for at-risk babies in the future. Nineteen mothers (4%) reported they did not like the heel-prick blood lances, which were part of routine clinical care and therefore not part of the trial protocol.
Conclusions: Clinical research is fundamental to improving outcomes for babies and their families. The majority of mothers enrolled in the Sugar Babies Study were positive about the experience, which may in part be due to the additional care given by the researchers.

DISAPPOINTMENT AMONG PARENTS TO NEWBORNS ALLOCATED TO THE CONTROL GROUP: A QUALITATIVE STUDY OF A RANDOMIZED CLINICAL TRIAL

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Introduction: Several studies have investigated patients' motives for participating in clinical trials. Altruism along with the hope of personal gain is mostly reported. When the patient is a child, the informed consent has to be given by the parents. Parental motives for participation are complex, but the hope of getting a new and better treatment for the child is important. The Danish Calmette study is a randomized clinical trial investigating the non-specific effects of giving BCG-vaccine to neonates in a high-income setting. The hypothesis is that a modulation of the immune system immediately after birth can reduce infectious diseases in the first years of life as well as the incidence of atopic dermatitis, asthma, and allergy. Parents are not blinded to randomization. We wondered how parents react when their child is allocated to the control group. We also wondered if their reactions influence their motivation towards continued participation in the trial.
Methods: We conducted, recorded and transcribed a focus group interview with parents of the first newborns randomized to the control arm at Rigshospitalet in Copenhagen. Afterwards we conducted semi-structured telephone interviews and noted the answers of the women we had been in contact with when recruiting for the focus group interview, until saturation was achieved. Thematic analysis was used to identify themes across the data sets. We addressed the question of how the parents perceived randomization, how they had reacted towards being allocated to the control group, and their future engagement in the trial. Findings The focus group interview was conducted with six parents from four families. The telephone interviews were conducted with 19 mothers. All mothers except one had medium or long higher educations. The parents reported good understanding of the randomization process. Their most common reaction to allocation was disappointment, though relief was also seen. 21 of 23 mothers expressed that they had hoped for their child to get the vaccine. The reactions differed in degree, but could for each parent be positioned along two continuities from 'Our participation in trial is not important' to 'Our participation in trial is important' and 'Vaccine not important to us' to 'Vaccine important to us'. Four very disappointed families had thought of getting the vaccine elsewhere, but of them only one had actually had their child vaccinated. All parents involved in the focus group or telephone interviews wanted to participate in the follow-ups.
Conclusion: This study identified an almost universal experience of disappointment among parents of infants who were randomized to the control group in a trial of BCG vaccination at birth, but also a broad expression of understanding and acceptance of the idea of randomization. Exploring and correcting the parents' understanding of the intervention, including potential harms and uncertainty of the effects might lessen the disappointment, but is only appropriate if they do not experience it as new information. A useful way for trial staff of dealing with the disappointment may be to emphasize the important role of the child in the control group and hence to focus on the altruistic motives for participation.

THE PREDICTIVE VALUE OF EARLY AEEG PATTERNS IN PRETERM INFANTS FOR THE NEUROPSYCHOLOGICAL OUTCOME AT EARLY SCHOOL AGE

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Background/objective: Previous studies suggest that the amplitude-integrated electroencephalogram (aEEG) is predictive for short-term neuropsychological outcome of preterm infants. The predictive value of aEEG for long-term outcome is still unknown. We aimed to determine whether early aEEG patterns in preterm infants are useful to predict neuropsychological outcome at early school age.
Methods: aEEG recordings were performed thrice in 48 very preterm born children (GA 26.0-32.9 wk), i.e. on day 0-2 , on day 5-9, and on day 12-16 after birth. The recordings were assessed off-line by pattern recognition, and by calculating the mean values of the 5th (p5), 50th (p50) and 95th (p95) centiles of the aEEG amplitudes. The neuropsychological outcome was determined at the age of 6-7 years by assessing motor, cognitive and behavioural outcome using standardized tests and questionnaires. We determined the relation between aEEG patterns and neuropsychological test scores using Spearman's rank or Pearson, when applicable, correlation test, and we calculated odds ratios (ORs) for the risk of abnormal neuropsychological performance by aEEG parameter. We adjusted the results for GA and Apgar score at 5 minutes.
Result: Mean p5 on day 0-2 after birth correlated negatively with verbal memory (r=-0.417, p=0.014). Mean p5 and p50 on day 5-9 after birth correlated negatively with long-term memory (r=-0.325, p=0.038; r=-0.379, p=0.015, respectively). The risk for abnormal scores on long-term memory was higher if p50 values on day 5-9 were higher (per microvolt increase: OR=1.37, p=0.028). Higher p95 values on day 12-16 after birth correlated positively with total and verbal IQ (r=0.500, p=0.013; r=0.518, p=0.010, respectively) and visual memory (r=0.438, p=0.041). The risk for abnormal scores on visuomotor integration was increased if p5 values were lower on day 12-16 after birth (OR=2.66, p=0.039). Trends were seen for higher total and/or performance IQ in case of more continuous aEEG patterns on days 0-2 and 12-16 after birth. No associations other than trends were found between aEEG patterns and motor and behavioural outcome.
Conclusions: In preterm infants, aEEG patterns recorded from day 5 on seem to be more predictive for outcome at early school age than aEEG patterns recorded directly after birth. Surprisingly, a more discontinuous aEEG (lower p5 and higher p95) was associated with better cognitive outcome, except for visuomotor integration. We found no clear association between aEEG patterns and motor and behavioural scores. Therefore the predictive value of aEEG for long-term outcome is limited in preterm infants.

AEEG AND FA OF THE PLIC IN VERY PRETERM INFANTS: THE POSSIBLE LINK BETWEEN FUNCTION AND STRUCTURE ON EARLY MRI

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Background: Amplitude-integrated electroencephalography (aEEG) assesses electrocortical activity with good predictive value for neurodevelopmental outcome in preterm infants. In parallel, Diffusion tensor imaging (DTI) enables the assessment of white matter (WM) integrity, and is particularly suited for studying WM and brain maturation. Our aim was to study the relation between early aEEG measures, recorded over the first three days of life in preterm infants and fractional anisotropy (FA), a measure of microstructure integrity in the posterior limb of the internal capsule (PLIC) calculated at 30 wks postmenstrual age (PMA).
Patients and Methods: 66 preterm infants (mean GA 26.6wks,range 24.5-27.6; mean birthweight 904.6g; range 460-1150) were enrolled between 2008 and 2012 and monitored during the first 72 hours of life with continuous aEEG, using the cross sectional P3-P4 channel (BrainZ, Natus, USA). Six periods of 2-4 hour were selected at 4-6h (P1),10-12h (P2), 20-24h (P3),32-36h (P4), 44-48h (P5), 68-72h (P6) , with more continuous activity and avoiding artefacts and episodes of suspected electrical discharges. Minimum, amplitude, % of time <5 μV, interSAT (spontaneous activity transient) interval, interSAT %,SAT/min were calculated using Signal Base (UMC, Utrecht). An MRI was performed at a mean PMA of 30.6 (range: 29.2-32) on a 3T Philips system. DTI images were collected and the FA-PLIC on both sides (corrected for PMA) was computed using a neonatal DTI-atlas (1). 27 infants received morphine in the first three days of life and were analyzed separately, as this could affect electrocortical activity. Only P3-4 recordings were taken into account since these are most predictive for neurodevelopmental outcome (2). Statistical analysis was performed using SPSS 20.
Result: The 27 infants who received morphine showed a significantly lower value of all aEEG variables for P 2-3-4-5-6. Furthermore, GA was significantly correlated with all aEEG parameters indepently from morphine. The multivariable analysis in 39 infants without morphine showed a significant association between % of time <5 μV in P3-P4 and corrected FA-PLIC on both sides at 30 wks of PMA (respectively for the left FA-PLIC vs P3: $p<0.05$, B -0.001, CI -0.001-0.000 and vs P4: $p<0.05$, B -0.001, CI - 0.002-0.000 and for the right FA-PLIC vs P3: $p<0.05$, B -0.018, CI -0.004-0.033 and vs P4: $p<0.05$, B -0.001, CI -0.002-0.005). The analysis was corrected for GA and the occurrence of severity of IVH. No associations were found between other aEEG measures and the FA-PLIC.
Conclusions: GA and morphine are important factors influencing the aEEG variables in very preterm newborns. Early aEEG maturity, in particular the % of time <5 μV between 20 and 36 h of life seems to be related to microstructure integrity measured as FA-PLIC within 2-6 wks after birth (PMA 30 wks) on early MRI. Whether there is an association with MRI at term equivalent age and neurodevelopmental outcome still needs to be elucidated.
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ASSOCIATION BETWEEN N-TERMINAL PRO BRAIN NATRIURETIC PEPTIDE AND CEREBRAL REGIONAL OXYGENATION IN NEWBORN INFANTS.

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Background: Cerebral blood flow influences cerebral oxygen delivery and cerebral regional oxygenation. Cerebral blood flow depends on cardiac output and cerebral vascular resistance. Cardiac pressure load and volume load determine release of N-terminal pro brain natriuretic peptide (NT-proBNP), a hormone synthesised by ventricular myocardium. An increase in NT-proBNP is associated with ventricular strain and cardiac stress. Aim of this study was to search for an association between NT-proBNP and cerebral regional oxygenation (crSO2) and cerebral fractional tissue oxygen extraction (cFTOE) in newborn infants.
Methods: In this prospective observational study crSO2 was measured by near-infrared-spectroscopy (NIRS) on the right side of the forehead for 24 hours starting within six hours after birth in preterm and term infants. Additionally the infants were monitored with a pulse oximeter, to measure the peripheral arterial oxygen saturation (SpO2). At the end of the NIRS measurement a blood sample was taken to measure NT-proBNP levels. cFTOE values were calculated by using the formular: [(SpO2-rSO2)/SpO2] We calculated mean crSO2 and cFTOE values for the 24 hour measurement period (crSO2_24h and cFTOE_24h) and mean values for the one hour period before collecting blood (crSO2_b and cFTOE_b) and checked for correlations with NT-proBNP values.
Result: 54 neonates were included in this study. Mean gestational age was 35±3 weeks and mean birth weight was 2282±805g. NIRS measurements started at 4±4 hours after birth and blood samples were taken at 24±5 hours after birth. Mean NT-proBNP was 4967±3627pg/ml. crSO2_24h was 74±9%, crSO2_b 75±8%, cFTOE_24h 0.22±0.09 and cFTOE_b 0.20±0.08. NT-proBNP correlated negatively with crSO2_b ($r = -0.491$, $p < 0.001$) and crSO2_24h ($r = -0.522$, $p < 0.001$) and positively with cFTOE_b ($r = 0.520$, $p < 0.001$) and cFTOE_24h ($r = 0.485$, $p < 0.001$).
Conclusions: We were able to show that higher NT-proBNP levels were associated with lower crSO2 levels in newborn infants during the first day of life. These findings may suggest that changes in NT-proBNP, which reflect changes in cardiac function, affect cerebral oxygenation.

CEREBRAL REOXYGENATION AFTER BIRTH - COMPARING INVOS® AND FORE-SIGHTÂ„¢ OXIMETERS

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Introduction Near-infrared spectroscopy (NIRS) enables real-time monitoring of regional cerebral tissue oxygenation (cStO2), that represents an estimate of the cerebral oxygen delivery-consumption balance. The variance of repeated measurements of cStO2 has been shown to be about 5-6% (SD). This is a problem as sick newborns, especially preterm, often are born in hemodynamic instability. Thus more reliable absolute values of cStO2 could be of clinical benefit. Our aim was to compare the absolute values of cStO2 of the neonatal sensors of INVOS 5100C and FORE-SIGHT in regards to sensitivity to changing oxygenation as well as the steady state mean levels and repeatability.
Methods: In a prospective observational study INVOS 5100C and FORE-SIGHT with neonatal sensors were compared on 12 term newborns delivered by an uncomplicated elective caesarean section (CS). During the 10 minutes following umbilical cord clamping, cStO2 was measured with the sensor from each device placed on each side of the forehead. The separation was always more than 6 cm. Pulse and arterial saturation was monitored by pulse oximetry. Furthermore, six repeated measurements of 20 seconds during steady state were done the next day. Bland-Altman plot was used to assess the agreement of the cStO2 values during the transition. The means of cStO2 in steady state were compared by a paired t-test and repeatability was estimated by ANOVA.
Results: There was a rapid increase in cStO2 from 3 to 8 minutes as expected. The mean value increased from 49.8% (CI 33.7-65.5%) to 86.3% (CI 80-91.9%) for INVOS and from 61,5% (55.3-67.7%) to 82.3% (CI 77,7-86,8%) for FORE-SIGHT. The inter-device difference was insignificant at 3 min (p=0,10) and 8 min (p=0,19). The Bland-Altman plot revealed a significantly increased difference (D) in absolute values (A) with decreasing cStO2 (D=0.67A - 45.7, p=<0.001). The weighted regression-based 95% limits of agreement were 0.67a - 45.7 ±15.7% (a is magnitude (average of device) of cStO2). The mean value for replacements measures on day two was 78.2% (CI 76.5-79.9%) and 86.1% (CI 85.4-86.9%) for INVOS and FORE-SIGHT respectively (p<0,001). The repeatability with-in standard deviation scores was 4.8% (CI 4,0-5,7%) for INVOS and 2.8% (2,0-3,2%) for FORE-SIGHT.
Conclusion:INVOS and FORE-SIGHT responded significantly different to cerebral reoxygenation in the minutes after birth, with the largest difference in the low oxygenation range. FORE-SIGHT had better repeatability than INVOS, but this may simply be due to the lower sensitivity to change in oxygenation.

SEX-RELATED DIFFERENCES IN AEEG SIGNALS IN PRETERM INFANTS

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Background: The amplitude-integrated electroencephalogram (aEEG) is a valuable tool for monitoring brain function in preterm infants. Previous studies have extensively discussed sex-related differences regarding neonatal morbidity and mortality. For now there has been no study published specifically evaluating potential sex-related differences in aEEG signals. The aim of the present study was to investigate potential sex-related differences in aEEG signals in the first four weeks of life in very preterm infants without morphological signs of brain injury.
Methods: The study survey area was Tyrol, a state in western Austria with 680,000 inhabitants and about 7,000 live births per year. 156 infants (85 male and 71 female) born with a gestational age between 28 and 31 completed weeks were evaluated in this study. Two-channel aEEG was performed at seven time points (postnatal day 1, 2, 3, week 1, 2, 3 and 4) and analyzed for the Burdjalov total score, number of bursts per hour and the visual background pattern.
Result: In both groups the proportion of infants with continuous activity increased from day 1 (male versus female: 18.8% versus 25.4 %) to day 3 (49.1% versus 51.0 %) and further from week 1 (66.2% versus 55.7%) to week 4 (92.6% versus 93.8%). We show no statistically significant difference in the percentage of continuous background pattern between male and female infants at any time point evaluated. The mean total score increased with postnatal age. The score was significantly higher in female infants at day 1 ($p<0.05$) and week 4 ($p<0.01$) and showed a non-significant trend of being higher at every observed time point. The number of bursts per hour decreased with postnatal age in both male and female infants. At week 4 the number of bursts per hour was significantly greater in male compared to female infants ($p<0.05$).
Conclusions: Sex-related differences are present in aEEG signals of preterm infants. The lower total score and the higher number of bursts might express a delay in brain maturation in male preterm infants.

SEX DIFFERENCES IN OUTCOME AND ASSOCIATIONS WITH BRAIN DEVELOPMENT IN CHILDREN BORN EXTREMELY PRETERM

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Background: The male disadvantage with regards to perinatal mortality and morbidities is well known. We aimed to investigate sex differences in neurological and developmental outcome in extremely preterm children, and explore associations with neonatal brain morphology.
Patients And Methods: A population based cohort of infants born <27 weeks of gestation underwent neurological and develomental assessment (Bayley Scales of Infant and Toddler Development, Third Edition, BSITD-III) at age 30 months corrected (n=86). Magnetic Resonance Imaging (MRI) was done at term equivalent age. In infants without focal lesions (n=27), automatic segmentation of brain tissues using SPM8 software, and voxel-based morphometry with DARTEL (Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra) was performed on 3D T1-weighted images. Statistical analysis was performed using Student t-test for continuous variables and Pearsons ?2 test for dichotomous data. Pearsons correlations were calculated to investigate relationships between global brain volumes and BSITD-III scores, and simple regression analyses were performed to test for relationships at voxel level between brain volumes and BSITD-III scores.
Results: Boys had lower mean cognitive composite scores (94±7 vs 98±11, p=0.03) and lower mean language composite scores (94±13 vs 101±15, p=0.04) compared to girls, while rates of cerebral palsy were similar. No individual perinatal factor explained the difference in outcomes. On visual inspection of T1-weighted and T2-weighted images, delayed myelination was more commonly found in boys, whereas cerebellar abnormalities were more common in girls. In the subgroup with normal structural MRI, boys still had poorer cognitive (p=0.015) and language function (p=0.008), despite larger volumes of supratentorial white matter (p=0.039) and cerebellar tissue (p=0.029). In boys, global cerebellar volumes correlated positively with BSITD-III cognitive and motor composite scores (p=0.04) and cortical grey matter correlated positively with BSITD-III cognitive scores (p=0.02). In girls, global volumes of supratentorial white matter, cortical and deep grey matter correlated positively with BSITD-III language subscores (p=0.03). At regional level, significant correlations with outcome were exclusively found in girls: cortical volume in pre-central regions correlated positively with BSITD-III language composite scores (p<0.001), supplementary motor cortex volumes correlated positively with BSITD-III fine motor scores (p<0.001) and white matter volumes in the precuneus correlated positively with BSITD-III expressive language scores (p<0.01).
Conclusion: Cognitive and language scores at age 30 months were lower in extremely preterm boys than girls. Sexual dimorphism was observed on neonatal structural MRI, in addition to differences in the patterns of correlations between brain volumes and developmental scores at both global and regional levels.

PLACENTAL TRANSFUSION IN PRETERM INFANTS: HOW LONG DOES THE TRANSFUSION LAST?

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Introduction: Current resuscitation guidelines suggest delaying umbilical cord clamping for at least one minute in infants born without compromise regardless of gestation (NLS 2010, ILCOR 2010). Much of the previous research into both the underlying physiology and outcomes has involved term infants rather than preterm infants; a population in which placental transfusion may be of greater benefit. Evidence suggests there may be benefits for preterm infants who have deferred umbilical cord clamping. These include reduced ventilation, reduced red cell transfusions, less ultrasound diagnosis of intraventricular haemorrhage (1). Optimal timing of umbilical cord clamping remains unclear. Previous research in preterm infants has used varying definitions of deferred clamping from 30 seconds to 3 minutes where stated, but in some studies the time has been poorly defined (1). A recent study weighing term infants showed the majority had completed transfusion by 2 minutes but there was evidence of continuing transfusion in some babies (2). This study repeated the same methodology in preterm infants to see if placental transfusion altered with gestation.
Methods: Infants were weighed during the first two to four minutes of life with the umbilical cord intact using high quality pharmacy scales (Mettler-Toledo). Infants were placed on the scales positioned on a trolley next to either the theatre or delivery bed depending upon the mode of delivery. The position of the baby relative to the Mother's abdomen was recorded and adjusted by raising or lowering the bed to an equivalent height. The infant was monitored by an experienced neonatologist using saturation monitoring and assisted by a research midwife.
Result: Seven preterm infants (34 weeks and four days to 36 weeks and 1 day postmenstrual age) were weighed with the time of cord clamping ranging from two minutes to three minutes fifty seven seconds. Three were delivered by lower section caesarean section and four by spontaneous vaginal delivery. Data on the duration of transfusion and the volume of blood transfused will be presented.
Conclusions: Our results suggest that in preterm infants placental transfusion is continuing beyond three minutes of age. With increasing interest and practice in deferring umbilical cord clamping it is important we understand the physiology behind the transfer of blood from the placenta to the baby. More studies need to be done in this area to determine the length and volume of transfusion especially in the preterm population.
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DEFINING OPTIMAL BLOOD PRESSURE BASED ON A NOVEL CEREBROVASCULAR REGULATION INDEX IN PRETERM INFANTS

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Introduction: Cerebral autoregulation ensures that cerebral perfusion remains constant over a range of arterial blood pressures. Defining optimal cerebral perfusion pressure, based on strength of cerebrovascular reactivity Improves outcome in adult neurocritical care1. The presence and limits of autoregulation in neonates remains uncertain and debate continues regarding the optimal blood pressure in these patients. The assessment of cerebrovascular reactivity should not rely on measurement of arterial blood pressure alone: there is evidence that increasing heart rate is effective in increasing cardiac output in neonates, as the ability to increase stroke volume is limited in this population. A novel index of cerebrovascular reactivity, called tissue oxygen heart rate reactivity (TOHRx) relates the correlation between the tissue oxygenation index (TOI) and heart rate (HR). We aimed to describe TOHRx in a cohort of preterm infants and investigate whether this index could be used to define optimal mean arterial blood pressure (MABPOPT) in this population.
Patients and Methods: 60 preterm infants born at median (range) gestational age of 26+0 (23+4 - 32+1) were studied with signed parental consent. Median (range) age at the study was 34 hours of age (5 to 228h) and median time of recorded data was 2 hours (1 - 24h). The cerebral tissue oxygenation index (TOI) was measured using the NIRO 200NX near-infrared spectrophotometer (Hamamatsu Photonics, KK, Japan). Real time recordings of mean arterial blood pressure, arterial oxygen saturation and heart rate were simultaneously recorded and analysed using ICM+ software2. Severity of clinical illness was assessed using CRIB II score. TOHRx was calculated from moving correlation coefficient, using 5-minutes time windows between 10 seconds average values of TOI and HR. Correlation between TOHRx and CRIB II was assessed using linear regression analysis. MABPOPT for individual patients was determined by dividing MABP into 2mmHg bins and averaging TOHRx within those bins. An automatic curve fitting method was applied to determine the MABP value with the lowest associated TOHRx value (corresponding to maximal cerebrovascular reactivity).
Result: The median (range) of TOHRx was -0.0223 (-0.4631 - 0.3218). TOHRx demonstrated significant correlation with CRIB II (R=0.35, p=0.006). The median (range) MABPopt was 34.5 (25 - 55). The values of MABPOPT calculated for each individual patient were used to determine the average distance of MABP from the ‘optimal'. This measurement of divergence from MABPOPT was significantly greater in those patients who died (4.2 +/-2.7mmHg vs 2.1 +/-1.6mmg, p=0.013 non-parametric test).
Conclusions: TOHRx is a novel index of cerebrovascular reactivity. TOHRx can be used to define a value MABPOPT; using this methodology there was a significant deviation from MABPOPT in those infants who died. The use of TOHRx to define MABPOPT may therefore be a valid approach to managing blood pressure in these infants.
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ASSOCIATION BETWEEN PERIPHERAL HYPOPERFUSION AND INTRAVENTRICULAR HEMORRHAGE IN VLBW INFANTS DURING THE FIRST 7 DAYS

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Background: Cardiovascular instability immediately after birth is associated with intraventricular hemorrhage (IVH) in very low birth weight (VLBW) infants. Blood pressure-oriented circulatory management has not always prevented the development of IVH. Since the ultimate goal of circulatory management is to maintain organ perfusion and oxygen delivery, the importance of evaluation of organ blood flow has been increasingly recognized. In this study, the relationship between peripheral perfusion within 48 h after birth and IVH was evaluated in VLBW infants.
Patients and Methods: In 83 VLBW infants born at Saitama Medical Center, Saitama, Japan, forehead skin blood flow (FBF) and lower limb skin blood flow (LBF) were measured for 48 h after birth using a laser Doppler flowmeter. LBF, FBF, and mean arterial blood pressure (MAP) were compared between infants with and without IVH at time points between 6 h and 48 h at 6 h intervals. Within-group values at these time points were also compared. Multivariate logistic regression analysis was performed to identify the risk factors for IVH, and receiver operating characteristic curve analysis was used to evaluate the diagnostic performance of these parameters.
Result: IVH developed in nine infants, of which eight occurred after 24 h. LBF was lower in infants with IVH than in those without at 18 h and 24 h, and it increased to the same level but not exceeding that of infants without IVH at 48 h. MAP was lower in infants with IVH than in those without at 12 h and 24 h. However, most values did not meet the criteria for hypotension at 24 h. Multivariate logistic regression analysis identified a correlation only between LBF and IVH at 18 h and 24 h. The receiver operating characteristic curve analysis revealed that LBF 13.8 mL/100 g/min at 18 h had 88% sensitivity and 93% specificity for predicting IVH. In addition, LBF, FBF, and MAP had negative predictive values of 99%, 93%, and 98%, respectively.
Conclusions: These findings were consistent with the hypoperfusion-reperfusion theory, which states that IVH develops after reperfusion subsequent to hypoperfusion. Given the present findings, future interventional studies in very preterm infants should focus on preventing systemic and brain hypoperfusion immediately after delivery or, if hypoperfusion is not preventable, controlling the reperfusion rate for potential improvement of short- and long-term neurodevelopment. Larger studies using additional measures of brain (such as near-infrared spectroscopy) and systemic (echocardiography, electrical impedance) blood flows with LBF and FBF measurements are required to further clarify these findings.

PERIPHERAL REGIONAL OXYGEN SATURATION IN PRETERM INFANTS WITH AND WITHOUT RESPIRATORY SUPPORT DURING NEONATAL TRANSITION

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Objective: To evaluate peripheral regional oxygen saturation during the immediate postnatal transition in late preterm infants with and without need for respiratory support.
Study Design: We performed a prospective observational study, using near infrared spectroscopy to evaluate changes in peripheral preductal regional oxygen saturation (rpSO2pre) (right arm) and peripheral postductal regional oxygen saturation (rpSO2post) (left lower leg). These variables were measured during the first 15 minutes of life after elective cesarean section. Peripheral oxygen saturation (SpO2) and heart rate (HR) were measured continuously by pulse oximetry. Fractional tissue oxygen extraction (FTOE) was calculated. Two groups were compared based on their need for respiratory support: a normal transition group (NT group) and a respiratory support group (RS group). Positive pressure ventilation was delivered with a T-piece resuscitator and oxygen was adjusted based on SpO2 values. A Florian Respiratory Function Monitor was used to record the ventilation variables.
Results: There were 25 infants in the normal transition group and 26 infants in the respiratory support group. Median gestational age was 35 weeks in NT group, and 34 weeks in RS group. As respiratory support was according to individual needs of the infants, start points and duration of PEEP and supplemental oxygen differed for each infant. The mean time for initiating respiratory support was at 2.9 (±2.2) minutes after delivery, duration of respiratory support was 9.3 minutes (±4.9). The mean PEEP level for the observation period was 6 (±0.8) cmH2O. Only one infant of RS group was intubated in the further course. Changes in HR over time were similar in both groups. Pre- and postductal SpO2 course showed significantly lower values in RS group throughout the whole observation period. In RS group rpSO2pre was significantly lower until minute 10, whereas rpSO2post values were lower throughout the whole period. Preductal FTOE was significantly higher in RS group from minute 6 to 8, whereas postductal FTOE was significantly higher until minute 10. There was a significant difference in course of pre and postductal rpSO2 (p=.006). Whereas in NT group pre- and post-ductal rpSO2 values showed a converging course over time, in RS group they showed a diverging course over time.
Conclusion: This is the first systematic analysis of pre- and postductal oxygenation in preterm infants with mild respiratory distress compared to infants with normal transition. There were significant differences in parameters representing pre- and post-ductal oxygen delivery and extraction. The continuation of differences in course of pre and postductal rpSO2 between the two groups to the end of observation period suggests, that differences in peripheral oxygenation persist longer than 15 minutes.

POSTNATAL ADAPTATION OF PULMONARY CIRCULATION IN EXTREMELY LOW BIRTH WEIGHT INFANTS

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Background and aims: In healthy term neonates, pulmonary pressures fall rapidly following birth and first breaths. However in the extremely low birth weight (ELBW; below 1000g) infants, there is very little information about the pattern of this physiological adaptation. The aim of our study was to prospectively measure pulmonary pressures following delivery.
Methods: All ELBW infants admitted to the neonatal intensive care unit in the Coombe Women and Infants University hospital were eligible for enrolment. Targeted echocardiography was performed at three, six and 12 hours of age to measure the size and flow pattern in the Patent Ductus Arteriosus (PDA) and the tricuspid regurgitation (TR) in m/sec as an indirect assessment of pulmonary hypertension (PH).
Results: Between November 2012 and April 2013 23 infants were enrolled. The mean gestational age of our cohort was 26.2 (±1.7) weeks of gestation and the mean birth weight was 795 g (±144). All infants had a PDA present on all measurements with mean ductal size 2.4 mm at three hours of age, decreasing to 2.0 mm at 12 hours of age (p= 0.003). Mean TR at three hours of age was 1.9 m/s, falling to 1.4 m/s at 12 hours of age (p= 0.02). 11 infants had TR above 2 m/s (estimated pulmonary pressure above 20 mm Hg) after three hours of age, suggestive of delayed transition.
Conclusions:PH with impaired transition could play a role in stabilisation of extremely preterm neonates. Further data are needed to confirm this finding with possible targeted approach to infants with delayed transition.

EFFECT OF BLOOD TRANSFUSION ON CEREBRAL AND INTESTINAL BLOOD FLOW DURING THE FIRST WEEK OF LIFE IN EXTREME PRETERM INFANTS

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Introduction: 90% of Extremely Low Birth Weight (ELBW) infants receive a blood transfusion 1. The benefits of transfusion are not clear 2, 3. Methodology: Aim: To study the effect of blood transfusion on cerebral and intestinal blood flow during the first week of life in extreme preterm infants. Cerebral blood flow was estimated by measuring anterior cerebral artery (ACA) velocities and superior vena cava (SVC) flows using Doppler ultrasound scan 20-30 minutes before and after blood transfusion. Superior mesenteric artery (SMA) velocities were measured as a surrogate for intestinal blood flow. Other data collected: gestational age, birth weight, pre and post-transfusion haemoglobin (Hb), pCO2 and lactate, enteral feed, cranial and cardiac ultrasound scan findings. Pre and post transfusion measurements were compared using t-test and ANOVA, and the correlation with pre-transfusion Hb was tested by regression analysis. The study was approved by Research Ethics Committee and informed written parental consent obtained.
Result: 18 infants were studied. The mean gestational age was 25 weeks (SD 1.23), birth weight 800 grams (SD 131.3), age 4 days (SD 2.2) and male: female ratio 10:8. 10/18 infants were fed; 3 were receiving higher than trophic feeds. 17/18 had PDA on echocardiography. 2 infants had Grade 2 and 3 infants had Grade 4 IVH. There was no difference in pre and post-transfusion pCO2 ($p=0.5285$), a significant increase in the Hb ($p<0.0001$; 95% CI -3.154 to -2.257) and decrease in lactate ($p=0.0181$; 95% CI 0.156 to 1.455) after blood transfusion. The mean ACA peak velocity decreased significantly from 0.33 to 0.27 m/sec ($p=0.0038$; 95% CI 0.0209 to 0.0924) following transfusion. There was no difference between infants with and without IVH ($p=1$). The mean SVC flow also reduced (106.8 to 93.04 ml/kg/min) significantly ($P=0.028$; 95% CI 1.68 to 25.97) following transfusion. There was no change in the SMA peak flow velocities ($P=0.2894$, 95% CI -0.0594 to 0.1871). There was a significant difference in SMA peak velocity between fed and unfed groups ($p<0.043$) but there was no significant difference in the pre and post transfusion measurements between these two groups ($p=0.72$). No correlation was noted between the pre-transfusion Hb and the changes in the ACA peak velocity ($r = 0.24$; $p = 0.34$) as well as SVC flow ($r = 0.30$; $p = 0.23$).
Conclusions: Blood transfusion reduced cerebral blood flow but not intestinal blood flow during the first week of life in extreme preterm infants. These changes did not show any correlation with the pre-transfusion Hb, IVH and enteral feed.
References: 1. Maier, RF et al. J Pediatr, 2000. 136(2): p. 220-4 2. Bell, EF et al. Pediatrics, 2005. 115(6): p. 1685-91 3. Kirpalani, H et al. J Pediatr, 2006. 149(3): p. 301-307

INJECTABLE HYDROGELS FOR TREATMENT OF OBSTRUCTIVE NEPHROPATHY

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Background: Congenital obstructive nephropathy is the leading cause of chronic kidney disease (CKD) in children. The cellular mechanisms of kidney injury caused by obstructive uropathy are interstitial inflammation, fibrosis, and apoptosis. Rodent models can be used to simulate obstructive nephropathy in the human kidney.
Objective: Our research uses injectable biomaterials for drug delivery to abate the progression of inflammation and fibrosis that leads to CKD.
Design/
Methods: Hydrogels: Dock-n-Lock gels are injectable biomaterials that can be used for drug delivery. IL-10 was added to the gel or mouse serum albumin (MSA) solution at a concentration of 0.33 mg/mL. Study Design: Eight cohorts were studied: healthy, sham, healthy + MSA, healthy + gel, unilateral ureteral obstruction (UUO), UUO + MSA/IL-10, UUO + gel, UUO + gel/IL-10. Each group included n=4, time-points 7, 21 and 35 days. 15 mL of MSA, gel, or gel/IL-10 was injected into the left kidney via 3 days after the initial obstruction or sham operation. Histological Analysis: Paraffin-embedded tissue was evaluated for histological analysis. Immunohistochemistry (IHC) was used to stain for macrophages via CD68 and apoptotic cells via TUNEL. Trichrome stain was used to evaluate fibrosis. For the IHC, 20 pictures were taken at 400x magnification, the positively stained cells were counted and the cumulative area measured to obtain #cells/mm2. For the Trichrome stain, the entire area was photographed at 20x magnification and software was used to quantify the % area of fibrosis. ANOVA with Tukey analysis was used to determine significance.
Result: Macrophage infiltration and apoptosis were significantly reduced in the treatment groups at day 21 and 35. By day 35, adding the IL-10 via gel injection reduced macrophage infiltration more than IL-10 alone and IL-10 alone did not reduce apoptosis. Fibrosis was decreased by day 35 in all treatment groups.

HIGHER (60%) VS. LOWER (30%) INITIAL OXYGEN INSPIRATORY FRACTION FOR VENTILATION OF PRETERM INFANTS IN THE DELIVERY ROOM: A RANDOMIZED, DOUBLE BLINDED, PILOT STUDY.

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Background: A recent meta-analysis1 has shown that the use of higher initial inspiratory fraction of oxygen (FiO2 >50%) vs. lower (FiO2 <50%) did not influence relevant clinical outcomes although a non-significant tendency towards increased mortality was assessed. We hypothesized that using a high (60%) vs. low (30%) initial FiO2 during postnatal resuscitation would increase the need for tracheal intubation in the DR in preterm infants. As secondary outcomes we evaluated mortality, and survivors' incidence of BPD, ROP, PDA and IPVH.
Method: Double-blinded, bi-center trial recruiting preterm babies <30weeks' gestation needing ventilation after birth. Patients were randomly allocated to LowOx (FiO2:30%) or HiOx (FiO2:60%). FiO2 was titrated according to SpO2 readings following Dawson's nomogram2. Oxidative stress biomarkers were analyzed in blood and urine using validated UPLC/MS/MS.
Result: Shown in table 1. No differences for intubation rate in DR were found. Mortality was higher in HiOx but not significant. Among survivors no difference in the incidence of long-term complications were found. GSH/GSSG ratio at 72 hrs was higher in the LowOx group but not significant. Urinary isofurans were higher in HiOx group at 24 hrs but not significant.
Conclusions: Initial ventilation with lower (30%) versus higher (60%) oxygen of preterm infants did not influence short and long-term clinical or biochemical outcomes. However, a tendency towards lower mortality in the low oxygen group prompts further research. 1Brown JVE, et al PLOS ONE 2013; 2Dawson JA, et al Pediatrics 2010.

NEUROLOGICAL INJURY AFTER NEONATAL CARDIAC SURGERY: A RANDOMIZED CONTROLLED TRIAL OF TWO PERFUSION TECHNIQUES

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Background: Complex neonatal cardiac surgery is associated with cerebral injury. Especially aortic arch repair, requiring either deep hypothermic circulatory arrest(DHCA) or antegrade cerebral perfusion(ACP), entail a high risk of peri-operative injury. It is unknown, whether ACP results in less cerebral injury than DHCA.
Patients and methods: Neonates with an aortic arch obstruction presenting for uni- or biventricular repair, were randomized to undergo surgery with either DHCA or ACP. Pre-operatively and one week after surgery, magnetic resonance imaging(MRI) was performed and the presence or absence of new cerebral injury was scored, as primary outcome.
Results were entered into a sequential analysis, which allows for immediate data analysis as study results accumulate. Multiple secondary outcomes were studied, including neurodevelopment at two years of age.
Results: Thirty-seven neonates were enrolled and in 36, pre- and postoperative MRIs were performed; one patient died during hospital stay(2.7%). When the result of the 36th patient was entered into the sequential analysis, it was clear that there was no difference between DHCA and ACP in terms of new cerebral injury(and was also not to be expected in a larger group). Pre-operatively, 50% of patients had evidence of cerebral injury. Postoperatively,14/18(78%) of DHCA patients had new injury, versus 13/18(72%) of ACP(p=0.66). White matter injury(WMI) was the most common type of injury before and after surgery in both groups, but central infarctions occurred exclusively after ACP(0 vs. 6/18[33%]; p=0.02). Early cognitive and motor outcome at 24 months was similar for the two groups (p=0×28 and p=0.25, respectively). Additional analysis revealed lower postoperative arterial pCO2 as risk factor for new WMI(p=0.04).
Conclusions: In this group of neonates undergoing complex cardiac surgery, ACP did not decrease peri-operative cerebral injury, compared to DHCA. Both techniques resulted in a high incidence of new WMI, but central infarctions occurred exclusively following ACP.

INCREASING AMINO ACID INTAKE DURING PARENTERAL NUTRITION (PN) AND PROTEIN INTAKE DURING ENTERAL NUTRITION (EN) IN EXTREMELY LOW BIRTH WEIGHT INFANTS (ELBWI) DO NOT IMPROVE SHORT-TERM GROWTH: A RANDOMIZED CLINICAL TRIAL

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Background: Early parenteral amino acid (AA) administration has become part of routine care in preterm infants. We recently showed that targeting PN to 4 vs. 2.5 g/kg/d AA did not improve growth and neurodevelopment (Burattini et al. JP 2013). The present study aimed at increasing AA intake from 2.5 (standard of care) to 3.5 g/kg/d during PN and also at increasing protein intake during EN by 1 extra g/kg/d. Two groups of preterm infants were thus randomized to receive a standard protein intake (StP) or 1 additional g/kg/d of AA/Protein (HiP) starting from birth to 1800 g body weight.
Patients and Methods: We randomized preterms with BW 500-1249 g to StP (PN=2.5 AA, EN=3.6 protein g/kg/d) or HiP (PN=3.5 AA, EN= 4.6 protein g/kg/d). The AA solution was TrophAmine 6% (Baxter) and the protein supplement during EN was a whey protein preparation (Beneprotein Nestlè). EN was either with fortified human milk or infant milk formula. Non-protein energy (NPE) was similar between groups by study design as the study consisted soley in an AA/Protein supplementation. The primary outcome was weight gain from birth to 1800 g and was powered to detect 1 g/kg/d difference with a 95% power.
Results: 226 patients were screened, 62 did not meet the inclusion criteria or were lost before 36w PMA, 164 were evaluated (82 StP and 82 HiP). Study groups had similar demographics and clinical characteristics at birth. Cumulative Nutrition Intakes from birth to 1800 g are reported below:

	StP	HiP	p
Fluid Intake (ml/kg)	7130±1763	7862±1715	0.010
AA/Protein Intake (g/kg)	178±42	223±45	<0.0001
Carbohydrate Intake (g/kg)	742±177	745±161	0.892
Lipid Intake (g/kg)	307±84	299±65	0.488
NPE Intake (kcal/kg)	5625±1387	5562±1172	0.756

Blood Urea was higher in StP than HiP both during PN and EN (p=0.004). Bicarbonate treatment was required significantly more often for HiP than StP patients (p=0.038).
Growth and body size at 36w are reported below:

	StP	HiP	p
Age at Max WT Loss (d)	4.4±2.2	4.0±1.5	0.542
Max WT Loss (%BW)	12.3±5.5	13.6±6.2	0.151
Time from Birth to Reg.BW (d)	12.2±5.1	12.7±5.0	0.593
Age at 1800 (d)	54±12	54±11	0.840
WT Gain from Birth to 1800g (g/kg/d)	12.3±1.6	12.6±1.7	0.294
WT at 36w PMA (g)	1958±345	1936±299	0.668
Head Circumference at 36w PMA (cm)	30.8±1.6	30.6±1.2	0.380
Total Length at 36w PMA (cm)	42.8±2.0	42.7±2.3	0.697

Conclusions: This is the first RCT on a combined protein supplementation firstly during PN and then during EN. Increasing protein intake of about 1 g/kg/d from birth to 1800 g BW in ELBWI did not improve growth and body size at 36w. Our results do not support the practice of adding AA/Protein above our current intakes (StP). The neurodevelopmental follow-up of the study patients is in progress.

EARLY MACROPHAGE ACTIVATION STATUS IN PRETERM BABIES: ROLE IN BRONCHOPULMONARY DYSPLASIA DEVELOPMENT.

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Background: among the macrophage population, classically activated (CAM) are known to be active in the early inflammatory response whilst alternatively activated (AAM) are known to promote angiogenesis, fibrosis and tissue remodeling in the secondary phase. Their role in bronchopulmonary dysplasia (BPD) remains unknown. A previous study in a rodent model of BPD has shown that treatment with a myeloid/macrophage progenitor normalizes alveolar and vascular structures. Furthermore, preliminary data in animals show an increase in bone marrow AAM/CAM ratio during the early stage of lung injury with a decrease in CAM when BPD has been established. Aim: to analyze AAM/CAM ratio in blood and bronchoalveolar lavage (BAL) of preterm babies at 48- 72 hours of life and to study the correlation with BPD development at 28 days of life.
Methods: data from preterm newborns admitted to a level III NICU (Padova-Italy) from January to August 2013 were collected. Exclusion criteria were: major malformations and cardiovascular defects, early onset sepsis and maternal chorioamnionitis. A blood sample (0.2 ml) and a BAL sample (only in intubated patients, n=16) were collected at 48-72 hours of life. The samples were analyzed by flow-cytometry to identify monocytes (CD33+/SSlow) and, among these, AAM (CD14+/CD16+) and CAM (CD14++/CD16-). At 28 days of life, BPD development was clinically assessed. Data are presented as means and standard deviations; significance level was set at $p<0.05$.
Result: a total of 42 newborns were included, 10 of them developed BPD (Table1). Higher levels of CAM in blood at 42-72 hours of life correlate with higher birth weight and gestational age, with reduced length of mechanical ventilation support and reduced length of O2 treatment. In blood samples, an increased AAM/CAM ratio (0,18±0,12; vs 0,11±0,06; p 0,02) with reduced CAM (57,65±17,44; vs 66,85±10,34; p 0,04) is associated with BPD development. BAL shows no significant difference in AAM/CAM ratio between BPD and control group (0,44±0,24 vs 0,57±0,50).
Conclusions: higher gestational age and neonatal weight are associated with higher levels of CAM in blood. This could be the result of a more mature and developed macrophage system, capable to push undifferentiated macrophages toward a classical activation pathway. According to our data these patients are the ones who need a shorter O2 treatment period and less days of mechanical ventilation support. Patients that do not develop BPD have a lower AAM/CAM ratio in blood in the first days of life, with an increased CAM level. This shift in macrophage population in the blood could represent and appropriate early reaction to the injury with inflammatory cells recruitment. Neonates that can not promote these self mechanisms of defense and have lower CAM levels could be at higher risk to develop BPD. To better understand the role of the macrophages in lung, we have also analyzed their ratio in BAL (withdrawn only from the 16 intubated patients). At the moment no difference has been found between the groups. Further analysis on a bigger sample will provide us a more detailed insight on the relation between this self-defense mechanism and the development of BPD.

DOPAMINE IS ASSOCIATED WITH IMPAIRED CEREBRAL AUTREGULATION IN PRETERM INFANTS

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Background: Dopamine is the most commonly used vasopressor in clinical neonatology. Dopamine is effective in raising the blood pressure in newborn infants and is used in hypotensive newborns with the aim of maintaining an adequate cerebral blood flow and oxygenation of the brain. Dopamine has, however, not been shown to improve the neurological outcome, and in some observational studies hypotensive infants who were treated with dopamine did worse than those who were left untreated. We therefore hypothesized that dopamine affects cerebral autoregulation, and thereby makes infants who remain hypotensive in spite of dopamine more vulnerable to brain ischaemia.
Patients and Methods: We had previously monitored cerebral oxygenation index (OI) and mean arterial blood pressure (MAP) for 1-3 hrs in 60 preterm infants (male/female:36/24) with a mean gestational age of 27±1.3 weeks and a mean birth weight of 908±258g. Ten epochs (range: 5-15 epochs) of ten minutes measurements were obtained from each infant. The cerebral autoregulation was described by the correlation between OI and MAP (COx). COx was calculated for a period of five minutes with a one-minute sliding window resulting in six correlation coefficients in each epoch. The mean of these six values gave the COx-value for each epoch. Furthermore, to quantify the oxygenation-blood pressure reactivity the regression coefficient was calculated for each epoch in the same manner.
Result: Thirteen infants received dopamine during the monitoring period and 47 did not. COx for those who received dopamine were higher compared to those who were not treated with dopamine indicating an impairment of autoregulation. This difference in COx was seen in the hypotensive infants defined as MAP below the gestational age (COx: 0.432±0.186 vs. 0.111±0.131, t-test: $p=0.005$) and the normotensive infants (COx: 0.348±0.121 vs. 0.093±0.135, t-test: $p<0.001$). Furthermore, the dopamine group had higher oxygenation-blood pressure reactivity compared to the non-dopamine group. This was again true in the hypotensive infants (regression coefficient: 0.262±0.117 vs. 0.030±0.050, t-test: $p=0.001$) and normotensive infants (regression coefficient: 0.173±0.106 vs. 0.056±0.118, t-test: $p=0.005$).
Conclusions: Both hypotensive and normotensive preterm infants who were treated with dopamine had an impaired autoregulation and were more pressure-passive compared to those who were not treated with dopamine. This may be explained by a direct effect of dopamine on the cerebral autoregulation or that those infants who were most ill and therefore had impaired autoregulation were those infants who were treated with dopamine.

THE POLYUNSATURATED FATTY ACID PROFILES OF HIGH RISK VERSUS NORMAL PREGNANT WOMEN AT BOOKING

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Background: It is now clear that nutrition for brain growth is quite different to that of the body. The brain is made largely of highly specialised fats. The major "essential fats" are arachidonic (AA) and docosahexaenoic (DHA) acids. Of the two, DHA is most limiting in the diet and its proportion in certain common foods has been declining. DHA is irreplaceable in the structure and function of the neurones and signalling systems of the braini. Babies at greatest risk to neurodevelopmental disorder are those born most preterm and lowest birthweights. Their mothers are more likely to be in high risk pregnancy groups. Our preliminary evidence shows that those at greatest risk have the lowest tissue levels of AA and DHA. The Barker Hypothesis identifies poor maternal-fetal nutrition being responsible for prenatal programming giving rise to the risk of diabetes, heart disease and stroke in later life. The bulk of neuronal development takes place before birth and disorder or damage during this process is life-long.
Methods: 300 pregnant women in high risk pregnancies or controls were recruited into a double blind placebo controlled study examining the effect of fish oil supplementation in high risk pregnant women on their lipid profiles and infant outcomes. At recruitment, their booking bloods were taken. Four groups were studied; normal healthy controls (NHC), gestational diabetics (GDM) and those at risk of pre-eclampsia (PET) or of delivering a low birthweight infant (LBW). Their booking bloods at recruitment prior to supplementation was analysed for the lipid profiles by sub-group.
Result: The n-3 and n-6 polyunsaturated fatty acids (PUFAs) were analysed and their ratios with linoleic acid (LA), an n-6 PUFA. The mean values of AA (n-6PUFA) was highest in NHCs, 13.06 (SD 1.51) compared to the LBW 11.90 (SD 1.61) and GDM 11.42 (SD 1.70) groups. The mean DHA (n-3 PUFA) levels in the NHCs was 7.65 (SD 1.10), LBW 6.97 (SD 1.62) and GDM 6.76 (SD 1.94). The LA/AA ratio showed the same trends and was lowest in the NHC group mean 1.07 (SD 0.23) and highest in GDMs 1.30 (SD 0.26) whilst the LA/DHA ratio in NHCs was 2.89 (SD 0.50) and in GDMs 3.71 (SD 1.36). The NHCs had the lowest mean monounsaturated and saturated fatty acids levels also when compared to the other sub-groups.
Conclusions: There are definite differences in lipid profiles of women in normal control pregnancies compared to those at risk of PET, LBW delivery or gestational diabetes early in pregnancy indicative of pre-pregnancy dietary status. These results may help identify women who would benefit from targeted antenatal supplementation.
(i) Crawford MA, Leigh Broadhurst C, Guest M, Nagar A, Wang Y, Ghebremeskel K, Schmidt WF (2013). A quantum theory for the irreplaceable role of docosahexaenoic acid in neural cell signaling throughout evolution Prostaglandins Leukot Essent Fatty Acids (PLEFA); 88(1):5-13.

CHANGES IN INTERLEUKIN-6 AND IMMUNOGLOBULIN-E LEVELS WITH CLINICAL IMPROVEMENT IN ASTHMATIC CHILDREN USING TRADITIONAL CHINESE ACUPUNCTURE

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Background: Bronchial asthma is one of the most common illnesses in children. The chronicity of the disease and the fear of steroid therapy cause many patients to seek alternative methods of treatment such as acupuncture. Immunoglobulin-E (IgE) is a marker of allergy and interleukin-6 (IL-6) is a marker of inflammation, so in combination they may indicate an improvement of the asthma of the child.
Objectives: To study changes in IL-6 and IgE levels and its relation to improvement in pulmonary function in asthmatic children treated with traditional Chinese acupuncture. Methods. We measured IgE, IL-6, and eosinophilic counts in peripheral blood and pulmonary function (VC%,FVC%,FEV1%,FEF25-75%,FEF25%,FEF50%,FEF75%,PEF%) before and after a series of traditional Chinese acupuncture sessions. The acupuncture points selected for bronchial asthma were used. Twelve sessions was given (3 times per week for 4 weeks). Each session lasted 20 minutes. Treatment by acupuncture was decided by the responsible clinician and the researcher. Data from 30 children aged 8-15 years was collected retrospectively from clinical records.
Results: In 11 of 30 patients there was a decrease in both IL6 and IgE. In these cases there was also statistically significant improvements in pulmonary function: VC% ($p=0.012$), FVC% ($p=0.03$),FEV1%($p=0.02$),FEF25 75%($p=0.002$), PEF%($p=0.002$), FEF25% ($p=0.004$), FEF50%($p<0.001$), FEF75% ($p=0.005$). In nine children, IL6 only decreased, and in eight children IgE only decreased, and in two children neither of them decreased. There was a significant decrease in eosinophilic count ($p<0.001$), a significant improvement in clinical symptoms and signs, and decrease in the use of medications. Conclusion. Asthmatic children treated with traditional Chinese acupuncture and who showed a decrease in IL-6 as well as IgE in peripheral blood also showed improvement in pulmonary function.

SUSTAINED LUNG INFLATION IN THE DELIVERY ROOM IN PRETERM INFANTS AT HIGH RISK OF RESPIRATORY DISTRESS SYNDROME (SLI STUDY): A RANDOMIZED CONTROLLED TRIAL.

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Background: Some studies suggested that the early sustained lung inflation (SLI) procedure is effective in decreasing the need of mechanical ventilation (MV) and improving respiratory outcome in preterm infants. We planned the present randomized controlled trial to confirm or refute these findings.
Methods: In this multicenter RCT all infants born at 25+0-28+6 weeks' gestation at high risk of respiratory distress syndrome (RDS) were randomized to receive the SLI maneuver (peak pressure = 25 cm H2O for 15 seconds) followed by nasal continuous positive airway pressure (NCPAP= 5cmH2O) or NCPAP alone (5 cmH2O) in the delivery room. SLI and NCPAP will be delivered using a neonatal face mask and a T-piece ventilator (Fisher & Paykel®). The primary endpoint was the need of MV in the first 72 hours of life.
Results: We studied 291 infants: 148 were randomized to receive the SLI maneuver (GA 26.8±1.1 wks; BW 893±241 g) and 143 were controls (GA 26.8±1.2 wks; BW 894±247 g). The need of MV in the first 72 hours of life was reduced by SLI procedure (53 vs. 65%; adjusted odds ratio by gestational age and center 0.57; 95% CI, 0.33 to 0.96; P=0.034). The risk of MV in the first 72 hours of life was affected also by gestational age (27-28 vs. 25-26 wks: adjusted odds ratio, 0.19; 95% CI, 0.10 to 0.35; P<0.0001).
Conclusions: Our data demonstrate that the SLI procedure by face mask was effective in lowering the need of MV in preterm infants at high risk of RDS and can contribute to decrease the ventilator-induced lung injury. Trial registration ClinicalTrials.gov Identifier: NCT01440868.

RANDOMIZED CONTROLLED STUDY COMPARING A NEONATAL-SIZED I-GEL AND THE LARYNGEAL MASK AIRWAY IN A NEONATAL RESUSCITATION MANNEQUIN

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Background: ILCOR's 2010 guideline recommends that a laryngeal mask should be considered for ventilating newborns weighing more than 2000 g or delivered after 34 weeks gestation during resuscitation if facemask ventilation is unsuccessful and tracheal intubation is unsuccessful or unfeasible. The i-gelTM (Intersurgical Ltd., Wokingham, UK), which is made of a soft, gel-like elastomer and has a non-inflatable cuff, is a relatively new disposable supraglottic airway device. Although several studies have reported the i-gel to be safe and effective for airway management in children, the device's effectiveness and safety in newborns has been unclear. Objective: The purpose of this research was to compare the performance of the neonatal-sized i-gel with a conventional laryngeal mask airway (LMA) in a neonatal mannequin to assess the benefits of the i-gel for neonatal airway management.
Methods and Study Design: Healthcare providers and nursing students who participated in the Japanese version of the neonatal cardiopulmonary resuscitation course (NCPR) were randomly divided into two groups: the LMA SolusTM (Intersurgical Ltd., Wokingham, UK) group (LMA group) and the neonatal-sized i-gel group (i-gel group). Random assignment was performed by means of a computer-generated list, and the manufacturer's instructions for the device in each group were read to the participants before insertion. Participants then attempted to insert the assigned device into the neonatal resuscitation mannequin. The time from the beginning of insertion to the point when participants self-judged a successful insertion was measured. The flow and pressure in the neonatal mannequin lung by ventilation with a self-inflating bag was measured using a respiratory function monitor. An insertion success was defined if lung pressure was above 20 mmHg. Measurement of insertion time and assessment of insertion success were performed by a non-clinical investigator blinded to the study conditions.
Result: A total of 43 medical experts of the following professions took part in this research: 11 doctors, 11 midwives, 19 nurses, and 2 nursing students. The successful rate of insertion was significantly higher in the i-gel group (95%, 21/22) than in the LMA group (24%, 5/21) ($P<0.01$). The insertion time (median [IQR]) was significantly shorter in the i-gel group (8.45 (4.725 [3.80-21.50])) than in the LMA group (18.2 (4.15 [13.60-35.50])) ($P<0.001$).
Conclusions: In this study, the success rate in the i-gel group was significantly higher than in the LMA group. Moreover, the insertion time needed in the i-gel group was significantly shorter than in the LMA group. These results suggest that the i-gel is a more useful device than the LMA, which is recommended in the guidelines, especially during time-sensitive neonatal resuscitation.

RESPIRATORY RATE DURING THE FIRST 24 HOURS OF LIFE IN HEALTHY TERM INFANTS

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It is commonly taught that a respiratory rate (RR) above 60 per minute may be a cause for concern, but after careful review of the literature it appears that this notion is based on repetitions from one textbook to the next, based on a limited number of unstructured observations before the 1960s. To our knowledge, a normal range of RR in full-term newborns has never been scientifically established. The aim of this study was to determine a normal range of RR in healthy infants born at term during the first 24 hours of life, paying careful attention to age (hours), nursing condition (cot vs. with mother), body temperature and wake/sleep status.
Patients And Methods: When workload in the maternity hospital permitted, 1000 infants were recruited consecutively. Infants with heavily stained amniotic fluid, birth asphyxia, birth defects, neurologic morbidity or exposed to medication (given to mother or infant) which may affect respiration, were excluded. The infants stayed with their mother, either in her bed or in a cot. When the newborn had been in a quiet state for 10 minutes, a nurse assistant or midwife counted the respiratory rate for a full 60 seconds by placing a stethoscope in front of the baby's nostrils / mouth. It was noted whether the baby was awake or asleep. If the baby started crying, the whole registration was postponed until a new quiet state was established. Apneas were considered normal and did not influence the registration. Heart rate, peripheral and core body temperatures and room temperature were also recorded. The Medical Birth Registry of Norway provided data on pregnancy, delivery and infant characteristics.
Results: Of 1000 consecutively born infants, 882 were eligible according to the study criteria. Mean (SD) gestational age was 40 (1.2) weeks and mean birth weight 3592 (479) grams, and 52% were boys. The mean (SD) age of the mothers was 29.9 (5.3) years and median number of previous births (range) was one (0-7). 10% had smoked during pregnancy, 1% had experienced preeclampsia and 2% had diabetes or gestational diabetes. Median respiratory rates (interquartile range) were: 46 (40-52) at age two hours, 42 (38-48) at four, 42 (38-48) at eight, 44 (40-50) at 16 and 44 (40-50) at 24 hours. The corresponding 95th percentiles of respiratory rate were: 64, 58, 59, 60 and 58.
Implications: Centiles established from this large systematic study provide a scientific basis for identifying newborns with abnormal RR and thereby identify infants with potentially severe disease, e.g. infections or congenital heart disease.

TIDAL VOLUME MEASUREMENTS DURING MASK VENTILATION VERSUS ENDOTRACHEAL VENTILATION

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Introduction/Background: Respiratory function monitoring has been used to improve mask ventilation at birth. We do not know what the appropriate range of tidal volumes should be at birth, but a similar range (4-8 mL/kg) as used in ventilated infants in the NICU has been recommended. It is possible that mask ventilation causes pressurization of the pharynx and contributes to the measured volume. In this observational study we have performed tidal volume measurements during positive pressure ventilation (PPV) of infants < 32 weeks of gestation before and after intubation directly after birth. Patients and **Methods:** All recordings using face mask ventilation were reviewed and infants who were intubated in the DR were included. Pressures given and tidal volumes 2 minutes before intubation and 2 minutes after intubation were measured and analyzed on a breath to breath basis. Inflations where breathing coincided were excluded.
Result: In total 10/206 recorded infants were intubated in the DR (50% males, median (range) GA 26 (24-31) weeks, mean (SD) birth weight 822 (346) grams). In total 1586 breath were analysed (843 before intubation and 743 after intubation). Peak inflation pressures were not significantly different before and after birth (28.0 (6.1) vs. 27.9 (6.0) cmH2O. Positive end expiratory pressures were significantly different before and after intubation (3.8 (3.3) vs. 5.1 (3.9) cmH2O; p<0.0001). A larger expiratory tidal volume was measured during mask ventilation when compared to after intubation (13.8 (7.9) vs. 9.9 (8.2) mL/kg (p<0.0001)). Leak was significantly different before- vs. after intubation median (IQR (0.0 (0.0-29.5) vs. (0.0 (0.0-0.0))%; p=0.01).
Conclusions: With similar pressures higher expiratory tidal volumes are measured during mask ventilation than during endotracheal ventilation. It is possible that pharyngeal pressurization during mask ventilation has to be taken into account when targeting volumes during mask ventilation.

PRECISION AND ACCURACY OF NELLCOR AND MASIMO PULSE OXIMETERS AT LOW OXYGEN SATURATIONS IN A LAMB MODEL

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Background: Recommendations for oxygen treatment in the delivery room are based on an oxygen saturation (SpO2) reference range. SpO2 values < 70 % are common in the first minutes of life. Accuracy of SpO2 measurement against the'gold standard 'arterial blood (SaO2) gas co-oximetry has not been determined in this range. The aim of this study was to determine the accuracy of Nellcor and Masimo oximeters at SaO2 <70%.
Method: Prospective study in ventilated anaesthetised normothermic newly born lambs with a carotid artery catheter in situ. Ventilation was adjusted to achieve saturations<70%. Nellcor (Oxi-Max 600 with Max-N sensor) and Masimo (Rad 4 with LNOP sensor) sensors were applied to the right forelimb. The location of sensors, proximal or distal was alternated. A Posey wrap prevented cross talk between sensors. Arterial blood samples were collected from the carotid artery at 5 minute intervals and concurrent oximeter readings were recorded. We used Bland-Altman analysis to determine precision and accuracy of each oximeter.
Result: 17 lambs were studied, 165 measurements were obtained. There were 123 measurements when SaO2 < 70%. The mean SpO2 - SaO2 (±1.96 SD) was 17(13)% for the Nellcor and 13(13)% for the Masimo oximeter. In clinical practice this means that when either oximeter displays a low SpO2 it is likely that the 'true' SaO2 is lower.
Conclusions: At SaO2<70 both monitors overestimated oxygen saturations compared to the gold standard.

IS THE COLOUR OF AN INFANT'S TONGUE A USEFUL CLINICAL SIGN TO DETERMINE THE NEED TO PROVIDE SUPPLEMENTAL OXYGEN IN THE DELIVERY ROOM?

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Background: It may take several minutes for infants to become pink after birth. An oxygen saturation (SpO2) <70% 3 min after birth is regarded as an indication to commence supplemental oxygen (Australian Resuscitation Council 2010). However, pulse oximetry is not available in many parts of the world. Skin colour has been shown to be a poor indicator of oxygen saturation. Our aim was to determine if the colour of an infant's tongue might be a better sign that supplemental oxygen is required. Method:Prospective observational study of infants delivered by caesarean section. Masimo (Rad 4 with LNOP sensor) sensor was applied to the infant's right wrist. Simultaneous recording of oxygen saturation level and visual assessment of the tongue were made at 1-7 minutes and at the 10th minute. Clinicians were asked whether the tongue was 'pink' or 'not pink'. A ROC-curve was generated to describe the relationship between SpO2 and colour of the infant's tongue.
Result: 68 infants were studied, 271 paired assessments were obtained. 45 clinicians, 38 midwives and 7 paediatricians, were recruited for the assessments. Infants mean (SD) birth weight was 3214 (545) grams and the mean (SD) gestational age was 38 (2) weeks. The area under the curve was 0.88. Tongue colour has sensitivity of 26%, specificity 96%, positive predictive value 61%, and negative predictive value 84% for detecting SpO2 <70%.
Conclusions: Tongue colour is a specific but insensitive sign to indicate when SpO2 <70%. When the tongue is pink it is likely that the infant does not require supplemental oxygen.

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Abstract Book

Poster Presentations

BREAST MILK FROM MOTHERS OF EXTREMELY PREMATURE INFANTS: VARIABILITY IN PROTEIN AND FAT CONTENT.

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Background: Breast milk (BM) is the preferred basis of nutrition for infants, including those born prematurely. To meet nutritional requirements for preterm infants, it is necessary to add human milk fortifier to BM. Information about energy and protein contents of BM is therefore desirable to avoid risk of undernutrition or overnutrition of the preterm infant. However, data of nutrient content in mother´s own BM given to extremely preterm infants (born<27 weeks of gestation) are limited and needs to be further investigated. The aim of this study was to describe the content of energy and macronutrients over time in BM from mothers who delivered extremely premature infants.
Method: Information of analyzed BM samples from Swedish mothers giving birth prematurely before 27 weeks of gestation during 2004-2007 was obtained from hospital records. Nutritional content of BM was determined using mid-infrared analysis (Milkoscan 4000 and Milcoscanâ„¢133). BM samples were divided into two groups, early BM (<28 days postpartum) and mature BM (>28 days postpartum). Mean and standard deviation (SD) were used to describe the nutrient content in the mother's milk and Paired Samples T-test was used in statistical analysis between early and mature BM.
Results: In total, 821 samples from 256 mothers were analyzed. Numbers of analyzed BM samples from each mother were skewed; median 2.0 (range 1.0-16.0). The first BM sample was produced and analyzed at 4 postpartum days and the last BM sample was produced and analyzed at 112 postpartum days. Nutritional content (mean±SD) in 100 mL early BM samples (n=380), was 1.8±0.4g for protein, 4.0±0.9g for fat, 6.8±0.4g for lactose and energy content was 73±9.2 kcal. Nutritional content in 100 mL mature BM samples (n=441), was 1.4±0.2g for protein, 3.9±0.7g for fat, 7.0±0.2g for lactose and the energy content was 70±7.2 kcal. Protein content in mature BM decreased biweekly until 57 days postpartum, thereafter more stabilized protein content was seen. Protein content (10th-90th percentile; 1.2-2.4 g/100 mL) decreased significantly between early and mature BM (p<0.001), reaching its lowest level after 57 postpartum days. Fat content showed the highest variability between mothers (10th-90th percentile; 2.9 - 5.0 g/100 mL), which was also reflected in variable energy content (10th-90th percentile; 61-85 kcal/100 mL).
Conclusion: Protein content in early BM is significantly higher than in mature BM. Protein content decreased over time and reached its lowest level after 57 postpartum days. BM fat and energy content was highly variable between BM samples. Weekly analyses of BM macronutrient content during the first 28 postpartum days and biweekly analyses after 28 postpartum days would therefore allow a more individualized nutritional support to this vulnerable group of infants.

PROTEIN CONTENT IN EXPRESSED BREAST MILK. INFLUENCE OF TIME INTERVALS BETWEEN BREAST MILK PUMPING IN MOTHERS OF PRETERM INFANTS

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Objective: Mothers may provide breast milk for their preterm infants for many weeks. After the first few weeks of life the milk is often fortified to increase protein content to promote faster growth. However, fortifiers based on cow milk might have side effects such as increased risk of necrotising enterocolitis, NEC. It is possible to measure the protein content in the expressed breast milk to optimize fortification; this is often done by measuring the protein content of the pooled milk from a 24 hour period. We investigated if the time interval between pumping influenced the milk protein concentration. We wanted to see 1) if we could reduce the use of fortifiers by selecting the milk with the highest protein content from the samples in a 30 hour period and 2) whether it is necessary to pool the expressed milk before analyzing the protein content. Design Ten healthy mothers who delivered sufficient milk for their infants on a daily basis were recruited in the study after informed consent. After instruction on standardized pumping technique, expressed breast milk was obtained from each mother over a 30 hour period at strictly planned and varying intervals between expressions: 2, 3, 4 and 6 hours. A different plan was used for each breast to increase the number of samples. 5 ml aliquot was frozen from the milk from both breasts. All samples were analyzed at the end of the study using Human Milk Analyzer from Miris AB, Sweden.
Results: The mothers were on average 25 days (min=10 days, max. =42 days) post partum. A total of 154 milk samples were analyzed. Average protein concentration in the expressed milk was 1.14 g/100 ml (SD=0.22, min= 0.5 g/100ml, max. =1.7 gram/100 ml). Univariate analysis was performed using ANOVA. Protein content varied significantly between the mothers ($p< 0.0001$). The variation within the milk samples from the individual mothers was very low (mean square=0.006 gram/100ml) during the 30 hour period and in a multivariate linear model including the mothers and the four different time intervals between the breast pumpings we found no effect on the protein content from the time intervals ($p=0.86$).
Conclusion: The protein content in expressed breast milk is not influenced by the time intervals between breast pumping during a 30 hour period. A single sample collected at any time during the day is representative for the protein content of a premature infant's mother's milk.

DONOR HUMAN MILK FOR INFANTS OF MUSLIM PARENTS

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Background and aims: Donor human milk (DHM) is expressed breastmilk provided to be fed to another mother's child. DHM has been shown to be superior to formula milk in the prevention of necrotising enterocolitis in preterm infants. Additional benefits may also include improvements in long term outcomes such as cardiovascular health, cognition and bone mineral content. A human milk bank collects, screens, stores, processes and distributes DHM. There are currently over 500 milk banks worldwide. The introduction of donor milk banks to countries with large Muslim populations has been complicated by the Islamic concept of milk kinship. The sharing of milk, historically in the form of a wet nurse, is believed to create kinship ties between the families of the donor and the recipient. Marriage between members of these two families is then prohibited. Neonatal units in Kuwait and Malaysia have resolved this by ensuring that donor and recipient mothers meet before milk is given. However in European countries standard practice is to give anonymised DHM. A 2004 ruling by the European Council for Fatwa and Research decreed that there was no barrier in Islam either to establishing milk banks or using anonymised donor milk provided by them. It is not clear whether beliefs about milk kinship affect current practice in neonatal units in Europe. We investigated whether Muslim parents in the United Kingdom expressed concerns about accepting DHM for their preterm infant.
Methods: We contacted all 17 human milk banks in the United Kingdom by email and telephone to conduct a semi-structured questionnaire. We asked them if Muslim parents had ever expressed concerns about DHM, and to provide details if this had been the case.
Result: 17 out of 17 milk banks replied to the survey. Six milk banks (35%) had never had DHM refused by Muslim parents. Eleven (65%) milk banks had DHM refused initially by Muslim parents. In four milk banks out of this group, it had occurred on two occasions or fewer. One milk bank replied that nurses' knowledge about milk kinship might have lead to DHM not being offered to Muslim parents. Another stated that they thought clinical staff needed more education on this topic. To resolve the issue of milk kinship, two milk banks had provided pasteurised milk from a donor known to the infant's parents, after she had undergone the usual screening procedures. Two milk banks had provided DHM from the mother of a child of the same sex as the recipient. One milk bank had a specific policy in place for providing DHM for Muslim infants.
Conclusions: Concerns about milk kinship can very occasionally lead to DHM being refused initially by Muslim parents. Practice in these situations varies. Neonatal unit staff should be aware that Islamic faith is not necessarily a contra-indication to giving anonymised DHM to infants. Milk banks and neonatal units should develop guidelines to enable staff to help Muslim parents make informed choices about the use of DHM.

EARLY MOTHER'S OWN RAW MILK ADMINISTRATION COULD FAVOUR BREASTFEEDING IN HOSPITALIZED NEONATES

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Introduction/Background: Pasteurized and/or frozen mother's own milk can be preferred to raw milk in the NICU because of infectious or processing concerns, but there is no consensus yet. To our knowledge, the impact of limitations or delays in the use of mother's own raw milk on breastfeeding success has not been studied. Our aim was to assess whether early administration of mother's own raw milk is associated to breastfeeding continuation at discharge.
Patients and Methods: This prospective observational study was conducted in 2 French NICUs between May 2012 and February 2013. After informed parental consent, all hospitalised neonates intended to be breastfed were eligible. During the study, pasteurization of mother's milk was recommended by the competent authorities for infants aged of less than 33 weeks of gestational age (GA) and the use of mother's raw milk varied under centre policies, care giver judgements, and patient clinical conditions. The primary outcome was breastfeeding rate at discharge that was compared between neonates receiving at least some mother's own raw milk before day of life (DOL) 7 and those who did not. A logistic generalized estimating equation (GEE) regression was performed to account for the correlated data with children nested in NICUs (Intraclass Correlation Coefficient=0.01).
Results: In all, 329 patients were included. Their mean±SD GA was 33.6±3.7 weeks, birth weight (BW) 2043±863g and NICU stay 33±24 days. The sex ratio was 1.3 and the frequency of multiple births 24%. Mother's raw milk was given in 265 (80.5%) infants, between DOL 1 and 104 (median: 4). When compared to patients that did not received early mother's own raw milk (n=140), patients that received at least once mother's own raw milk before DOL 7 (n=189) had higher GA and BW with shorter NICU stay (34.7±3.3 versus 32.3±3.8 weeks, p<10-4; 2250±819 versus 1765±844g, p<10-4; 27±20 versus 40±27 days, p<10-4, respectively). Univariate analyses showed a significant association between the administration of mother's own raw milk before DOL 7 and the continuation of breastfeeding at discharge (OR=3.01, 95% CI : 1.73-5.22, p<10-4). Other co-factors significantly associated to breastfeeding at discharge were: GA (+1week : OR=1.17, 95% CI :1.08-1.27, p<10-4), BW (+100g : OR=1.06, 95%CI: 1.02-1.10, p=0.002) and duration of the NICU stay (+1week : OR=0.86, 95%CI :0.80-0.93, p<10-4), while gender and multiple births did not affect breastfeeding issue in our population. After adjustments for mean NICU stay and GA, the positive association between early mother's own milk administration and breastfeeding at discharge remained significant (aOR=2.33, 95% CI : 1.42-3.82, p<10-4). Conclusion(s) These novel results suggest that administration of mother's own milk during the first week of life could positively impact on breastfeeding continuation in hospitalized neonates, independently of their gestational age at birth and of the duration of their NICU stay. Future researches need to further assess the benefit/risk ratio of using early mother's raw milk. National and international evidence-based recommendations are required. Acknowledgements: This study was supported by research grants from the SICPA SA, the Société Académique Vaudoise, and MILUPA SA.

CHANGES AND CHALLENGES IN SUSTAINED BREAST-MILK FEEDING IN VERY PRETERM INFANTS - A POPULATION BASED COHORT STUDY

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Background: Breast milk is the optimal nutrition for very preterm infants and neonatal care should therefore promote breast milk production and breastfeeding. Prior studies indicate that breastfeeding rates drop after discharge from hospital. The aim was to study changes in breast-milk intake in very preterm infants between 36 and 40 weeks post menstrual age (PMA), a period when most preterm infants in Sweden are being discharged from hospital.
Method: The study was performed in a population based regional cohort consisting of 267 live-born very preterm infants (<32 weeks of gestational age) born in April 2011 to March 2012 in Stockholm, Sweden. At 36 weeks PMA, 229 (86%) were still alive. We included 196 (86%) infants that had a mother who wished to breastfeed, who had no medical contraindications, and with complete nutritional data at both week 36 and 40. Breast milk feeding was defined as (1) exclusive: infant eating directly from mother's breast or fully fed with mother's own expressed milk (tube/bottle), (2) partial: mother's own milk and formula or donor breast milk and (3) no breast milk: only formula and/or donor breast milk.
Results: At baseline, 156 infants (80%) were fed breast milk, of whom 92 (47%) were exclusively, and 64 (33%) partially breast milk fed. Infants born before 28 weeks (n=53) were at higher risk of not receiving any maternal milk at 36 weeks of PMA, 34% vs. 19% in infants born at 28-31 weeks (p=0.006) Between 36 and 40 weeks, the proportion of breast milk feeding decreased overall. Out of 92 exclusively breast milk-fed infants at 36 weeks, 66 (72%) were still exclusively breast milk fed at 40 weeks and 22 partially (24%). Among the 64 partially breast milk fed infants at 36 weeks, 43 (67%) did still receive maternal milk at 40 weeks. Four infants (6%) increased their breast milk intake from partial to exclusive during the same period. The proportion of infants born before 28 weeks that did not receive any maternal milk had increased to 43% vs. 29% in infants born at 28-31 weeks (p=0.06). Among 70 exclusively breast milk fed infants at 40 weeks PMA, 48 (69%) were exclusively breastfed directly from the mother's breast.
Conclusion: Most very preterm infants receive breast milk at 36 weeks of PMA. The decline in maternal breast milk intake between 36 and 40 weeks PMA is however significant. Further studies of very preterm infants and their mothers are needed to identify predictors of changes in breast milk intake at near-term age.

TELEPHONE-BASED SUPPORT INCREASES BOTH EXCLUSIVE AND PARTIAL BREASTFEEDING IN PRE-PREGNANT OBESE

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Background: Obese women (body mass index ³ 30 kg/m²) have difficulties in initiating and maintaining breastfeeding compared to normal weight women. Being born of an obese mother increases the risk of developing obesity in childhood and adulthood. Breastfed infants grow slower than formula fed counterparts and early growth rate is also linked to subsequent obesity and metabolic disease. The present study aimed to evaluate whether telephone-based intervention could increase the duration of exclusive and partial breastfeeding in obese women and thereby reduce offspring adiposity at six months.
Subjects and methods: We consecutively recruited dyads of obese mothers and their singleton, healthy, term infants. The women had participated in the Treatment of Obese Pregnant women (TOP) study at Hvidovre Hospital, and had received intervention, 1:1:1 (A: diet and exercise, B: exercise alone or C: controls), in order to minimize the weight gain during pregnancy (end-point: gestational weight gain < 5 kg). The women were randomized to six months breastfeeding support or control that included standard care. One International Board Certified Lactation Consultant carried out the support. The intervention was based on structured interviews, and consisted of nine scheduled supportive telephone calls. Exclusive breastfeeding was defined as breastfeeding only supplemented with vitamins, minerals and water. Partial breastfeeding was defined as breastfeeding along with formula and or complementary feeding. Any breastfeeding was the duration of exclusive and partial breastfeeding together.
Results: 226 dyads were randomized, 108 to breastfeeding support and 118 to control group. At six months there were 207 in study, 105 support in the support group and 102 in the control group. The support group breastfed exclusively for a mean of 92 (2-185) days, compared to 68 (1-102) days for controls (p=0.003). Any breastfeeding was maintained on average 135 (2-185) days for the support group versus 101 (1-185) days for controls (p=0.002). Support increased the adjusted odds ratios for exclusive breastfeeding at three months to 2.45 [1.36, 4.41] (p=0.003) and to 2.25 [1.24, 4.08] (p=0.008) for partial breastfeeding at six months. Cox regression demonstrated an overall better breastfeeding rate in the intervention group for both exclusive (p=0.032) and any breastfeeding (p=0.02). Although days of exclusive breastfeeding were inversely associated with weight ß - 4.39 g/day [-0.66,-8,11] (p=0.021) and length ß - 0. 012 cm/day [-0.004,-0.02] (p=0.004) at six months, the breastfeeding support did not have a significant effect on infant weight, height and adiposity at six months (n=192). TOP study intervention did neither affect breastfeeding duration nor infant weight and length (birth and six months post partum).
Conclusion: Telephone-based advisory support prolongs both exclusive and partial breastfeeding in obese women. No association between intervention and infant adiposity was observed but the duration of exclusive breastfeeding was inversely associated with infant weight and length at six months. The data indicate that breastfeeding diminishes growth rate in obese mothers offspring, which may be related to reduced incidence of childhood obesity and metabolic long-term morbidity.

EARLY DISCHARGE AND BREASTFEEDING CAN BE PROMOTED IN VERY PRETERM INFANTS

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Background and aims: During the last years, in clinical practice, we have actively supported mothers to preterm infants to breastfeed. Secondly, our aim has been to discharge the infants at around 35 gestational weeks (gw). We studied retrospectively the influence of our actions comparing two local cohorts of preterm infants with gestational age less than 32 gestational weeks taken care in level II hospital after NICU care. The exclu-sion criteria was length of stay over one month of corrected age. Breast milk was enriched with protein fortifier, nutritional guidelines for preterm infants were used.
Subjects and Methods: Groups of infants born in 2008 (n=36, gw [± SD] 29.4 ± 2.0, mean birth weight [± SD] 1326 ± 425 g) and in 2012 (n=37, 28.8 ± 2.0 gw, 1248 ± 346 g, respectively) were studied. Mothers were advised on regular pumping and frequent kangaroo care combined with early non-nutritive sucking. Breastfeeding was encouraged, and mostly nasogastrial tube was left at discharge. After discharge a neonatal nurse visited families to weight the infant, to evaluate the feeding and the need for nasogastrial tube, and to support the mothers to maintain breastfeeding.
Result: The infants were discharged in 2008 at mean gw of 37.1 ± 2.2 with a mean weight of 2348 ± 337 g, mean weight SDS -2.1 ± 1.0. In 2012, the mean gw at discharge was earlier, at 36.2 ± 1.9 (p= 0.029), mean weight 2330 ± 413 g, weight SDS -1,7 ± 0.8 (p= 0.07). At term age (38-42 gw), in 2008, the mean weight was 3058 ± 549 g, and in 2012, the mean weight was higher, 3424 ± 454 g (p= 0.003). In 2008, at discharge, 44% of the infants received exclusively breast milk, 19 % received both breast milk and formula, and 36 % received formula. At term, the rates were 42 %, 17 %, and 42 %, respec-tively. In 2012, at discharge, 60 % of the infants got exclusively breast milk, 35 % breast milk and for-mula, and 5 % exclusively formula. At term, the rates were 46 %, 27 %, and 27 %, respectively. Thus, at discharge, the proportion of infants getting exclusively or partially breast milk was increased from 2008 to 2012 (64 % vs. 95 %, p= 0.001).
Conclusions: Early discharge and breastfeeding can be promoted with active clinical support including nasogastrial tube after discharge.

NEWBORN FEEDING BEHAVIOUR DEPRESSED BY INTRAPARTUM OXYTOCIN: A PROSPECTTIVE CASE-CONTROL STUDY

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Introduction: Synthetic oxytocin (Oxt) is the most commonly used drug to induce or augment labour contractions. The assumption that exogenous oxytocin does not cross the placenta and the fetal blood-brain barrier has been questioned. Several peptide manipulations during the time surrounding birth can alter the specific neurohormonal status both in the mother and in the newborn brain. The consequences of these manipulations remain largely unknown. The objective of the study is to evaluate the effect of Oxt used during induced labour on primitive neonatal reflex.
Material and Methods: Prospective case-control study approved by Local Ethical Committee. Women were requested to participate in the study upon arrival at the delivery room and asked to sign a consent form if they agreed to participate. 98 women with vaginal delivery were studied (n=45 in the vaginal delivery group without Oxt, 'control group'; and n=53 in the vaginal delivery group with Oxt, 'Oxt group'). All had singleton, healthy pregnancies and newborns were placed in skin-to-skin contact with the mother after delivery. Wish to breastfeed, Apgar 5m>7 and correct understanding of language were other inclusion criteria. Patients were excluded if caesarean section was made after study inclusion or newborn was admitted in NICU. 41 patients in the control group and 45 patients in the Oxt group fulfilled inclusion criteria. Administration of Oxt during labour induction in the 'Oxt group' commenced by preparing 10 IU of Oxt in 500 mL of 0.9% saline serum. Obstetricians commenced administration of 2 mIU, doubling the dose every 15 min until at least three contractions were attained in 10 min, up to a maximum of 40 mIU. Final dose of intrapartum oxytocin was recorded by midwives. 15 primitive reflexes (endogenous (n=7), antigravity (n=1), motor (n=4) and rhythmic (n=3) reflexes) were recorded during 15 minutes in Biological Nurturing position in the first 48h of life. The filming was carried out more than 1h after the last breastfeeding with the intention to guarantee a seeking behaviour. State of arousal at baseline was evaluated with the Brazelton's scale. One blind observer coded newborn reflexes (as reach/ not reach) watching videotapes. This research was supported by a grant from the Fondo Investigaciones Sanitarias (grant number: PI10/00791) from the Spanish Ministry of Science.
Results: Mean GA and birth weight was 39.2±1.2w and 3239.9±476g in the control group and 39.6±1w and 3323.8±375g in the Oxt group (NS). 26.8% of the control group received epidural analgesia Vs 95.6% in the Oxt group ($p<0.01$). There were no differences in sex, reanimation, state of arousal or educational level. Endogenous reflexes were reached in 77.6±27.1% in the control group Vs 67.2±31.3% in the Oxt group ($p=0.07$); antigravity reflex was obtained in 87.8±33.1% Vs 73.3±44.7% ($p=0.09$); motor reflexes were obtained in 80.4±29.8% Vs 66.6±36.1% ($p=0.05$); and rhythmic reflexes were obtained in 45.5±49.3% Vs 20.7±39.1% ($p=0.01$). Percentage of all primitive reflexes were obtained in 79.8±48.8% of the control group Vs 58.4±28.9% in the Oxt group ($p=0.005$).
Conclusions: Oxt infused during labour may affect primitive neonatal reflexes related to breastfeeding.

AN INTEGRATIVE REVIEW OF THE LITERATURE ON THE CHIROPRACTIC CARE OF INFANTS WITH BREASTFEEDING DIFFICULTIES

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Background: Breastfeeding confers lower risk factors for a number of infant conditions such as acute otitis media, gastroenteritis and diarrhea, severe lower respiratory infections, asthma, sudden infant death syndrome, and obesity in addition to enhancing brain development. Despite it demonstrable benefits, the practice of breastfeeding is globally suboptimal resulting in more than 1 million child deaths per year and increased levels of childhood morbidity. Of the various complementary and alternative medicine (CAM) therapies, chiropractic has been documented as the most popular and highly utilized practitioner-based CAM therapy for children. Chiropractors have long advocated on the benefits of breastfeeding and given the realized and potential role of chiropractors in the care of infants with breastfeeding difficulties, we performed this integrative review of the literature in keeping with evidence-informed practice.
Method: The integrative review of the literature utilized the methodology by Whittemore and Knafl. We sampled both empirical and theoretical perspectives on the subject to allow for varied, disparate and comprehensive perspectives/approaches to clinical care. The review sought to characterize the patient population, the nature of their presenting complaint(s), the care provided and the theoretical and clinical framework upon which care was predicated upon. The search for relevant literature began consulting the databases Pubmed [1966-2013], Manual, Alternative and Natural Therapy Index System [1964-2013] and Index to Chiropractic Literature [1984-2013] for the years indicated. Search terms included 'breastfeeding', 'breast feeding', ‘breastfeeding difficulties', 'breastfeeding difficulty', 'TMJ dysfunction', 'temporomandibular joint', 'birth trauma' and infants' with the appropriate Boolean operator. In addition, the Journal of Pediatric, Maternal & Family health - Chiropractic, Clinical Chiropractic, the Journal of Clinical Chiropractic Pediatrics and the journal of Canadian Chiropractic Association were hand-searched for the previous 5 years of publication for additional articles. Inclusion criteria for review included manuscripts that addressed or described the chiropractic care of infants with breastfeeding difficulties, regardless of peer-review. In addition, the ancestry approach was used to continuously assess for additional references from full manuscripts obtained. Conference proceeding abstracts were not included in this review.
Result: The initial search identified 246 articles from the Index to Chiropractic Literature, 64 articles from the Manual, Alternative and Natural Therapy Index System and 6 articles from Pubmed. Accounting for duplicates, the remaining titles and abstracts were reviewed for their relevance. A total of articles 21 articles met our inclusion criteria. These consisted of 7 case reports, 3 case series, 3 cohort studies and 4 commentaries. Four manuscripts were also identified - 2 case reports and 2 case series that described the care of infant(s) with breastfeeding difficulties as a co-morbidity.
Conclusions: An integrative review of the literature on the chiropractic care of infants with breastfeeding difficulties was performed. The literature consists of lower level research designs (case reports/series and cohort studies) that described addressing dysfunctions in the cervico-cranio-mandibular complex through the use of low force manual therapies. This review sought to provide authenticity, representativeness and informational value of the literature to inform clinical practice, research and policy.

INCIDENCE OF BREASTFEEDING IN LATE PRETERM NEWBORNS: THERE'S PLACE FOR IMPROVEMENT?

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Background: Nutritional status of a late preterm newborn is a serious topic because an appropriate nutrition in first days of life could reduce the onset of several complications. Breastfeeding is the feeding practice recommended for late preterm newborns, nevertheless neonatal factors and maternal factors can delay or prevent the initiation of breastfeeding. Feeding difficulties (easy fatigability, inadequate autoregulation skills, uncoordination of oropharyngeal movements) require great competence for suction.
Aims: To investigate breastfeeding rates in a population of late preterm newborns in association with main neonatal factors (gestational age, birth weight for gestational age, unit of hospitalization) at Neonatal Care Unit and Neonatal Subintensive Care Unit of San Paolo Hospital, University of Milan.
Methods: This observational study recruited a sample of late preterm newborns (G.A. 34-36+6 weeks) born between January 1st 2010 and June 30th 2012 (n=194).
Result: Breastfeeding initiation rate is lower in late preterm population (78,4%) than in term newborns (94,3%). Late preterm newborns in Neonatal Care Unit, also because of the possibility to practice rooming in, have increased exclusive breastfeeding rates. Breastfeeding rates are directly proportional to gestational age and to birth weight. Low birth weight is a risk factor for unsuccessfully exclusive breastfeeding. Breastfeeding rates in SGA newborns are lower than in AGA newborns. LGA newborns have increased rates of exclusive breastfeeding.
Conclusions: Late preterm newborns are at greater risk of being artificially fed. Findings of this study agree with other scientific evidences (Arch Dis Child Fetal Neonatal Ed. 2008 Nov; 93(6):F448-50). Promotion of WHO/UNICEF ten steps, a personalized nutritional plan and an evidence based time of discharge could be strategies to improve breastfeeding rates in late preterm newborns.

PHYSICAL-CHEMICAL PROFILE OF HUMAN MILK MILKED AT HOME AND AT THE MILK BANK OF THE UNIVERSITY HOSPITAL OF THE UNIVERSITY OF SÃO PAULO.

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Background: The properties of human milk can change due to temperature and the proliferation of microorganisms that degrade lactose with the production of acids. High acidity is associated to the decrease of immunological factors and to the destabilization of casein micelles with a reduced bioavailability of phosphorus and calcium.
Objective: to analyze and compare the measurable acidity in Milked Human Milk (MHM) obtained at the donor's home and the milk from the Human Milk Bank of the University Hospital of the USP (HMB-UH).
Methodology: Retro-prospective study analyzing samples of human milk processed from March 2010 to February 2011. The samples were obtained from healthy mothers, at home and from the HMB-UH. The donors received information about hygiene and storage in freezers for up to 15 days. The samples were transported in isothermal boxes, with a strict temperature control, to the HMB-UH, where the organoleptic characteristics were evaluated, and those samples which did not fit the criteria were rejected. Next, the measurable acidity was evaluated using the Dormic acidity technique. The final acidity value corresponded to the arithmetic average of the three values obtained from each sample. The human milk that was considered suitable for consumption had acidity values of 1 to 8°D. All the samples, including those with values of more than 8°D were included in the study.
Result: 4031 samples were analyzed: 1976 (49.02%) obtained at the HMB-UH and 2055 (50.98%) at home. The average storage time prior to the analysis was of 5 days for the HMB-UH samples and 11 days for the home samples, where the storage time was greater at home (p=0.0001). The average measurable acidity was 4.659 for the HMB-UH samples and 5.147 for the home samples (p=0.0001). Even though the average values were not greater than the accepted limit, there were more samples that had to be rejected from the home group.
Conclusions: Regarding the acidity, both conditions for collection and storage differed significantly, the variability that was observed proves the importance of storing human milk for as little time as possible. The use of the measurable acidity test constitutes an important tool for the quality control of human milk.

GOING BACK TO WORK WITHOUT FORMULA; SUPPORTING A BREASTFEEDING-FRIENDLY WORK PLACE

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Background: In the US nurseries, the breastfeeding rates range between 40-95% depending on the cultural population and the lactation support which is provided. Most of the childbearing age women are in the workforce and they are expected to return to work, most of them at 6 to 12 weeks postpartum. Breastfeeding rates decrease when mothers return to the work environment. Electric or manual pumps may increase exclusivity and duration of breastfeeding especially when mothers return to work or school. Significant percentage of lactating mothers face difficulties when they request pumps from their insurances for medical necessity.
Objective: To support lactating women to continue breastfeeding after they return to work environment. We hypothesize that the breastfeeding duration and exclusivity will increase after our interventions in multiple levels.
Design/Methods: Newborn mothers from a large urban pediatric private practice who were willing to breastfeed and would eventually return to work were enrolled. The mothers were provided with extensive counseling for breastfeeding, educational material, weekly phone follow up and a complimentary service for breastfeeding issues by the staff. A letter of support along with educational material for the employer was offered. Specific plan for breastfeeding at work (including employer supportiveness, duration, frequency, specific place, refrigerator for storage, privacy, supportive family members and/or co-workers) was discussed. Medical necessity letter for the insurances was provided for pumps when needed
Result: Mothers of 58 newborns were enrolled so far who breastfeed and returned to work at 6 weeks postpartum. At 7 weeks postpartum 95% (n=51) of them continued to breastfeed and only 35% (n=20) used formula supplementation. Pumps were used by 90% (n=45) of these mothers. At 13 weeks postpartum, 80% (n=46) continued to breastfeed and formula supplementation was used by 45% (n=21) of the mothers. Pumps were used by 100% of the mothers at that time. Out of the 20% (n=11) of the mothers who had stopped breastfeeding at 13 weeks postpartum, 1 mother received non-compatible with breastfeeding medications and 10 mothers stated that they were not provided with the adequate support from the employer and/or family members.
Conclusions: The primary pediatrician may play a key role and improve the duration and exclusivity of breastfeeding even after the mothers return to work.

DETECTING BACTERIAL GROWTH IN RAW DONOR HUMAN BREAST MILK PRIOR TO FEEDING PRETERM INFANTS

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Introduction: Human breast milk is the best nutrition for early feeding in preterm infants. Research suggests that the risk of necrotizing enterocolitis can be reduced by feeding raw human breast milk compared to pasteurised human breast milk or formula. Not all mothers of preterm infants are able to provide own breast milk. In these infants, donor human breast milk is the preferred nutrition. Donors are screened for serology and laboratory findings, antibody negative mothers for certain viruses are accepted. Little is to be found in literature about detecting and testing human milk to exclude contaminated milk for feeding as donor milk, so that for security reasons often pasteurised milk is chosen instead of the raw human donor milk, whereas raw human milk has the most advantages if bacterial and virological unharmful.
Objective: To provide preterm infants with save raw donor breast milk if no own mothers´ breast milk is available by a safe procedure to exclude bacterial pathogen contamination. For this purpose the need of testing each bottle of donated milk was examined to exclude contamination of pathogen bacteria that could possibly harm the immunocompromised premature infant. Method: Before freezing the fresh raw donor milk aliquots were taken from every donated bottle. The amount of milk in each bottle could be different. The milk was only expressed under supervision of our nurses. Each collected bottle was tested and labelled as same as the syringe with the sample to ensure the reconnecting of sample and bottle. Donor milk was set on different agar plates as well as dilution.
Result: 27.2 litres were screened from 8 donors between november 2011 - april 2012. 16.3 litres were sterile or without growth of pathogens. In 10.9 litres pathogens were detected (108 samples). In 106 samples Enterococci, in 6 MSSA (methicillin sensitive Staphylococcus aureus), in 4 gram negative bacteria were found. In 3 donors Enterococci were found in every sample (7.3 litres). Only bottles with sterile samples or without growth of pathogens were given to the preterm infants. 40% of the collected donor milk was disposed. No adverse effect related to feeding of raw breast milk in any preterm infant was seen in this period of time under this policy.
Conclusions: The high number of disposed bottles was mainly due to Enterococci found in 3 colonised donors. Even under high hygienic regime no eradication of these positive Enterococci testing in these donors could be reached. Colonisation of mamillary duct by Enterococci has to be presumed. Screening of every bottle of donated milk is a save method to exclude contaminated raw donor breast milk for feeding to preterm infants. Further investigations of analyzing human breast milk and detection of bacterial growth are needed to standardise this procedure.

ENERGETIC AND MICROBIOLOGICAL ANALYSIS OF HUMAN DONOR MILK OBTAINED AT HOME AND MILK BANK IN A TEACHING HOSPITAL IN SAO PAULO, BRAZIL.

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The human milk contains several necessary nutrients for the infant development and the fat content is the most wavering one. The donned milk from the Hospital Universitário da Universidade de São Paulo Milk Bank (BLH-HU) comes from mothers who drawed it at home or at the milk bank and it goes through energetic content analysis, pasteurization and microbiological culture to assure its quality before being offered to hospitalized newborns. Objectives: to compare the crematocrit (a well established parameter for energetic content in human milk) from milk obtained at both locations, through the lactation length and the pasteurization efficiency by milk sample cultures.
Methods: A prospective study was held with data obtained in one year period (March 2010-February 2011) from human bank samples that followed the National Sanitary Surveillance Agency specifications. The crematocrit technique was performed with milk samples before the pasteurization and the afterwards culture was done inoculating pasteurized milk sample in brilliant green broth.
Result: there were 3020 samples, 1131 (37%) obtained at the BLH-HU and 1889 (63%) at the donor's home. The mean crematocrit value was higher in the milk obtained at home group than BLH-HU group (71,05 x 67,49 Kcal per 100mL, p=0,0001) respectively. Concerning the lactation length, 29% of the samples were colostrum or transition milk and 71% were mature milk (15 days after labor). Home obtained milk tended to be more mature (p=0,000). There were 5,84% of positive cultures.
Conclusions: the milk obtained at home had higher energetic levels, which is probably related to more mature samples and it is very important to hospitalized newborns nutrition. The number of positive cultures was below the tolerable limit by National Sanitary Surveillance Agency, showing the good quality of pasteurization.

NEWBORN FEEDING BEHAVIOUR MAY BE AFFECTED BY MODE OF DELIVERY

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Introduction: Several hormonal manipulations during the time surrounding birth can alter the specific neurohormonal status both in the mother and in the newborn brain. From a neurobiologic perspective, the most frequent manipulations that can affect mother and newborn include labour induction or augmentation with exogenous oxytocin [frequently combined with epidural analgesia (EDA)] and elective caesarean with no prodromal labour. Data from animal research have revealed that perinatal manipulation of the oxytocinergic system in mammals can have lasting effects on attachment, social, feeding and sexual behaviour. The objective of the study is to evaluate the effect of elective caesarean delivery (without endogenous or exogenous oxytocine (Oxt)) on primitive neonatal reflex.
Material and Methods: Prospective case-control study approved by Local Ethical Committee. Women were requested to participate in the study upon arrival at the delivery room and asked to sign a consent form if they agreed to participate. 90 women were studied (n=45 in the vaginal delivery group without exogenous Oxt, 'control group'; and n=45 in the caesarean delivery group, 'Cs group'). All had singleton, healthy pregnancies and newborns were placed in skin-to-skin contact with the mother as soon as possible. Wish to breastfeed, Apgar 5m>7 and correct understanding of language were other inclusion criteria. Patients were excluded if the newborn was admitted in NICU. 41 patients in the control group and 42 patients in the Oxt group fulfilled inclusion criteria. In the Cs group, 26.1% have breech presentation and 73.8% have previous Cs delivery. 15 primitive reflexes (endogenous (n=7), antigravity (n=1), motor (n=4) and rhythmic (n=3) reflexes) were recorded during 15 minutes in Biological Nurturing position in the first 48h of life. The filming was carried out more than 1h after the last breastfeeding with the intention to guarantee a seeking behaviour. State of arousal at baseline was evaluated with the Brazelton's scale. One blind observer coded newborn reflexes (as reach/ not reach) watching videotapes. This research was supported by a grant from the Fondo Investigaciones Sanitarias (grant number: PI10/00791) from the Spanish Ministry of Science.
Results: Mean GA and birth weight was 39.2±1.2w and 3239.9±476g in the control group and 38.9±0.9w and 3322.4±354g in the Oxt group (NS). There were no differences in sex, reanimation, state of arousal or educational level. Endogenous reflexes were reached in 77.6±27.1% in the control group Vs 72.4±24.7% in the Cs group (p=0.19); antigravity reflex was obtained in 87.8±33.1% Vs 69±46.7% (p=0.03); motor reflexes were obtained in 80.4±29.8% Vs 70.2±30.3% (p=0.05); and rhythmic reflexes were obtained in 45.5±49.3% Vs 33.3±26.7% (p=0.2). Percentage of all primitive reflexes were obtained in 79.8±48.8% of the control group Vs 63.6±26.7% in the Cs group (p=0.05).
Conclusions: Elective caesarean section (without endogenous or exogenous Oxt) may affect primitive neonatal reflexes related to breastfeeding.

MARKED VARIATION OF BLANCHING PRESSURE APPLIED BY PAEDIATRIC STAFF DURING CAPILLARY REFILL ASSESSMENT ALTERS THE MEASUREMENT RESULT

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Introduction: Capillary refill time (CRT) forms an important part of clinical care and is a key component of international guidelines when assessing ill children. Whilst a number of studies have demonstrated the usefulness of CRT when assessing ill children it has marked variability which can be dependent on a number of factors. These include observer differences, temperature, age and blanching time (Bumke 2001). No study has formally assessed the importance of blanching pressure, how much variation is seen between observers and the effects it has on the CRT. We hypothesised that health care professionals (HCPs) would demonstrate variation in the blanching pressure applied for CRT and this would affect the measurement result.
Methods: Paediatric HCPs at a University Hospital were asked to perform a normal CRT assessment on one of the researchers as they would usually do in their clinical practice. To ensure the site did not vary we asked them to perform the assessment on the hand of one of the research team. A thin (0.2mm), flexible calibrated electronic force sensor (Tekscan Flexiforce) was attached to the tip of the index finger tip of the participant's dominant hand. Following a period of practice, with the participant blind to the pressures applied, each participant then performed three CRTs and the average blanching pressure and time were calculated. The length of blanching and pressure applied were recorded continuously by the sensor and software. Once the range of blanching pressure was determined we performed CRT assessment on healthy adult volunteers at a range of pressures. These were videoed and quantified by a single researcher (EL). Ethical approval was given for the study.
Result: 74 HCPs (25 doctors and 49 nurses) participated in the blanching analysis. Of the 232 CRT assessments, only 67 (29%) applied pressure for the recommended 5s (with ±0.5s tolerance). Overall the blanching time varied from 1-13s with 48% of assessments being <4.5s. Pressure applied also demonstrated marked variation with a mean 1.6 Newtons (N) (SD 1.2N) but a range of 0.1-6.4N. 24 healthy adults (median age 20, 10 male and 14 female) then had CRT assessment using pressure applications of 0.5, 1, 2 and 4N for 5s. As application pressure increased there was a stepwise reduction in CRT with 35% >2s at 0.5N but only 24% at 4N.
Conclusions: Paediatric HCPs demonstrated marked variation with blanching time and pressure when performing CRT assessments. These data suggest that CRT is affected by the amount of pressure applied potentially altering the resuscitation strategy for the patient. Better standardisation of this assessment could improve the clinical usefulness of this widely used method. Acknowledgement: This study received funding from the Nottingham Hospitals Charity (PP Don Sharkey)

SHORT TERM CLINICAL OUTCOMES OF NEONATES WITH SEVERE PERINATAL ACIDOSIS: A PROSPECTIVE STUDY.

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Background: Therapeutic hypothermia improves outcomes for asphyxiated infants, however not all infants born with severe acidosis are assessed as eligible for cooling and few data describe short-term clinical outcomes for the whole cohort of babies with severe perinatal acidosis.
Aim and Methods: We conducted a prospective study over a 17-month period (June 2011-November 2012) to determine short-term clinical outcomes in the whole cohort of infants born at >35 weeks gestation who had an arterial cord or first hour pH of =7.10.
Result: 69 infants were admitted with severe acidosis. CTG abnormalities were present in 71% of cases. Overall, 31/69(45%) infants showed signs of hypoxic-ischaemic encephalopathy (HIE) and 12/69(17%) were cooled. Of non-cooled infants, 8/57(14%) developed moderate-severe HIE (Table 1). Table 1 Short-term clinical outcomes of infants born with perinatal acidosis Outcomes All Infants Not Cooled Cooled N= 69 N=57 N=12 HIE any grade 31(45%) 19(33%) 12(100%) HIE grade 1 13(19%) 11(58%) 2(17%) HIE grade 2 12(17%) 6(31%) 6(50%) HIE grade 3 6(08%) 2(10%) 4(33%) Clinical Seizures 16(23%) 9(16%) 7(58%) Respiratory Support 24(35%) 14(24%) 10(83%) Hypoglycaemia 18(26%) 14(24%) 4(33%) Feeding problems 48(69%) 36(63%) 12(100%) Age at full Suck Feeds Median (range), days 1 (0-13) 1 (0-13) 6 (1-13) Age at discharge home Median (range), days 3(0-23) 2 (0-16) 10 (3-23) Died 1(1) 0 1(8)
Conclusions: Short term morbidities are common in the whole cohort of infants born with severe perinatal acidosis, including in infants initially evaluated as not meeting current criteria for cooling Other co-morbidities and prolonged hospitalisation are also common Babies born with severe perinatal acidosis need careful identification, assessment, and routine early monitoring.

THE VALUE OF EARLY AMPLITUDE-INTEGRATED EEG IN NEONATES WITH SEVERE PERINATAL ACIDOSIS, NOT SELECTED FOR THERAPEUTIC HYPOTHERMIA

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Introduction/Background: Perinatal asphyxia is associated with a low cord pH at birth. Infants born with severe acidosis are at risk of early and late neurological morbidity. While many are selected for cooling, few data describe early functional brain activity in the whole cohort of infants admitted with severe acidosis. The objective of the study was to describe early functional brain activity as recorded by amplitude-integrated (a)EEG in neonates admitted with severe umbilical artery acidosis who did not receive whole-body hypothermia within 6 h of birth because deemed not to fit accepted cooling criteria on early screening.
Patients/Methods: In a prospective study over a 17-month period, infants =35 weeks' gestation admitted to a tertiary-level NICU with an arterial cord pH or first hour pH of =7.10 who did not fulfil current accepted criteria for therapeutic hypothermia received routine early digital aEEG monitoring (started within <24 h of birth). aEEGs were assessed by a blinded independent expert for initial background voltage, onset of sleep-wake cycling (SWC), and seizures.
Result: Of 69 infants admitted with pH =7.10 in the study period, 37 were excluded because of early cooling or not meeting the other eligibility criteria. 32 babies underwent expert review of their early aEEGs. Median (IQR) postnatal age at aEEG commencement was 98 min (67 to 165 min) and duration of recording was 13 h (9 to 24 h). aEEG background at commencement was classed as continuous normal voltage (CNV) in 29/32 (91%) and as discontinuous normal voltage (DNV) in 3/32 (9%). Median postnatal age at of onset of SWC was 3 h (range: 36 min to 83 h) and was already present at aEEG commencement in 14/32 (44%) cases. Seizures were present on aEEG in 5/32 (16%) cases (sporadic n=1, frequent n=3, status n=1), with onset detected at a median postnatal age of 14.8 h (range: 3.8 to 20.4 h). 3 of 4 infants with frequent seizures or status showed DNV background at aEEG commencement.
Conclusions: Our study shows that early digital aEEG monitoring is valuable in asphyxiated newborns who do not fulfil accepted criteria for therapeutic hypothermia, because a substantial proportion go on to develop electrographic seizures that may indicate reconsideration for hypothermia treatment.

A RETROSPECTIVE STUDY OF CEREBRAL FUNCTION IN A COHORT OF NEONATES COOLED AT A TERTIARY NEONATAL CENTRE-IMPLICATIONS FOR PRACTICE

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Introduction: Therapeutic hypothermia is a standard of care in the UK for neonates with hypoxic ischaemic encephalopathy for neuroprotection. Meeting neurological criteria are essential for recruitment of neonates for treatment. Neurological symptomatology may be subtle and the role of cerebral function monitoring though not essential for starting treatment has been endorsed by the British Association of Perinatal Medicine.
Method: A retrospective study to review the management of neonates with suspected hypoxia ischaemia who underwent therapeutic hypothermia was carried out in a tertiary neonatal centre. Information was taken from the patient record and TOBY forms regarding recruitment as per standard criteria, and neurological symptoms. A confidential review of their Cerebral Function traces was performed where available. They were classified according to the classification described by Hellström-Westas (1) as being continuous normal voltage, discontinuous normal voltage, burst suppression, low voltage or inactive.
Results: 29 cases underwent therapeutic hypothermia during the period August 2009-August 2011 with a total of 1979 cooling hours provided. Cerebral function traces were reviewed in 28 out of 29 cases with one not obtainable. 4 cases had continuous normal voltages, 14 cases had discontinuous normal voltage, 3 had burst suppression, 6 were low voltage or inactive. 2 cases had only seizures. Of 29 cases 2 had neonatal encephalopathy which may have been attributable to other causes. All the cases with burst suppression, low voltage or inactive trace that normalised their CFM records within 72 hours were discharged feeding orally. Cases with burst suppression, low voltage, or inactive trace that did not normalise to their trace all died.
Conclusion: All neonates undergoing therapeutic hypothermia should have cerebral function monitoring initiated if available. Used adjunctively with the presentation, clinical course and neuro-imaging it may be a prognostic indicator of survival and acute outcomes in such neonates. Cerebral function monitor traces need cautious interpretation for artefacts. Background and improvement of the trace in neonates may be affected by anti-epileptic medication. It is important to investigate other causes for neonatal encephalopathy in neonates undergoing therapeutic hypothermia who meet criteria but have normal CFM traces. It is inevitable that some neonates with borderline neurology and continuous normal voltage appearance will be cooled. This work highlights the pitfalls of interpreting traces of neonates being cooled for neonatal neurologists and neonatologists.

1. Hellström-Westas L, Rosén I, de Vries LS, Greisen G (2006) Amplitude-integrated EEG Classification and Interpretation in Preterm and Term Infants. NeoReviews 7 (2):e76-e87. doi:10.1542/neo.7-2-e76

DOUBLE COOLING IN THE FIRST WEEK OF LIFE: PERICARDIAL TAMPONADE AND CARDIAC ARREST FOLLOWING NEONATAL ASPHYXIA

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Therapeutic hypothermia as treatment of brain injury due to asphyxia, cardiac arrest and brain trauma in childhood is a hot field of research. We report a case of a term female treated with therapeutic hypothermia for hypoxic-ischaemic encephalopathy who suffered a cardiac arrest after rewarming and underwent a new therapeutic hypothermia course. Despite compelling evidence showing that moderate hypothermia improves outcome in neonates and children with brain injury, double hypothermia within the first week of life for different causes has not been previously described. A female infant was born at term from CS due to dystocia, from a 32-yr healthy female. Premature rupture of membranes occurred one week before, and meconium-stained amniotic fluid was detected. At birth, she presented cardio-respiratory depression (Apgar score 1/3). After resuscitation she was referred to our PICU for therapeutic hypothermia, still presenting cardiovascular impairment (HR 75 bpm, BP 45/25, lactate > 5 mmol/L). Due to kidney injury (creatinine 2.3 mg/dL, day 6), urine output was maintained with fenoldopam infusion. TT-Echocardiography showed pulmonary hypertension, while left ventricular contractility was supported by dobutamine. A 3-Fr central venous catheter (CVC) was inserted through right IJV and right radial artery was cannulated. Fluid and inotropic support was continued and core temperature was decreased to 33.5°C using Criticoolâ„¢ system for 72 hours, according to the Italian Society for Neonatology cooling protocol. Rewarming phase was uneventful as well as weaning: nasal CPAP was introduced and inotropic support discontinued (day 5). On day 7, respiratory conditions worsened, with increased oxygen need and tachypnea. Chest X-rays showed a massive right lung atelectasis with mediastinal right shift. The CVC tip appeared displaced while if drawing blood normally. After tracheal intubation and main right bronchus aspiration lung re-expansion was achieved. Few hours later, the patient suddenly developed a PEA and, despite early start of CPR according to the ILCOR 2010 Guidelines, the condition evolved into asystole. During CPR, ultrasound examination was performed. On subcostal view of the heart, pericardial effusion causing right ventricle collapse was detected. Pericardiocentesis yelded a lipid emulsion fluid, revealing a CVC-related complication. After removal of 20 mL of pericardial fluid, cardiac contractile activity and spontaneous circulation were resumed. The baby was on CPR for 40 minutes, showing metabolic acidosis and lactate level 15 mmol/L. A new hypothermia course was induced with a deep sedation and providing goal-directed haemodynamic support. The ‘displaced' CVC was removed and a new vascular access device was placed through the left femoral vein. On day 12, after safe extubation, she was shifted to nasal CPAP again. No seizures were detected on continuous EEG. A slight legs hyperreflexia with elicitable clonus was no longer appreciable after sedation discontinuation; both cerebral US and MRI were normal. She was discharged from PICU on day 15 and sent home 18 days after admission, with no neurological and feeding problems.This report confirms the value of neuroprotection achieved with hypothermia in neonates, associated with optimal support of haemodynamic and global care.

ASSESSMENT OF PREDICTIVE EFFECTS OF SERUM LDH, CPK AND SGOT ENZYMES IN EARLY DIAGNOSIS OF NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY.

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Key Words: Creatinine Phosphokinase (CPK), Lactat Dehydrogenase(LDH), serum glutamic-oxaloacetic transminase (SGOT),Hypoxic-Ischemic Encephalopathy(HIE).
Introduction: In the 21th century; Hypoxic-Ischemic Encephalopathy (HIE) remains the single most important perinatal cause of neurologic morbidity in both the full term as well as the pre term newborns (1).Animal data suggests that the intervention is most effective when implemented within 6 hours of the event (2).the aim of our research is to assess the hypothesis that SGOT,LDH and CPK enzymes are also an early predictor of neonatal Hypoxic-Ischemic Encephalopathy diagnosis.
Methods: Our study was experimental random clinical trial type which performed from march 2011 to march 2012 in neonatal wards of social security organization hospital of zanjan in Iran. Sample size was 75 newborns that divided in two as case group (37 newborns) and control group (38 newborns). Inclusion criteria for case group were: 1- history of distocia 2- related clinical symptoms 3- white matter hypodancity in brain CT scan 4- metabolic acidosis by ABG 4- term gestational age of neonates. Serum level changes of CPK, SGOT and LDH enzymes in first day of HIE occurrence detected and analyzed by SPSS statistical software, pearson's r correlation and independent-samples T TEST.
Results: Mean serum levels of SGOT,LDH and CPK in control and case groups were 93,2830,41 mg/dl and 214,2867,178 mg/dl ,and so their mean difference were 121,37,137 mg/dl.compare means by correlation coefficient of pearson's r were significant for SGOT and CPK. Independent T TEST indicated significant correlation coefficient for SGOT and CPK means [correlation coefficient was 0.735($p>0.5$)].so there was strength relationship between serum level of SGOT, CPK and early diagnosis of neonatal HIE.
Conclusion: Serum levels of SGOT and CPK in the first 24 hours of complicated labour can be used as predictive indicator for early diagnosis of neonatal HIE and hypothermic therapy initiation.

THERAPEUTIC HYPOTHERMIA FOR NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY: TEMPERATURE CONTROL DURING TRANSPORT

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Background: Therapeutic hypothermia (TH) is currently recommended for the treatment of hypoxic-ischemic encephalopathy. TH reduces mortality and improves neurodevelopmental outcome of survivors. Early achievement of neuroprotective temperature with passive cooling is important and depends on starting adequate measures at the referring hospital or during transport. This study aims to assess the adequacy of temperature control during transport of patients referred for TH at our unit and to evaluate the occurrence of complications when temperature control was not adequate and the patients arrived with excessive hypothermia (<33ºC).
Patiens And Methods: Transport data of all patients referred for TH at our NICU during a period of 30 months was reviewed retrospectively, as well as our prospectively collected database of infants treated with TH, including baseline characteristics, admission temperature, clinical and laboratory monitoring.
Results: 40 infants were treated with TH at our NICU during the study period and 37 only 3 were inborn, so 37 were evaluated. Median of transport distance was 134km (3-420) and median of transport time was 1.5h (0.2-3.9). Distance between referring hospital and our NICU or duration of the transport were not associated with risk of excessive hypothermia. Despite relatively late beginning of TH at mean age of 7h (2.3-13), 75% of infants with adequate transport records had a reading of neuroprotective temperature before 6h. Significant correlation was found between the lack of adequate temperature records during transport and excessive hypothermia on admission. There was a trend towards increased incidence of coagulation issues (both lab and clinical) for infants who had admission temperatures below 32ºC. The incidence of seizures or hypotension was not significantly associated with excessive hypothermia on admission.
Conclusion: Passive cooling is simple and effective to ensure early achievement neuroprotective temperature, but it should be done carefully with continuous temperature monitoring in order to avoid excessive cooling that can be related to complications.

PHENOBARBITAL DOSING DURING THERAPEUTIC HYOPTHERMIA - SHOULD WE CHANGE OUR PRACTICE?

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Introduction: Phenobarbital is a first-line anticonvulsant for neonatal seizures, including during therapeutic hypothermia. The most commonly used initial dose is 20mg/kg and further 5mg/kg doses are given to achieve seizure control. Due to changed drug metabolism during hypothermia, there is some concern that this dosing schedules can lead to toxic phenobarbital levels during hypothermia. We aim to study phenobarbital levels of newborns treated with hypothermia after receiving different phenobarbital dosing schedules.
Patients and methods: We analysed retrospectively data from patients submitted to therapeutic hypothermia at our NICU during a 3-year period (2010-2012). All patients who received phenobarbital during the first 24 hours of life were included. Patients were divided into 3 groups according to the total dose received: A) <20mg/kg; B) 20mg/kg; C) >20mg/kg. Phenobarbital levels were analysed in 4 consecutive time periods: 1) 12-24h; 2) 24-48h; 3) 48-72h; 4) >72h. If additional doses were given after 24 hours of life, subsequent levels were not considered. Statistical analysis was performed using Kruskal-Wallis test with post-hoc analysis on SPSS 19 software.
Results: 37 patients were submitted to therapeutic hypothermia at our NICU during this time period and 34 were outborn. We evaluated 31 patients who received phenobarbital during the first 24 hours of life. Passive hypothermia was achieved at a median time of 1 hour of life and active cooling was started at a median time of 6 hours of life. Median phenobarbital dose was 20mg/kg and different dosing schemes were used according to different protocols at referring hospitals and patients' needs. Significantly differences were found between groups A, B and C at all the 4 time periods studied, mainly due to differences between groups A and C. Toxic levels were found systematically in group C (31.7-35.4), whereas in groups A (15.0-19.1) and B (20.4-22.7) therapeutic levels were present for all time periods.
Conclusions: Our data reveals that there was a significant risk of using doses above 20mg/kg in this group of patients treated with hypothermia. This finding can be explained by delayed clearance of phenobarbital that can be partially attributed to hypothermia. The obtainment of therapeutic levels with total doses under 20mg/kg suggests that an initial dose of 10mg/kg followed by additional doses of 5mg/kg up to a total dose of 20mg/kg could be a safer protocol, and alternative anticonvulsant drugs should be considered if seizure control is not achieved after that maximal dose of fenobarbital is given.

RESPIRATORY FUNCTION PARAMETERS IN VENTILATED NEWBORN INFANTS UNDERGOING WHOLE BODY HYPOTHERMIA

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Introduction/Background: Whole body hypothermia (WBH) exerts proven beneficial effects as a neuroprotective strategy against hypoxic-ischemic encephalopathy (HIE). Hypothermia could impact on respiratory function in mechanically ventilated newborn infants by a variety of possible pathophysiological mechanisms. This effect has not been adequately studied in full-term ventilated infants undergoing WBH for HIE. Our aim was to obtain preliminary data of respiratory function from a retrospective review of patients undergoing WBH in a regional neonatal intensive care unit.
Patients and Methods: The medical notes of 31 full-term newborn infants that underwent WBH for HIE and were mechanically ventilated were retrospectively reviewed. Fraction of inspired oxygen (FiO2), partial pressures of arterial gases, ventilatory pressures, Tidal Volume (TV), Mean Airway Pressure (MAP), Minute Ventilation (MV), Static Compliance of the respiratory system (CstatRS), Ventilation Efficiency Index (VEI), Alveolar-arterial gradient (A-a gradient) and Oxygenation Index (OI) were recorded before and during hypothermic treatment as well as during and after rewarming.
Results: FiO2, MAP, OI and A-a gradient decreased during induction of hypothermia and exhibited a tendency to increase during rewarming. CstatRS, VEI and TV increased during induction of hypothermia and exhibited a tendency to decrease during rewarming. None of the changes achieved statistical significance.
Conclusions: These results suggest that whole body hypothermia might affect respiratory function in mechanically ventilated infants with HIE. Probably as a result of decreased metabolism, oxygenation might be facilitated by hypothermia while the work of ventilation might also be alleviated as a result of the effect of hypothermia on lung mechanics. Further prospective studies would be able to investigate this further and ensure that ventilation strategies are appropriate for this vulnerable population group.

PROSPECTIVE MULTICENTER PROGRAM FOCUSSED ON EARLY SYSTEMATIC MONITORING OF INFANTS WITH PERINATAL ASPHYXIA TO IMPROVE NEUROLOGICAL OUTCOME.

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Most infants with HIE are born at hospitals without available hypothermia treatment and with different skills at management of perinatal asphyxia. Since hypothermia is widely used, early identification of infants with moderate or severe HIE is essential. However, surveillance should include systematic monitoring focused on respiratory, hemodynamic, metabolic and other disorders, in order to reduce risk factors that can worsen the neurological status in the first hours of life.
Objective: To monitor all infants with perinatal asphyxia during a two year program to identify infants with HIE. To establish guidelines to treat any disorder that may contribute to worsen the neurological status in the first 6 hours of life.
Patients And Methods: All newborns > or = 35 weeks´ gestation with perinatal asphyxia (umbilical-cord or in the first hour pH < or= 7.00, need of deep resuscitation, or 5-minute Apgar score < or = 5) born between June 2011 and June 2013 were admitted to the neonatal unit and systematically monitored for at least 6 hours. 13 hospitals entered the program. All infants were examined through a designed exam for the identification of HIE at 1, 3 and 5 hours. Video recording of the exams were performed for blinded assessing purposes. If suspicion of moderate or severe HIE was detected, the patient was sent to a reference hospital for hypothermia treatment. Guidelines for the transport were established. If available, infants were continuously monitored with aEEG within 6 hours after birth or until the record was normal (continuous normal voltage with sleep-wake cycling and no seizures). Continuous central temperature monitoring was used to avoid hyperthermia and overcooling. Hemodynamic and respiratory monitoring was established to detect hypotension, hypo and hypercarbia. Metabolic investigation focussed on the detection of acidosis, hypoglycemia, hypocalcemia and hypomagnesemia. Other disorders to be investigated if repercussion of the hypoxic ischemic insult was present were gastrointestinal disturbances, coagulopathy, heart failure and oliguria. Use of volume expansions was assessed. Reccomendations to treat different disorders were clearly stated.
Results: At 20 months´ recruitment, 190 infants met the inclusion criteria. Two hospitals were removed for the analysis because cord blood pH was not routinely determined. Therefore, 169 out of 22375 births were finally included (incidence of 0.7%). Success in the monitoring and treatment will be assessed after final recruitment by June 2013.
Conclusion: Specific programs for hospitals with a low training in the management of infants with perinatal asphyxia may improve neurological outcomes. Systematic monitoring with established treatment guidelines can help to avoid and reduce the deleterious effect of some risk factors in infants with perinatal asphyxia and to identify those with HIE to start hypothermia treatment.

THE NEONATAL ASPHYXIA POPULATION BEFORE AND AFTER INTRODUCTION OF HYPOTHERMIA TREATMENT: A LOCAL EXPERIENCE FROM LAUSANNE.

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Introduction: Hypoxic-ischemic encephalopathy (HIE) occurs in 1-2 per 1000 newborns in Switzerland, moderate to severe forms representing more than half the cases. Hypothermia has been recognized as a neuro-protective therapy in cases of moderate to severe HIE. The treatment was introduced in 2009 in the Clinic of Neonatology in Lausanne/Switzerland and a national asphyxia register has been created in 2011 in Switzerland. Objectives of the present study were to describe the asphyxia population after the hypothermia treatment with a comparative historical group from 2006-2007 before hypothermia introduction.
Methods: Retrospective observational study on the population of neonates born between 01.01.2010 and 31.12.2011, with birth asphyxia. Inclusion criteria were a pH < 7.0 (umbilical cord or in the 1st hour of life), or an Apgar score <5 at 5 minutes or a diagnosis of HIE according to Sarnat. Epidemiological and clinical data were collected. For the survivors, neurological development at 6 and 18 months was also noted. We compared our results with those of the historical group (2006-2007) with the same inclusion criteria.
Result: 45 newborns met the criteria for the period 2010-2011 compared to 47 for the period 2006-2007; mean gestational age was 38 4/7 (±4 days) and mean birth weight was 3040 g ± 825SD. The rate of outborn accounted for 64.4%. The average transfer time in the neonatal intensive care unit level III was 3h23' ± 0.11 SD. In 14 patients an acute event was identified: placenta abruptio was the most frequently found. Twenty seven children had a HIE diagnosis: 10 Sarnat I, 15 Sarnat II and 2 Sarnat III. Of the 15 Sarnat II, 80% were outborn and hypothermia treatment was applied to 8/15. Indications for no hypothermia were persistent pulmonary hypertension (n=2), late transfer (n=1), and apparently missing criteria at admission (n=4). These 4 babies showed all a pathological MRI and longterm outcome was compromised. Compared to the group 2006-2007 there was less HIE Sarnat III (8 versus 2), and there was a significant decrease in time of transfer to the NICU especially for the population of outborns (9h35'(2006-2007) to 4h08',(2009-2010) $p<0.05$). Incidence for asphyxia for the large hospital network was 1.92/1000 live births for 2006-2007 and 1.8/1000 live births for 2010/2011, with important differences between the different referring hospitals (n=11).
Conclusions: In this observational study, we observe that the incidence of neonatal asphyxia has remained low and stable over time between the two periods and interestingly the transfer time to a hypothermia center has significantly decreased, reflecting the good cooperation within the network. Despite decreased transfer time, still too many children don't profit from hypothermia. Therapeutic hypothermia implementation seems to be possible and feasible in a large hospital network but inclusion criteria for hypothermia have to be constantly addressed in order to increase the benefice for the target population.

IS EARLY AEEG IN INFANTS WITH PERINATAL ASPHYXIA A RELIABLE TOOL TO IDENTIFY HIPOXIC-ISCHEMIC ENCEPHALOPHATY (HIE)

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aEEG during the first six hours after birth provides a simple objective measure for the presence of encephalopathy. Clinicians may find aEEG an easier and more reliable tool than clinical status to identify infants with significant HIE (specially those with moderate HIE). However, aEEG has limitations as the background pattern within 6 hours after perinatal asphyxia that may not accurately predict the presence of significant HIE and secondly, clinicians with different training may misdiagnose the interpretation.
Objective: To assess whether early aEEG is a reliable tool to identify significant HIE in newborns infants after perinatal asphyxia by different experienced clinicians.
Patients And Methods: Newborns = 35 weeks´ gestation with perinatal asphyxia (umbilical cord or first hour pH = 7.00, need of prolonged resuscitation, or 5-minute Apgar score = 5) born between June 2011 and June 2013 were monitored with aEEG during the first 6 hours of life. Background pattern (BP) (continuous normal voltage (CNV), discontinuous normal voltage (DNV), burst suppression (BS), low voltage (LW) and flat trace (FT)), and sleep-wake cycling (SWC) (absent, suboptimal and normal), were assessed in two periods of time (0-3 h and 3-6 h). Clinicians on call classified the aEEG traces and recordings were re-classified by two trained neonatologists blinded to the study. Interobserver agreement between trained readers and between clinicians on call and an agreed interpretation by the two experts on aEEG BP and SWC classification was assessed by calculating a weighted k statistic. Kappa, S, E and PPV and NPV values of a normal vs abnormal BP (CNV/DNV vs BS/LW/FT) with respect to the presence of significant HIE (moderate or severe) at one and five hours of life were calculated.
Results: 49 infants were included in the study. Preliminar data of 49 patients are presented. Weighted kappa coefficient between experts was 1.00 and 0.83, respectively for the evaluation of BP and SWC classification. If SWC were classified as absent or normal, Kappa rised up to 0.91. Kappa between trained readers and clinicians on call for BP at 0-3 hours and 3-6 hours was 0.77 and 0.84 respectively. Kappa for SWC between trained and clinicians on call was 0.31 at 3-6 hours period. aEEG BP (abnormal vs normal) was analyzed by experts and compared to the presence of significant HIE. 5/6 patients with significant HIE had abnormal BP. The BP had 100% S, E, PPV and NPV at 0-3 hours and 80%, 100%, 100%, 97.8%, respectively at 3-6 hours.
Conclusions: Staff on duty classified properly aEEG BP of newborns with perinatal asphyxia in first 6 hours of life. Early aEEG BP has a high correlation with the absence or presence of significant HIE and seems to be a good tool for early identification of HIE.

PROSPECTIVE STUDY TO DETERMINE THE CORD PH LEVEL TO BE MONITORED TO IDENTIFY INFANTS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) TO START THERAPEUTIC HYPOTHERMIA

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Early identification of infants at risk of perinatal asphyxial encephalopathy is crucial to detect significant HIE to start therapeutic hypothermia. Acidaemia with cord blood pH < 7.0 is considered essential feature of perinatal asphyxia. However, HIE can occur with levels of pH above 7.00. We questioned if newborns with cord blood pH 7.01-7.10 are safe not to be systematically monitored to detect HIE.
Objetive: To determine what cord blood pH level is worth monitoring with neurological evaluation within the first 6 hours of life to detect HIE.
Methods: All newborns = 35 weeks´ gestation with cord blood pH < or = 7.10 were prospectively included between June 2011 to June 2013 at University Hospital of Burgos, Spain. Cord bloold pH is rutinely determined in all newborns in our hospital. Two groups were made according to the threshold < or = 7.00 and 7.01 - 7.10. Variables regarding pregnancy and perinatal issues were compared between both groups. All infants who met inclusion criteria were neurological evaluated following a structured exam to identify and classify the degree of HIE at 1, 3 and 5 hours.
Results: Preliminary data of all newborns > or = 35 weeks´gestation between June 2011 and January 2013 are presented. There were 3780 births and 217 newborns had cord blood pH < or = 7.10 (incidence of 5.7%), 53 of them had pH < or = 7.00 (1.4% of all births). Infants with pH < or = 7.00 at birth had significantly more difficult deliveries (emergency cesarean section or instrumental), lower Apgar scores at 1´and 5´, more need of resuscitation, (oxygen, positive ventilation, intubation or chest compressions). 13 % and 5.6% in the pH < or = 7 group needed intubation and chest compressions, respectively vs 1,2% and 1.2% ($p<0.001$). Cord blood base deficit > 16 was more frequent in th pH < or = 7.00 group (63.6 vs 21.7%, $p<0.001$). There were 6 newborns out of 217 (2.7%) diagnosed of moderate or severe HIE, 5 of them (9.4%) in the pH < or = 7.00 group ($p < 0.001$).
Conclusion: Perinatal acidosis has a low incidence (5.7 % for pH < or = 7.10, and 1.4% < or = 7.00). HIE happened more frequently in newborns with pH < or = 7.00 thus it seems worth monitoring these infants to detect HIE

PREDICTIVE VALUE OF NEUROLOGICAL IMPAIRMENT OF AMPLITUDE INTEGRATED ELECTROENCEPHALOGRAM (AEEG) IN NEWBORNS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE): NEW METAANALYSIS CONSIDERING HOURS OF LIFE AND HYPOTHERMIA TREATMENT

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Background: the analysis of aEEG´s predictive value of neurological impairment was part of a Clinical Practice Guideline on neonatal HIE´s management developed in our country during year 2012.
Methods: GRADE methodology was used. First, a complete bibliographic search was performed in main databases until December 2012. No language restriction was applied. Bibliographic references were tracked. From the initial 292 papers, 23 meeting inclusion criteria (newborns with HIE evaluated during the first 3 days of life using aEEG´s background pattern with long term follow up of at least one year after discharge) were first selected by two independent reviewers. 14 papers comprising 722 patients were finally included (exclusion criteria: absence of long term data (2) serbian language (1), duplicated data (1) no raw data available (2) evaluation of sleep wake cycles (2) low quality metaanalysis (1)). Pretest probabilities were extracted from the metaanalysis published by Tagin 2012 (death or disability 63,17% in patients not treated with hypothermia, 47,88% in patients treated with hypothermia)
Result: Prognostic value for death or severe disability was calculated for patients not treated with hypothermia (Group 1) and receiving this therapy (Group 2). At 6 hours of life, Group 1 (10 studies 464 patients) positive likelihood ratio (+LHR) 5.18 (2.33 to 11.54), negative likelihood ratio (-LHR) 0.23 (0.13 to 0.36), diagnostic OR 30.69 (10.09 to 93.31) Group 2 (5 studies, 144 patients) +LHR 1.59 (1.25 to 2.01), -LHR 0.14 (0.04 to 0.49), diagnostic OR 12.74 (3.24 to 50.16) At 24 hours of life (5 studies, 267 patients) Group 1 +LHR 22.48 (8.07 to 62.59), -LHR 0.16 (0.11 to 0.24,) diagnostic OR 237.61 (56.47 to 999.89) Group 2 (3 studies, 78 patients) +LHR 3.58 (2.15 to 5.95), -LHR 0.09 (0.02 to 0.41), diagnostic OR 41.87 (7.01 to 250.02). At 36 hours of life, Group 1 (3 studies, 76 patients) +LHR 19.29 (4 to 92.9), -LHR 0.21 (0.09 to 0.49), diagnostic OR 104.25 (16.549 to 656.74) Group 2 (2 studies, 66 patients) +LHR 8.93 (1.44 to 55.19), -LHR 0.11 (0.03 to 0.37), diagnostic OR 115.21 (16.56 to 801.44) At 48 hours of life, Group 1 (3 studies, 77 patients) +LHR 16.42 (3.43 to 78.65), -LHR 0.26 (0.16 to 0.45), diagnostic OR 76.88 (12.72 to 464.89) Group 2 (2 studies, 65 patients) +LHR 34.32 (4.86 to 242.2), -LHR 0.22 (0.10 to 0.47), diagnostic OR 157.76 (16.59 to 1499.9) At 72 hours of life, Group 1 (3 studies, 64 patients) +LHR 5.66 (1.65 to 19.41), -LHR 0.32 (0.19 to 0.52), diagnostic OR 42.68 (6.97 to 261.57) Group 2 (2 studies, 66 patients) +LHR 24.86 (3.37 to 186.4), -LHR 0.43 (0.22 to 0.85), diagnostic OR 60.29 (6.74 to 539.48)
Conclusions: this is the first metaanalysis incorporating hours of life and hypothermia treatment in the analysis of aEEG´s prognostic value. It shows that aEEG is useful from a very early moment and that its predictive value is delayed in newborns treated with hypothermia. Information about care withdrawal is usually missing in studies and could affect prognostic value of aEEG when evaluating death.

KINETICS OF CIRCULATING PROGENITOR CELLS AND CORRELATION WITH BIOMARKERS IN FULLTERM NEWBORNS WITH PERINATAL ASPHYXIA - AN ENDOGENOUS REGENERATION EFFORT? (PRELIMINARY REPORT)

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Background: Preclinical work has shown that endogenous regeneration effort does take place in perinatal brain injury, especially in terms of neural stem cell migration from subventricular zone to the damaged area. Moreover, pluripotent progenitor cells derived peripherally in models of perinatal asphyxia were steadily shown to enter blood-brain barrier and ameliorate the effects of the devastating event in multiple possible ways. However, kinetics of endogenous Circulating Progenitor Cells (CPCs) from periphery in fullterm newborns is not known, particularly their possible role after perinatal asphyxia (PA).
Objective: He hypothesized that progenitor cells from periphery might play a role in a possible endogenous regeneration effort after perinatal asphyxia. We tried to outline the related pathophysiology regarding kinetics of biomarkers of brain injury, chemoattractants and CPCs.
Patient And Methods: 30 fullterms were enrolled (GA>37w) during years 2010-1013. 19 of them underwent perinatal asphyxia, whereas 11 of them were assumed as controls. Peripheral blood at days(d) 1,3,9,18,45 after birth were analyzed using flow cytometry, focusing on EPCs (Endothelial Progenitor Cells), HSCs (Hematopoietic Stem Cells) and VSELs (Very Small Embryonic-Like Stem Cells). At the same days S100b, Neuron-specific Enolase (NSE), Erythropoietin (EPO) and SDF-1 were measured.
Results: In newborns with PA a significant increase of markers of brain injury was observed especially at d1 and d3, with a contemporary significant increase of EPO compared to controls. Concomitant significant increase of CPCs at the days following was observed only in patients. In particular, EPCs, HSCs and VSELs were increased from d3 to d45 ($p<0,05$, $p=0,086$, and $p<0,05$ respectively, Friedman test). Kinetics and correlations of CPCs are shown in figures.
Conclusion: Increased levels of biomarkers of brain injury (S100b,NSE) and EPO early after birth followed by a subsequent mobilization of CPCs suggest a possible endogenous regeneration effort. We speculate that imitating and enhancing this effort in terms of stem cell type and timeframe might prove to be a good therapeutic model in the future. More studies and correlation with outcome are necessary before successful attempt for exogenous administration of stem cells.

INCREASED CORD LEVELS OF UBIQUITIN CARBOXYL-TERMINAL HYDROLASE L1 IN NEONATAL HYPOXIC ISCHAEMIC ENCEPHALOPATHY

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Introduction/Background: Hypoxic ischaemic encephalopathy (HIE) is a catastrophic condition which may result in severe secondary sequelae. A rapid and reliable biomarker would ensure early diagnosis and classification of infants with HIE and aid targeted neuroprotection. Ubiquitin carboxyl-terminal hydrolase L1 (UCHL-1) is a neuron specific protein which has been linked to neurodegenerative disorders. This protein, which is abundantly expressed in the cortex, has been suggested as a potential biomarker in HIE. A sudden release of UCHL-1 into the blood stream is believed to be indicative of neuronal cell death and brain injury. Similarly, the brain specific protein; glial fibrillary acidic protein (GFAP), may also represent a potential biomarker as GFAP is believed to be released into the blood stream only after astrocyte death. The aim of this study was to examine the potential use of UCHL-1 and GFAP as a specific biomarkers of HIE.
Patients /Methods: Infants with suspected perinatal asphyxia (PA) and HIE were enrolled in the BiHiVE Study (Validation of Biomarkers in Hypoxic-Ischaemic Encephalopathy) in Cork University Maternity Hospital between 2009 and 2012. Enrolment criteria were: term gestational age with evidence of PA defined as; cord pH <7.1 and/or five minute Apgar score = 6 and/or requirement for intubation or CPR at birth. Following diagnosis at delivery, umbilical cord blood is drawn, processed and bio-banked. HIE grade was confirmed with early continuous EEG monitoring and clinical examination. Matched, healthy control samples collected with identical methodlogy were chosen from an ongoing birth cohort study, the Cork BASELINE Birth Cohort Study. UCHL-1 and GFAP analysis was carried out by Banyan Biomarkers ®, Florida using Banyan Biomarker's proprietary sandwich Enzyme-Linked Immunosorbent Assays (ELISA) specific to UCHL-1 and GFAP independently. Results In total 99 infants (controls=57, cases=42) were included in the study. Cases included both infants with perinatal asphyxia (PA) and EEG graded hypoxic ischaemic encephalopathy (HIE) (asphyxia=27, mild=11, moderate=3, severe=1). Following analysis, case infants (PA/HIE) showed a significant (p-value=0.0084) elevation of UCHL-1 expression in serum umbilical cord samples compared to samples from healthy control infants (fold change >1.2). When examined as 3 discrete groups: control vs PA vs HIE ANOVA testing again showed a significant difference (p=0.0129). When analysis focussed on detecting those infants eligible for therapeutic hypothermia the fold change increased (p=0.0172, fold change 1.6). No significant difference was found in levels of GFAP measured between any of the study groups; case vs control (p=0.2588) and control vs PA vs HIE (p=0.04894).
Conclusion: We have shown significant elevations in UCHL-1 levels in infants with perinatal asphyxia and particularly in those with moderate/severe HIE. UCHL-1 has been previously reported as an early marker in post-natal samples in infants with HIE and we have shown that this protein is elevated at the time of delivery in cord blood. GFAP was not elevated in cord blood samples and this is consistent with its previously reported peak elevation at 48 hours post-injury.

CEREBRAL PALSY IN CHILDREN PRESENTING TO PAEDIATRIC SERVICES IN KAMPALA, UGANDA: WHAT PERCENTAGE IS ATTRIBUTED TO ACUTE INTRAPARTUM RELATED ENCEPHALOPATHY?

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Background: Worldwide an estimated 200 million children are disabled, including those with cerebral palsy (CP); 80% live in low-income countries. Large cohort studies in high-income countries attribute 80% of CP to antenatal causes (1). These data are difficult to obtain in resource-poor settings where the proportion of intrapartum events is higher, with an estimated 1 million survivors of neonatal encephalopathy developing cerebral palsy and other neurological sequelae every year (2). We hypothesised that intrapartum events and neonatal encephalopathy would be a major contributor to the aetiology of CP in a sub-Saharan Africa setting. Aims: (i) To describe the aetiological distribution of CP in affected children presenting to Mulago Hospital, Kampala, Uganda. (ii) To determine the proportion of CP in this group which is attributed to preventable causes in the perinatal and postnatal periods (iii) To describe the patterns of CP seen in the children attending the hospital
Methods: Ethical approval was granted by Mulago Hospital, Uganda National Council of Science and Technology and UCL. Seventy-four children with CP presenting over a 6-week study period were recruited from all in- and out-patient Paediatric services at Mulago, a tertiary referral hospital. Consent was sought. Assessment involved (i) Detailed retrospective history obtained from the mother or primary caregiver, including any self-identified antecedents to the onset of motor impairment; and (ii) Neurological examination to describe the pattern of cerebral palsy and assign a Gross Motor Function Classification System score. Neuroimaging was not available.
Result: Mean age was 25.4 months; 58% were aged <2 years (mean 9.7m). Fifty-one percent were new to Paediatric services (mean 24.1m); 49% were attending follow-up (mean 26.7m). According to maternal report 93% of infants were born at term. Overall, 49% had spastic quadraplegia; 3% spastic diplegia; 8% hemiplegia; 9% choreoathetoid; 8% hypotonic; 22% mixed pattern impairment. Seventy percent (52/74) of mothers gave a peripartum history consistent with neonatal encephalopathy, of whom 46% (24/52) gave a history of neonatal encephalopathy with signs of associated infection. Eight percent of mothers attributed cerebral palsy to neonatal jaundice; 3% to neonatal sepsis and meningitis; 1% to prematurity. Overall 83% attributed CP to illness in the newborn period.
Conclusions: In this retrospective questionnaire-based study, 70% of mothers attributed their child's CP to intrapartum events and/or neonatal encephalopathy. Although a single tertiary centre study and not a population based study, these data contrast with the estimated 10% of CP due to intrapartum events in high-income country population studies (1). Intrapartum and newborn care are key priorities for the prevention of CP in this resource-poor setting.
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VISUAL ASSESSMENT OF JAUNDICE IN THE NEWBORN - HOW GOOD IS IT?

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Background: Jaundice is one of the most frequent indications for diagnostic and therapeutic intervention in an otherwise normal newborn infant. Although bilirubin levels in an infant can be measured both transcutaneously with a bilirubinometer (TcB) or invasive in a blood sample (TSB), jaundice is usually first visually observed by caretakers or parents. Although the eye is generally a good photometer, visual assessment of jaundice has not been considered adequate in the clinical routine. Objective Visual assessment of jaundice as a basis for measurement of TSB in the clinical routine was evaluated in a cohort of 3 568 infants in a normal newborn nursery. Of these, 593 infants had a TSB measurement ordered after a visual assessment of the infant being jaundiced by caretaker or health personnel. The TSB values obtained were compared to treatment indications according to the Norwegian guidelines for treatment of neonatal jaundice (1).
Results: While many infants had TSB levels far below treatment levels, most infants actually had TSB levels close to treatment criteria. On the other hand 77 infants (13%) had TSB levels above treatment criteria at relevant postnatal age. In one infant TSB was 80 µmol/L above treatment criteria. Eleven infants had TSB levels above 300 µmol/L, with a range from 302 to 340 µmol/L.
Conclusions: Visual assessment of jaundice seems to both underestimate and overestimate TSB levels in newborn infants. However, visual assessment will usually identify infants with TSB levels approaching treatment indications. Interns and residents should therefore be trained in visual assessment of jaundice as a first line clinical procedure, as well as a basis for evaluating the reliability of a TcB measurement performed in the infant. 1.Bratlid D, Nakstad B, Hansen TWR. National guidelines for treatment of jaundice in the newborn. Acta Paediatr 2011; 100: 499-505.

ARE BLOOD BILIRUBIN MEASUREMENTS MADE ON A BLOOD GAS ANALYSER PRECISE ENOUGH TO BASE CLINICAL DECISIONS ON?

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Introduction/Background: Neonatal jaundice is very commonly a cause for in hospital treatment and stay. High jaundice levels can also lead to severe neurological sequelae (kernicterus). The jaundice is objectively quantified by using the serum bilirubin measurement (SBR) and the result is plotted on specific gestational age graphs. It is also possible to measure the total blood bilirubin (TBR) concentration on a small blood sample (0.175 ml) using the Siemens Rapidlab 1265 blood gas analyser (BGA). TBR measurements have been made on all blood gas samples in our tertiary neonatal unit for the past three years although there has been no written guideline on the use of these measurements. We aimed to assess whether the precision of these measurements (TBR) is adequate to guide clinical decision making in the management of neonatal jaundice when compared to the SBR measurements. If adequate enough, using the TBR measurements would lead to less blood needed for analysis and a faster turn-around-time and treatment decision time.
Patients and Methods: We retrospectively analysed the results of paired measurements of TBR (on the BGA) and SBR (in the laboratory - Abbott Architect 4000/8000) over a period of three years. Electronically stored results from the BGA and the laboratory were obtained and measurements were matched using the hospital number and the date/time of results.
Results: In total, 4873 pairs of results (1360 separate patients) were included in the study. The median (range) laboratory SBR concentration was 138 µmol/L (13 to 595 µmol/L). Correlation between the two methods was good with Spearman's rho 0.955 ($p<0.0001$). Agreement was also good with a mean bias (Lab - BGA) of 8.7µmol/L (95% limits of agreement -28.8 to +46.3 µmol/L) and no evidence of variation in precision across the range measured.
Conclusions: Measuring the blood bilirubin using the BGA has the advantage of a small blood sample size and provides an immediate result allowing more timely clinical decisions. The methodology could be used to ‘screen' jaundiced babies to determine whether or not a laboratory measurement was necessary (with no need to perform a laboratory measurement if the result was more than 46 µmol/L above or less than 29 µmol/L below a treatment action line). Alternatively given the weakness of the evidence base on which the neonatal jaundice treatment limits are set and the known imprecision in standard laboratory methods of measuring SBR, it may be reasonable to accept this degree of imprecision and use the TBR (BGA method) for all measurements.

EFFECT OF PHOTOTHERAPY ON CEREBRAL OXYGENATION AND CARDIORESPIRATORY STABILITY IN SPONTANEOUSLY BREATHING NEWBORN INFANTS WITH A GESTATIONAL AGE = 32 WEEKS

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Background and aims: We asked whether phototherapy affects cerebral oxygenation and cardiorespiratory parameters in spontaneously breathing term and late preterm infants.
Methods: Term and preterm infants with a gestational age = 32 weeks in need of phototherapy for hyperbilirubinaemia breathing spontaneously and treated in the NICU were included. Regional cerebral oxygen saturation (rSAT) as measured by near infrared spectroscopy, body temperature, heart rate, respiratory rate, arterial oxygen saturation (SPO2), and transcutaneous (tc)pCO2 were continuously registered for 12 h (3 h before, 6 h during, 3 h after phototherapy). Blood pressure was measured intermittently. We calculated fractional oxygen extraction (FOE) and counted episodes of desaturation and bradycardia. Parameters were compared for the periods before, during, and after phototherapy.
Result: Thirty-two infants were included (10 female), median gestational age 34 (range 32-40) weeks, birth weight 2150 (1230-3970) g, age at study 4 (1-7) d. Five infants were on caffeine, 5 on CPAP, and 2 on supplemental oxygen. As compared to baseline, rSAT did not change significantly during and after phototherapy (86.5/83.5/86.0 %; p = 0.2) whereas SPO2 increased significantly after phototherapy, as compared to the time before and during phototherapy (96.8/96.8/97.4 %; p = 0.016). There was no change of FOE. In contrast to our data in very low birth weight infants, no increase in body temperature was observed. Nevertheless, heart rate increased during and after phototherapy (135/142/145 bpm; p < 0.001) while blood pressure, respiratory rate and (tc)pCO2 did not change significantly. Episodes of bradycardia and desaturation did not increase during phototherapy.
Conclusions: In term and late preterm infants breathing spontaneously, there is a slight rise of arterial oxygen saturation after phototherapy while cerebral oxygenation remains unaffected. These results are in line with those of very low birth weight infants on caffeine and CPAP.

SUPERIOR MESENTERIC ARTERY AND CELIAC ARTERY BLOOD FLOW VELOCITY PROFILES AFTER INTRAVENOUS IMMUNOGLOBULIN THERAPY IN NEONATES: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

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Introduction: Intravenous immunoglobulin (IVIg) has been used as an alternative treatment modality for prevention of exchange transfusion among neonates with Rh-isoimmunization. Although IVIg therapy is considered safe in neonates, a few case reports have suggested an association between IVIg therapy and development of necrotising enterocolitis. The mechanisms proposed for such association include alteration in organ blood flows secondary to increase in viscosity after IVIg therapy. There is no data related to the changes in intestinal blood flows after IVIg therapy in neonates. Hence we planned this study to investigate the changes in blood flows in celiac artery and superior mesenteric artery among neonates receiving intravenous immunoglobulin therapy.
Methods: This prospective, single arm, observational cohort study was conducted in the Level III NICU of tertiary care referral teaching hospital of North India from July 2011 to August 2012. The study was approved by institute ethics committee. All consecutive neonates with Rh-isoimmunization or neonatal alloimmune thrombocytopenia, who were eligible for immunoglobulin therapy, were enrolled irrespective of gestational age. Neonates with established NEC or surgical abdomen were excluded. The decision to give immunoglobulin therapy was taken by bedside pediatrician and a dose of 0.5-1.0 g/kg of IVIg was infused over 2 hours as per the standard unit protocol. Hemodynamic assessment in superior mesenteric artery (SMA) and celiac artery blood flow [Peak systolic flow (PSV), End diastolic flow (EDV), Time-average mean velocity (TAMV), Resistive index (RI), Pulsatility index (PI) and systolic to diastolic ratio (SD)] was performed at baseline (prior to immunoglobulin infusion). The hemodynamic assessment was repeated at the end of immunoglobulin infusion and after 12 hours of IVIg infusion. Baseline hemodynamic variables were compared with those measured at 2 hours and 12 hours by Wilcoxon signed rank test.
Result: A total of 33 neonates were enrolled. Their mean (SD) gestation was 36 (2) weeks, mean (SD) birth weight was 2597 (563) grams and proportion of male sex was 58%. Rh-isoimmunization was main indication of IVIg therapy in 29 (88%) neonates. At baseline, median (interquartile range) PSV, EDV, TAMV, RI, PI and SD ratio in celiac artery were 83 (67 to 96), 23 (12 to 29), 23 (17 to 36), 0.80 (0.69 to 0.94), 1.4 (0.9 to 1.6) and 3.4 (2.6 to 6.3) respectively and in SMA were 65 (45 to 87), 8 (2 to 16), 11 (7 to 18), 0.95 (0.77 to 1.11), 1.9 (1.3 to 2.8) and 7 (4 to 14), respectively. There was no significant difference in various hemodynamic variables immediately after and 12 hours after completion of IVIg infusion as compared to baseline in both SMA and celiac arteries.
Conclusions: There was no difference in hemodymanic variables related to superior mesenteric artery and celiac artery blood flow immediately after and 12 hours after intravenous immunoglobulin infusion as compared to baseline. The study results suggest that IVIg does not alter intestinal perfusion.

INTENSIVE MANAGEMENT FOR LATE HYPREBILIRUBINEMIA REDUCES ATHETOTIC CEREBRAL PALSY IN PRETERM INFANTS

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Background: Late hyperbilirubinemia (defined as postnatal age >2 weeks) has been recognized in preterm infants. However, the pathophysiological significance of late hyperbilirubinemia in preterm infants has not been fully elucidated. Additionally, to date, there are no consensus guidelines for the management of late hyperbilirubinemia. Objective: To compare neurodevelopmental outcomes before and after the introduction of intensive management for late hyperbilirubinemia in preterm infants.
Methods: A total of 455 infants <31 weeks' gestation were admitted between January 2004 and December 2009. Nineteen infants with congenital anomalies, 4 infants who had gastrointestinal surgery, 35 infants who died before discharge, and 65 infants who did not undergo neurodevelopmental assessment at 18 months postconceptional age (PCA) were excluded. An intensive management for late hyperbilirubinemia was introduced in 2007. Study infants were divided into two groups, before and after the introduction of intensive management; group A (n=179, 2004-2006) and group B (n= 153, 2007-2009). Serial serum bilirubin measurement was done until 14 days of age in both group A and group B, and continued routinely until discharge in group B. Phototherapy was offered according to the recommended serum bilirubin thresholds for low birth weight infants. The duration of phototherapy and neurodevelopmental outcomes at 18 months PCA were compared between the groups.
Result: There were no differences in the mean gestational age (27.7 vs. 27.3wks, group A vs.B) and the mean birth weight (973 vs. 940g) between the groups. The incidence of non-athetotic cerebral palsy was similar between the groups (32/179(17.9%) vs. 18/153(11.8%), p=0.12). However, the incidence of athetotic cerebral palsy was significantly lower in group A than group B (12/179(6.7%) vs 1/153(0.9%), p=0.004). Serum bilirubin level above threshold for exchange transfusion was shown in 8 of 12 infants with athetotic cerebral palsy, and no infant with late hyperbilirubinemia in group B. The duration of phototherapy before 14 postnatal days was similar between the groups (3(1-11) days vs. 4(1-11) days, p=0.05), while that of after 14 postnatal days was significantly higher in group A than group B (0(0-4)hrs vs. 2(0-14)hrs, p<0.0001).
Conclusions: The incidence of athetotic cerebral palsy was decreased after the implementation of intensive management for late hyperbilirubinemia, suggesting etiological significance of late hyperbilirubinemia on the pathogenesis of athetoic cerebral palsy in preterm infants.

THE PROTECTIVE EFFECT OF GINKGO BILOBA ON THE BILIRUBIN NEUROTOXICITY

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Introduction: Despite recent improvements in neonatology, neurotoxicity caused by hyperbilirubinemia is still being an important problem. Bilirubin is known to have two sided effects on neuron cells, being antioxidant at physiological levels, while causing oxidative injury and apoptosis at pathologic levels. Ginkgo biloba is known to have antioxidant, antiapoptotic, antinitrosative, and antiinflamatory effects, but there is no knowledge about its effects on neurotoxicity caused by hyperbilirubinemia. This study aimed to evaluate the cytotoxic effects of unconjugated bilirubin and the protective effects of gingko biloba (EGB-761) on astrocyte cells culture.
Methods: Astrocyte cells culture were prepared from brains of 1-day-old Wistar albino rat pups by a modification of Cole and de Vellis method. The viability of astrocyte cells decreased with unconjugated bilirubin treatment in a dose-dependent manner. Ginkgo biloba administration before and after unconjugated bilirubin application caused an increase in cell viability. Unconjugated bilirubin concentration toxic to 50% of astrocytes (TC50) and ginkgo biloba (EGB-761) concentration that increased cell viability 100% were determined as 10 µM and 10 µg/ml respectively. The study included control, bilirubin10, ginkgo10, ginkgo10+bilirubin10, and bilirubin10+ginkgo10 groups. In bilirubin10 and ginkgo10 groups, 10 µM bilirubin, and 10 µg/ml EGB-761 were administered to astrocyte cells culture for 48 hours, while no medication was given in control group. In ginkgo10+bilirubin10 group, 4 hours after 10 µg/ml EGB-761 pretreatment, 10 µM bilirubin was administered to astrocyte cells culture for 48 hours, while in bilirubin10+ginkgo10 group 4 hours after 10 µM bilirubin administration, 10 µg/ml EGB-761 was given for 48 hours. The apoptotic cell death due to bilirubin was evaluated by TUNEL staining method.
Result: Compared with the control group, approximately 50% decrease in cell viability, and five times increase in apoptosis was found in bilirubin10 group (p:0.001, p:0.001). EGB-761 administration for prophylaxis and treatment was found to significantly increase cell viability (p:0.001, p:0.001), and significantly decrease apoptosis (p:0.001, p:0.001), when compared with the control group.
Conclusions: This study clearly demonstrate that unconjugated bilirubin has strong cytotoxic effects on mouse astrocytes in-vitro, moreover, ginkgo biloba pre-/post-treatment strongly inhibit bilirubin cytotoxicty of mouse astrocytes.

A NATIONAL GUIDELINE (NICE) ON NEONATAL JAUNDICE: WILL IT REALLY WORK TO REDUCE RATES OF KERNICTERUS?

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Background: Kernicterus is a serious, avoidable condition affecting newborn infants. Its complications include severe disability and death. In 2010, the U.K.'s National Institute for Clinical Excellence (NICE) released guidance for the monitoring and early detection of jaundice in neonates1. This highlighted the dominance of babies with dark skin in international kernicterus registries. It also recommended that any baby with evidence of jaundice should be evaluated by a rapid test and not subjective clinical judgement. Increased surveillance should reduce this small but devastating health burden2. Our objective was to study rates of serum bilirubin testing performed for each ethnic group following the introduction of the guideline. An under-representation of Afro-Caribbean babies would suggest that a problem lies with clinical identification rather than the threshold at which clinicians request laboratory evaluations.
Methods: We collected birth data, including ethnicity, for all babies born in the Nottingham area from November 2011 to November 2012. Laboratory data for all serum bilirubin tests performed during this period was matched by unique National Health Service number. Centralisation of laboratory services resulted in the availability of all serum bilirubin tests, whether performed in the hospital or in the community. Babies born at less than 35 weeks gestation or those whose first bilirubin was performed on the neonatal intensive care unit were excluded from this population study of asymptomatic near-term infants. Babies were grouped by ethnicity and the proportion of serum bilirubin tests performed was compared using a chi-squared analysis.
Results: 9896 babies were included in the study, of whom 83.8% were of Caucasian origin and 4.3% were of Afro-Caribbean origin. 1137 had been tested for jaundice within the first fourteen days of life. The service witnessed a significant increase in overall serum bilirubin testing following release of the NICE guideline (48 tests per month in 2010 to 120 per month in 2012). Despite this increase, babies of Afro-Caribbean ethnicity were significantly less likely to be identified and have subsequent bilirubin measurement. Rates of bilirubin measurement were similar in babies of Caucasian and Asian origin (Caucasian: 11.6%; Asian: 10.8%; $p=0.4$), but were significantly lower in those of Afro-Caribbean origin (Afro-Caribbean: 8.2%; $p<0.05$).
Conclusions: Since introduction of the U.K.'s national guideline on neonatal jaundice, serum bilirubin testing for visible jaundice has increased 2.5 fold. However, in this regional population of predominantly Caucasian origin, a lower proportion of Afro-Caribbean babies undergo serum bilirubin testing despite being at greater risk of kernicterus3. This study suggests that adherence to national guidance on testing for visible jaundice may not have the desired impact in reducing the prevalence of kernicterus in this high risk group, and brings into question how jaundice is identified in these healthy newborn infants.
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THE UGT1A1*28 ALLELE AND EXTREME NEONATAL HYPERBILIRUBINAEMIA, A NATIONAL DANISH CASE-CONTROL STUDY.

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Background: Extreme neonatal hyperbilirubinaemia (serum bilirubin>420 µmol/L) is an important risk factor of severe bilirubin encephalopathy. In a considerable number of patients the reason of extreme hyperbilirubinaemia is never established. UGT1A1 is the rate limiting enzyme in bilirubins metabolism. The UGT1A1*28 allele causes a markedly reduced activity of this enzyme, but the influence on hyperbilirubinaemia is unsettled and the risk of extreme hyperbilirubinaemia not studied. Objective: We aimed to test whether the UGT1A1*28 allele is associated with extreme hyperbilirubinaemia.
Methods: The UGT1A1*28 allele was assessed in a case-control study of all 257 incident extreme hyperbilirubinaemia cases of Caucasian descent in Denmark 2000-2007 and 514 Caucasian controls. Case status was obtained from The Danish Extreme Hyperbilirubinaemia Database and genotypes obtained through The Danish Newborn Screening Biobank.
Result: We observed no association between UGT1A1*28 allele genotype and risk of extreme hyperbilirubinaemia in 207 cases (50 pending analysis): compared to controls, newborns with extreme hyperbilirubinaemia had an odds ratio of 0.9 (95 % CI: 0.5-1.7) for being UGT1A1*28 homozygous. For a subgroup of blood type AB0 incompatible newborns with extreme hyperbilirubinaemia, we found an odds ratio of 1.6 (95 % CI: 0.6-3.7) for being UGT1A1*28 allele homozygous.
Conclusions: Our study explored whether the UGT1A1*28 allele is associated to risk of developing hazardous serum levels of bilirubin. This was not found for Caucasian infants born in Denmark, but may be the case in newborns with AB0 incompatibility.

HOW SHOULD WE INVESTIGATE CONJUGATED JAUNDICE IN PRE-TERM NEONATES? AN EXPERIENCE OF THREE YEARS IN A BUSY TERTIARY CENTER IN THE UK.

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Background: Conjugated jaundice in infants born at below 30 weeks gestation is a common problem encountered in neonatal intensive care. Preterm infants are more likely to suffer from conjugated jaundice because of a combination of factors including delayed liver maturation, parenteral nutrition, delayed enteral feeds, and septic episodes. The rationale for investigation and management is predominantly based on experience from managing term neonates and little has been done to rationalise and optimise the investigation and management of conjugated jaundice in preterm infants.
Methods: We performed a retrospective study of 361 infants born between January 2010 and December 2012 at 30 weeks or less gestation at a tertiary neonatal unit near London. We audited the investigation of the infants against our hospital protocol. We also looked at what factors had influenced those investigations and also at the final outcomes of all infants involved. Currently in our unit we perform the following investigations for cases of conjugated jaundice; TFTs, Gal-1-PUT activity, LFTs, coagulation profile, Hepatitis B and C serology, alpha 1 antitrypsin level and phenotype, plasma amino acids, ammonia level and lactate, Serum IRT, urine reducing substances, urine M, C and S, urine organic acids and a liver Ultrasound scan.
Results: Of the 361 infants there were 42 cases of confirmed conjugated jaundice (Jaundice for 21 days with a conjugated fraction greater than 15%). The mean age was 25 weeks and 4 days with a mean weight of 768g. Of the 42 confirmed cases 37 (86%) had resolved by discharge and 39 (91%) had been diagnosed as either having TPN related conjugated jaundice or were found to have no underlying diagnosis. Of the 5 cases with ongoing conjugated jaundice at discharge two were diagnosed as having hypothyroidism and three were still under investigation at a tertiary Liver centre with no cause identified. There were no cases of biliary atresia, and no cases of metabolic diseases such as galactosaemia. No infants were fully investigated as per the protocol but all patients received LFTs and clotting and 72% received a liver ultrasound (all of which were normal except for one case of an incidental cyst and once subcapsular haematoma). The remainder of the mandatory investigations were completed at a rate of between 20% (viral hepatitis) and 77% (TFT). The predominant reasons for non-completion of investigations were confounding factors such as parenteral nutrition (43% of amino acid abnormalities were attributed to parental nutrition) or difficulties with sampling requiring several repeats.
Conclusion: From our experience conjugated jaundice affects 11.6% of infants born at less than 30 weeks gestation. This is typically due to a combination of parenteral nutrition and prematurity, the vast majority of which (86%) resolves by discharge. We are currently revising our conjugated jaundice protocol to provide a simplified step wise approach that minimizes and prioritizes investigations in this population.

BIOCHEMICAL ASSESSMENT OF NEONATAL CHOLESTATSIS : THE PART OF HEPATORENAL TYROSINEMIA IN OUR INFANCY POPULATION

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Neonatal cholestasis (NC) refers to conjugated jaundice that appears beyond 14 days and within 3 months of life. It requires prompt etiologic evaluation as timely intervention can prevent liver cirrhosis and death.Varieties of extra and intra-hepatic affections are incriminated with poor clinical indices that point to a specific disorder. At our laboratory, we receive about 90-100 requests for biochemical diagnosis of NC per year.
Objective: We develop the practical diagnostic approach to NC and explore differences in biochemical indices between Tyrosinemia type 1 (inborn disease caused by deficiency of the last enzyme in the tyrosine degradation) and other etiologies.
Subjects and Methods: Four hundred forty patients (275 males/165 females; from 3 weeks to 8 months of age) who were referred for investigation of conjugated hyperbilirubinemia from January 2009 to March 2013 were eligible for this study. The liver function parameters analyzed were: total and direct bilirubin, aspartate and alanine aminotransferases (ASAT, ALAT), alkaline phosphatase (PAL), gamma-glutamyl-ltranspeptidase (GGT) and ?-foeto-protein (AFP). Hormonal evaluation included determination of TSH, FT4, cortisol, ACTH. The metabolic selective tests provided were serum tyrosine and ?1-antitrypsine, measure of glycogen in leucocytes, urinary succinylacetone, urine reducing substances and thin layer chromatography of sugars.
Result: on the basis of our screening procedure and the clinical features, following cases have been categorized: - 51 hepatorenal tyrosinemia (25 children died within a few weeks of diagnosis before therapy was initiated. 26 children were treated with NTBC). - 5 congenital galactosemia (with a favourable outcome after diet restriction). - 3 congenital hypothyreosis (with a favourable outcome after levothyrox therapy). - 1 Progressive familial intrahepatic cholestasis type 3 (diagnosis established without genetic study).
Conclusions: Cholestasis in infants constitutes one of the most important diagnostic challenges of the biochemist and pediatric hepatology. In our population, etiologic evaluation shows that hepatorenal tyrosinemia accounts for 11% of inborn errors of metabolism diagnosed. To this preliminary study, we may add limitations that concern the deepening of investigation, which is indispensable for the diagnosis of mitochondrial disorders and peroxisomal metabolism disturbances.

CHANGES OF RESPIRATORY CARE IN EXTREMELY LOW BIRTH WEIGHT INFANTS: A REPRESENTATIVE SURVEY IN GERMAN SPEAKING COUNTRIES 1997 AND 2011.

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Introduction: In the last 20 years an increasing number of studies have been published, which substantially changed the existing evidence in almost every area of neonatal care. However, little is known about changes of treatment strategies. Therefore, we conducted a survey in German speaking countries in order to assess to which extent the treatment intentions of extremely low birth weight (ELBW) infants have changed between 1997 and 2011.
Methods:A questionnaire regarding the routine treatment of newborns between 750g and 1000g was developed in 1996. This questionnaire was sent to all German neonatal intensive care units (NICUs) assumed to care for VLBW infants in 1997. Based on the first questionnaire, a web based follow-up survey was sent to the head of neonatal departments of all Swiss (n=9), German (n=171) and Austrian (n=15) neonatal units caring for extremely low birth weight ELBW infants in 2011. Intensive care units were categorized into university and non-university hospitals. Small, medium and large NICUs were arbitrarily defined as units with annual admissions of =12, 13-30 and >30 ELBW infants, respectively.
Results: In 1997, a completed questionnaire was available for analysis from 126 NICUs. In 2011, 195 neonatal departments were approached and 129 answered (66.2%). Comparison between countries indicated that most therapies are applied at similar frequencies. University hospitals and non-university hospitals, as well as small, medium and large volume NICUs mostly showed no different treatment strategies. During resuscitation the fraction of inspired oxygen has decreased significantly between 1997 and 2011 with more units using 21%, 30%, 31-40% and less units giving 50%, or 51-100% (all $p<0.001$). Furthermore, the administration of hydorgencarbonate has decreased from 1997 to 2011 ($p<0.001$), whereas calcium and atropine have not changed. Mask ventilation for pulmonary resuscitation was performed in 29% with initial inspiratory pressures of 20 cmH2O or less in 1997, compared to 69% 2011 ($p<0.001$). Mechanically ventilated ELBW infants were treated less frequently with sedatives in 2011 compared to 1997; the frequency of analgesia did not change. Routine administration of muscle relaxants was very low in both surveys. However, the combined frequency of 'always', 'frequent' and 'rare' administration of muscle relaxants, compared to 'no administration' showed a significant reduction from 1997 to 2011 ($p=0.008$). Treatment of BPD with corticosteroids was reduced ($p<0.001$). Furthermore the drug of choice changed significantly with a decreased use dexamethasone ($p<0.001$) and increased use of hydrocortisone ($p<0.001$) in 2011 compared to 1997. The application of inhalations and mucolytics were reduced in 2011 compared to 1997 ($p<0.001$ and $p<0.001$, respectively). The increased use of diuretics was borderline significant ($p=0.056$).
Conclusion: Treatment strategies in ELBW infants, regarding administration of muscle relaxants, corticosteroids, inhalative drugs and mucolytics, changed significantly in neonatal care between 1997 and 2011 in Germany, as well as resuscitation strategies in terms of FiO2 , hydrogencarbonate and inspiratory pressures. No substantial differences exist between German, Austrian and Swiss neonatal centers as well as between centers of different size or level of care in 2011.

CAN A QUALITY IMPROVEMENT PROCESS REDUCE THE INCIDENCE OF BRONCOPULMONARY DYSPLASIA IN EXTREMELY LOW BIRTH INFANTS?

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Background: There has been significant improvement in the survival rates for extremely very low birth weight infants (ELBW) in the past two decades. Unfortunately, Broncopulmonary dysplasia (BPD) remains a considerable problem in this population. Few interventions may reduce the rate of BPD in these infants. We embarked on a bundle quality improvement activity to reduce the incidence of BPD.
Objective: The purpose of this study was to compare the incidence of BPD in ELBW after the introduction of a bundle of potentially better interventions in our NICU.
Methods: We reviewed the electronic medical data from January 2006 through June 2012 of all ELBW infants admitted to our NICU. A bundle quality improvement activity was introduced in January 2009. This included: increased use of prenatal steroids, caffeine and vitamin A administration shortly after delivery and frequent challenges to room air keeping oxygen saturation above 88%. We compared maternal, neonatal characteristics, and the incidence of BPD in infants before and after implementation of these changes. Appropriate statistical tests were applied.
Results: Three hundred ninety four infants were included in the study (196 before and 198 after implementation of quality improvement process). There were no significant differences in maternal and neonatal characteristics. A significant reduction in the incidence of BPD in ELBW infants was noted between the periods from 61.7% to 45.6% ($p < .001$). The reduction of BPD in 500-750 g and 751-1000 g infants was 11% and 17.6%* ($p<0.01$) respectively. The overall relative risk reduction for BPD was 26%.
Conclusions: By using a quality improvement process that included prenatal steroids, routine use of caffeine and vitamin A, and adoption of challenges to room air, a significant reduction in the incidence of BPD was observed in ELBW infants. Although several confounders cannot be excluded, it is likely that changes in these clinical practices may be in part responsible for the decrease in rates of BPD in this population.

PATENT DUCTUS ARTERIOSUS (PDA) AND BRONCHOPULMONARY DYSPLASIA (BPD): THE INFLUENCE OF STAGING AND DURATION OF DUCTAL SHUNT.

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BACKGROUND: PDA in premature infants is commonly considered as a risk factor for BPD, even though this association has been not clearly demonstrated and is still an open debate. Recent studies reported controversial data showing that PDA surgical ligation may be more a risk rather than a protective factor for the onset of BPD, neonatal morbidities and mortality. But the epidemiological studies did not focus on the combined effects of duration and magnitude of ductal shunt.
Aim: To assess whether duration and magnitude of ductal shunt are related to an higher incidence of BPD or death.
Methods: In this hospital-based retrospective study we enrolled 233 inborn premature infants with gestational age (GA) = 28 wks, admitted to our NICU from January 2007 to December 2012. Exclusion criteria were: early death and major malformations. The infants who developed BPD or died (Group 1) were then compared with infants without BPD (Group 2). We analysed their serial echocardiographic exams, performed before 36 wks of post-menstrual age (PMA). The entity of PDA shunt was classified according to staging system proposed by McNamara and Sehgal in four increasing grades: from E1= no evidence of ductal flow to E4= large haemodynamically significant PDA. We estimated the duration (days) of ductal patency also considering possible treatment failures and late reopening. Univariate and multivariate analysis was performed to assess the association between PDA parameters and the onset of BPD or death at 36 wks PMA, adjusted for main known risk factors for BPD. BPD was defined as need for oxygen supplementation at 36 wks PMA.
Results: Group 1 (99/233 or 42,4%) compared to Group 2 (134/233 or 57,6%) presented lower GA and birth weight (BW) (mean GA 25,6 wks; mean BW 760gr), worse Apgar score at 1' and 5', more severe Respiratory Distress Syndrome (RDS), higher FiO2 in the first 48 hours of life, greater incidence of hypotension and a lower percentage of patients treated with antenatal steroids. Group 1 compared to Group 2 presented a significant longer duration of E3 and/or E4-PDA: 4,9 vs 2,3 days respectively ($p<0,001$), while duration of E2-graded PDA was not associated with BPD. In the univariate analysis the incidence of surgical ligation was higher in Group 1, while in multivariate analysis, adjusted for BW and RDS severity, only E3- or E4-PDA duration remained signi?cant higher in BPD group (OR 1.06, 95% CI 1,01-1,13 per day of E3-or E4-PDA), but not surgical ligation. The surgically treatment was performed later in Group 1 compared to Group 2 (22 days vs. 33 days; $p=0.03$).
Conclusions: A longer duration of E3 and/or E4-PDA is related to BPD, while the duration of E2-PDA is not. Surgical ligation of PDA itself does not seem an independent risk factor for BPD. A standardized staging system of the severity of ductal shunt is essential to correctly evaluate the association between PDA and the other complications of prematurity.

PULMONARY HEMORRHAGE AMONG VERY-LOW-BIRTH-WEIGHT INFANTS: A NESTED CASE-CONTROL STUDY OF RISK FACTORS, INTERVENTIONS AND OUTCOME.

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Background: Pulmonary Hemorrhage(PH) is continuing to be a critical problem for very-low-birth-weight(VLBW) infants. The small numbers of PH makes it difficult to study prospectively.Despite recent advances and interventions;PH still has a high mortality rate. Objective: 1-Analyse the clinical course of PH among VLBW infants. 2-Determine the risk factors associated with PH. 3-Study the effect of interventions on the outcome of PH infants.
Design/Methods: A retrospective nested case-control study of 23 infants with PH, all were =1250gm and 23 controls; matched for birth weight, gestational age and sex. The study was conducted at King Fahd Armed Forces Hospital, Jeddah, Saudi Arabia for the period from January 2008 to August 2011. In the study period hospital deliveries were 19,655. The number of infants =1500gm:311, infants =1250gm:209 comprising 5.3% of NICU admissions, males:109(52%), length of Hospital stay(LOS):49±39 days and survival to discharge:70%.
Result: PH occurred among 23 infants (7.4%) =1500gm, 74% were males. PH occured at age of life: 46±24.6hr, 35% were extubated for a mean 7.9±9 hours when PH occured. Risk factors associated with PH and control respectively were: Apgar_5min median[IQR]:6[6-8] vs 7[7-8], P<.017, CRIB_score median[IQR]:8[5-9] vs 5[1-7], p<.001 ,C-section: 70% vs 21.7%. p<.001, PDA size(mm): 2.03±0.8 vs 1.53±.65, p<0.04, low CO2 within 48hr prior to PH:33.8±5.6 vs 36.9±6.7 p< 0.003, antenatal_Dexamethasone: 82.6% vs 61%; difference statistically insignificant. There was no difference between groups regarding RDS, surfactant, surf_doses, venti_mode, MAP, IVH, NEC and Sepsis. Surfactant use and packed-red-blood-cell-transfusion during PH were associated with survival. Endotracheal Epinephrine, MAP, other blood products and Vitamin K did not favor survival. Mortality among PH_infants was 65.2% and occurred among 64.7% of males and 66.7% of females with PH. LOS was 110.43±46.5 vs 68.13±28.7, P<.019 among PH_survivors and control respectively.
Conclusions: Pulmonary Hemorrhage occurred three times more among males =1250gm with high equal mortality in both sexes. Sicker neonates at delivery, PDA and Hypocapnia were associated with PH. Surfactant administration during PH could favor survival. Hypocapnic alkalosis potentiated ischemia-reperfusion-induced lung injury could be associated with PH.

RESPIRATORY DISORDERS AND NEONATAL OUTCOME OF TRIPLETS VERSUS TWINS - OWN EXPERIENCE

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Introduction: Due to advances in reproductive medicine and the wide use of artificial reproductive technologies (ART) a significant increase in multiple pregnancies has been observed in the past years. Aim. To compare respiratory disorders (respiratory distress syndrome, requirement for respiratory support, development of chronic lung disease), duration of hospitalization and other neonatal outcome between newborns born from triplet and twin pregnancies.
Methods: The retrospective study population consisted of 21 sets of triplets (63 newborns) and 54 sets of twins (108 newborns) delivered at the place of study between 2007 and 2012. Data were collected on prenatal and perinatal findings, neonatal complications and duration of hospitalization.
Result: Triplets had higher risk of respiratory insufficiency requiring ventilation support than twins ($p<0,00001$). The incidence of respiratory distress syndrome (RDS) was also larger in this group ($p<0,0001$). No differences were found between both groups in the rate of intraventricular haemorrhage, necrotizing enterocolitis and retinopathy of prematurity. Triplets were more likely to develop chronic lung disease but without statistical significance ($p=0,05$). Compared to twins, triplets have longer duration of hospitalization ($p<0,0001$).
Conclusions: Triplet gestation carry an increased risk of premature delivery and neonatal respiratory complications in compare to twins. Both the maternal and neonatal outcome may be improved by antenatal and postnatal care in specialized tertiary centers of perinatal care.

POSTNATAL SYSTEMIC STEROIDS FOR INBORN INFANTS < 27 WEEKS GA STILL INTUBATED AT 14 DAYS OF LIFE: SHORT- AND LONG-TERM (2 YEARS) OUTCOMES IN TWO LEVEL 3 CENTRES WITH PERMISSIVE AND RESTRICTIVE POLICIES.

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Background: Early postnatal dexamethasone for preventing bronchopulmonary dysplasia (BPD) in premature infants impairs neurodevelopment. However postnatal steroids are sometimes used to wean premature infants from mechanical ventilation. Some data suggest that hydrocortisone could improve short-term respiratory outcome without long-term toxicity. We conducted a retrospective study in a subpopulation of extremely premature infants with prolonged ventilator dependency in two NICUs with different policies for postnatal steroids therapy, in order to compare short- and long-term outcomes with permissive or restrictive postnatal systemic steroid use.
Methods: Retrospective 2 centres study from 2005 to 2008 including inborn preterm infants < 27 weeks gestational age (GA) receiving invasive ventilation at 14 days of life. For these patients, local protocols recommended hydrocortisone use in NICU 1 and no or exceptional systemic steroids in NICU 2. Baseline characteristics, short-term outcomes and long-term neurological outcomes were compared between centres. Abnormal neurological outcome at 2 years corrected age was defined by the presence of any of the following criteria: motor impairment, developmental score (Brunet-Lezine or Bayley III) < 85, abnormal neurodevelopment based on clinical assessment if a score could not be obtained or sensory impairment. Variables were compared between groups with Fisher's exact test or Student's t test when appropriate.
Result: During the study period, 107 inborn infants < 27 weeks GA were admitted to NICU 1 and 113 to NICU 2. Results are expressed as mean ± SD or percentage, for NICU 1 vs NICU 2. - On day 14, 17% were dead in each centre. The proportion of infants still intubated on day 14 was higher in NICU 1 (n=62) vs NICU 2 (n=48) ($p<0.05$). Perinatal characteristics of studied infants were similar between centres: 25.6±0.8 vs 25.7±0.8 wks GA, 727±148 vs 762±129 g birth weight, 90% vs 94% prenatal steroids. Evolution during the first 14 days of life was similar between centres except for management of patent ductus arteriosus, mean airway pressure and weight on day 14. - After day 14, 57 infants (92%) in NICU 1 vs 6 infants (13%) in NICU 2 received systemic steroids ($p<0.0001$). Cumulated duration of invasive ventilation (25±14 vs 25±14 d) and mortality (8% vs 10%) were similar between centres. Cumulated duration of non-invasive ventilation (24±10 vs 31±11 d, $p<0.001$), corrected age at oxygen weaning (34.6±4.1 vs 37.8±3.7 wks, $p<0.0001$), corrected age at discharge (40.5±4.5 vs 42.7±3.6 wks, $p<0.05$) and BPD at 36 weeks (30% vs 71%, $p<0.0001$) were significantly reduced in NICU 1. -At two years, 51 (89%) and 37 (86%) of surviving infants were examined. A developmental score was obtained for 89% of examined infants. Developmental scores (94±8 vs 92±12) and abnormal neurological outcome (18% vs 30%) were similar between centres.
Conclusions: In a population of inborn neonates <27 weeks GA still receiving invasive ventilation on day 14, a permissive policy concerning hydrocortisone treatment is associated with reduced duration of non-invasive ventilation, oxygen therapy and hospitalisation, and reduced BPD at 36 weeks. No difference was found concerning duration of intubation, mortality before discharge or neurodevelopmental outcome at two years corrected age.

IS EARLY EAR CANAL (EC) CULTURE FOR MYCOPLASMA AND UREAPLSMA AN INDICATOR OF BRONCHOPULMONARY DYSPLASIA (BPD) AMONG INFANTS < 32 WEEKS GESTATIONAL AGE?

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Introduction: Mycoplasma and Ureaplasma spp. bacterial strains are known to be responsible for chorioamnionitis leading to premature birth and increased risk of developing bronchopulmonary dysplasia (BPD) among premature infants. Isolation rates of Ureaplasma spp. from the chorioamnion are higher in infants who weigh <1,500 g at birth and are born before 32 weeks of gestation. Aim: Our aim was to test if ear canal (EC) culture from premature infants for presence of Mycoplasma and Ureaplasma spp. At the admission to NICU can serve as indicator for developing BPD in our population.
Methods: Infants < 32 weeks admitted to the nursery and NICU had EC culture taken for presence of Mycoplasma and Ureaplasma spp. Medical records from 1/1/2010 to 9/31/2012 were analyzed. Infants were divided into two groups: Mycoplasma/Ureaplasma positive and negative. Data were analyzed according to clinical outcomes: IVH, PVL, NEC, ROP, BPD. Mann-Whitney, Fisher's Exact and logistic regression analysis were used.
Result: 55 infants < 32 weeks were screened for presence of Mycoplasma and Ureaplasma in the EC. Among them 21 were positive and 34 negative. There were no differences in gestational age and birth weight between study groups. There was significantly higher risk for BPD when EC culture was positive OR(95%CI) = 5.17 (1,12-23,8) when corrected for death. Neonatal outcomes are presented in tab.
Conclusions: A positive EC culture for Mycoplasma/Ureaplasma spp. for presence of these organisms in the amniotic fluid may be useful in predicting infants most likely developing BPD at 36 weeks post-menstrual age to receive interventions likely to reduce its severity. Myc/Ure + Myc/Ure - P N=21 N=34 birth weight (g) 1372±367.9 1504±416.5 NS gestational age (weeks) 29±2.2 30±1.4 NS Length of IMV (days) 11.6±16.6 6.96±13 0.0567 Length of stay (days) 38.5±25.0 38.7±25.2 NS IVH III & IV 1 (4.8%) 1 (2.9%) NS NEC 3 (14.3%) 4 (11.8%) NS ROP 5 (23.8%) 3 (9.1%) NS BPD 7 (33.3%) 3 (8.8%) 0.0325 Death 1 (4.8%) 4 (11.8%) NS

EFFECT OF MATERNAL MEDICAL CONDITIONS AND PERINATAL COMPLICATIONS ON NEONATAL MORBIDITY

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Background: Previous studies have investigated the consequences of moderately preterm birth between 32 - 36 weeks' gestation, but the effect of maternal medical conditions and perinatal complications on the morbidity of the newborn is less well investigated. Objective: To assess the effect of selected maternal medical conditions and complications of pregnancy on the risk for morbidity among moderate and late preterm neonates. Design: Retrospective cohort study.
Material and Methods: Preterm infants of 32/0 - 36/6 weeks' gestation without congenital anomalies, born in the Children's and Maternity Hospital Linz, Austria between January 2007 and June 2010 were included. Information regarding gestational age, mode of delivery, maternal age, pre-existing medical conditions [hypertensive disorders of pregnancy (HDP), diabetes, renal/gastrointestinal diseases, malignant tumours] and complications of pregnancy [antepartum hemorrhage, oligohydramnion, preterm premature rupture of membranes (PPROM)] were obtained and associated with neonatal morbidity. Newborn morbidity was defined by combining specific diagnoses, length of hospital stay, and admission to the Neonatal Intensive Care Unit (NICU).
Result: Lower gestational age was clearly an independent risk factor for increased neonatal morbidity ($p<0,001$). Of 870 infants included the incidence of neonatal morbidities increased from 24% at 36 weeks to 43% at 35 weeks', 55% at 34 weeks', 75% at 33 weeks' and 93% at 32 weeks' gestation. 209 mothers (24%) had reported maternal medical conditions. Infants who were exposed to antepartum hemorrhage or oligohydramnion more frequently required parenteral nutrition ($p<0,05$) and had longer stays in the NICU ($p<0,001$). There was a clear correlation between longer stays in the NICU and HDP ($p<0,05$). After the administration of antenatal steroids infants were substantially shorter in the NICU and needed more frequently only noninvasive respiratory support ($p<0,05$). IUGR (intrauterine growth restriction) infants more frequently had hypoglycemia ($p<0,05$), needed parenteral nutrition ($p>0,001$) and were longer hospitalized ($p<0,001$). Longer hospitalizations were also present in multiple gestations($p<0,05$). Phototherapy due to hyperbilirubinemia was required more frequently after PPROM ($p<0,001$) and for male infants ($p<0,05$).
Conclusions: In addition to the extent of prematurity, maternal medical conditions independently contribute to the morbidity of newborns.

NEURALLY ADJUSTED VENTILATORY ASSIST (NAVA): A NEW TOOL FOR INFANTS DIFFICULT TO WEAN FROM INVASIVE MECHANICAL VENTILATION?

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Introduction: Neurally Adjusted Ventilatory Assist (NAVA) is a new mode of mechanical ventilation based on the electrical diaphragmatic activity (Edi) of the patient, which provides a synchronized and proportional ventilatory support on a breath-by-breath basis (Servo-I ventilator, Maquet, Solna-Sweden). We report a series of six patients who had repeated extubation failure episodes, in whom NAVA successfully facilitated the extubation process and subsequent weaning from non-invasive ventilation (NIV).
Case reports: A 7-month-old infant with alpha-dystroglycanopathy was intubated for severe RSV-bronchiolitis. After failing three extubation attempts he was switched in NAVA mode, successfully extubated after 2 days and placed in NAVA-NIV through nasal mask or RAM cannulae® for 2 weeks. Two young infants, two-month and six-month-old, respectively, had paralysis of one hemidiaphragm as a consequence of cardiac surgery, being ventilator-dependent. In NAVA mode they were quickly extubated and supported by NAVA-NIV for about two weeks, either through nasal mask or RAM cannulae®. A 10-month-old infant affected by spine muscular atrophy type-1 suffered acute respiratory failure due to infection. After failing extubation twice she was started on NAVA, extubated on day 2, and then continued on NAVA-NIV for 2 weeks until completion of weaning. All these four patients were eventually discharged at home. Finally, a 30-week premature infant, intubated since birth, was diagnosed myotonic dystrophy type-1 and transferred to our Unit at 40 weeks. After 4 days on NAVA the baby was successfully extubated and supported in NAVA-NIV through nasal cannulae for few weeks. He eventually died due to progressive cardiac failure. The NAVA mode seemed to be well tolerated by all patients, with no adverse effects.
Comment: Our preliminary data suggest a potential role for NAVA in patients with severe respiratory failure of different etiologies, who are difficult to wean from mechanical ventilation. NAVA facilitated extubation and provided an effective and prolonged ventilator support also non-invasively, thus allowing the successful completion of the weaning process. Further research is needed to confirm these preliminary observations. The authors have no potential conflicts of interest to disclose.

CHANGE IN DENTAL ENAMEL IN PREMATURE CHILDREN WHO RECEIVED OR NOT INVASIVE MECHANICAL VENTILATION.

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Few studies describe changes in the oral cavity and tooth development in premature infants discharged from the nursery or suffered some traumatic oral manipulation. The aim of this study was to verify the presence of alterations in dental enamel from preterm infants who received invasive mechanical ventilation (IMV) in relation to those that not receiving invasive ventilation and were treated with CPAP (Continuous Positive Airway Pressure).
Methods: We studied 37 premature children aged between 12 and 24 months, which were classified according to the type of ventilatory assistance received after the birth: Group 1 (G1) consisted of 19 children who received IMV, and group 2 (G2) formed by 18 children who used CPAP.
Result: We recorded data on gestational age (GA), birth weight, duration of mechanical ventilation and the presence or absence of changes in enamel. Data were analyzed by chi-square and Student t tests (a = 5%). The G1 had a mean age of 15.5 (± 3.1) months, G2 and the average age was 18.5 (± 4.6) months. The groups were similar for sex (p = 0.700) and race (p = 0.771). There was no statistically significant difference between groups in relation to gestational age of birth (p = 0.093), weight (p = 0.171) and duration of intubation in days (p = 0.374). There was also no statistically significant difference regarding the presence of changes in enamel (p = 0.206). These were found only in 05 cases from G1 (26.3%) and one case from G2 (5.5%).
Conclusions: This study showed that prematurity, low birth weight and duration of mechanical ventilation were not decisive for the occurrence of the change in the structure of the enamel of primary teeth in premature children.

UNDIFFERENTIATED CELLS IN THE PALATAL TISSUE OF CHILDREN WITH CLEFTS

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Background: Clefts are the second most common congenital anomaly with multifactorial etiology. The embryonic palatal epithelium during the palatal fusion undergoes influence of TGFbeta3 which induces part of epitheliocytes to transfer into the undifferentiated cells. Despite the already described role of TGFbeta3 in the pathogenesis of clefts there are not enough of data about the phenotype of these undifferentiated cells and precise localization of them. Thus, aim of our study was the evaluation of appearance and patterning of undifferentiated cells in cleft affected palatal tissue.
Patients and methods: We obtained material from 6 children (5 months to 7 years old) who underwent primary plastic on lip, soft and hard palate due to the complete unilateral cleft lip palate, and 6 children (6 months to 9 years) who underwent osteoplastic due to the complete bilateral cleft lip palate. Tissue was proceeded for TGFbeta3, neuroendocrine stem cell marker nestin and mesenchymal stem cell marker CD34 by immunohistochemistry.
Results: As cleft patterns didn't show clear correlation between the data, data were analyzed additionally by taking into account the patient dentition age. There were 7 children aged from 5 month to 3.5 years in group before and during primary dentition, and 5 children aged 7 to 9 years in mixed dentition group. So, patients aged before and during mixed dentiton demonstrated variable - from few to numerous nestin-containing cells in the palatal epithelium, while patients of mixed dentition possessed stable numerous to abundant number of such epitheliocytes. Connective tissue of both groups showed numerous nestin positive cells. Abundance of CD34-containing cells was seen in wall of blood vessel in both dentition ages patient, while connective tissue only of younger children showed these cells from few to numerous. TGFbeta3 was detected only in occasional cells in one case from younger, but in three cases - from the eldest children group.
Conclusions: Palatal epithelium is rich source for the neuroendocrine origin cells with prevalence of them in cleft patients of mixed dentition age. Wall of blood vessel and partially connective tissue in palate is homing site for the mesenchymal origin undifferentiated cells, but mainly for cleft children aged before and during primary dentition. TGFbeta3 is practically absent for cleft affected tissue. Presence of neuroendocrine and mesenchymal cell precursors seems to characterize the clefts generally and depend on the dentition age rather than from the pattern of disease.

SNORING IS NOT A SPECIFIC SYMPTOM OF OBSTRUCTIVE SLEEP APNEA IN CHILDREN

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Objective: To determine if snoring is a specific symptom of obstructive sleep apnea (OSA) in children. Materials and Methods. We performed a retrospective study of 141 Chinese patients who were referred to a pediatric sleep laboratory for possible OSA in Beijing, China . The parents of each patient answered a questionnaire before their child underwent polysomnography in the laboratory. During polysomnography, the average duration of each snore, total snoring duration, and ratio of snoring duration to total sleep duration were simultaneously recorded using a microphone. An apnea-hypopnea index (AHI) greater than five on nocturnal polysomnography was defined as OSA. A sleep laboratory physician interpreted the nocturnal polysomnography and snoring data. The occurrence ratio of snoring, observable apnea during sleep, mouth breathing, and restlessness were compared between the OSA and non-OSA groups by the chi-square test. The Pearson correlation test was also used to determine the correlation of the average duration of each snore, total snoring duration, and ratio of snoring duration to total sleep duration with AHI. The correlation of the occurrences of observable apnea during sleep, mouth-breathing, and restlessness with AHI was also determined by the Pearson correlation test.
Results: Among the 141 patients aged 21 months to 12.8 years, 78 (55%) had OSA as determined by polysomnography. No significant difference was found between the OSA and non-OSA groups in terms of the occurrence ratio of snoring based on the data from the questionnaire. The occurrence of observable apnea during sleep, mouth breathing, and restlessness was significantly different between the OSA and non-OSA groups. The average duration of each snore, total snoring duration, and ratio of snoring duration to total sleep duration were not correlated with AHI. However, the occurrence of observable apnea during sleep, mouth breathing, and restlessness were correlated with AHI.
Conclusions: Snoring is not a specific symptom of OSA in children. Observable apnea during sleep, mouth breathing, and restlessness were more important in the diagnosis of OSA in children. Key words. Snoring, OSA, Children

COMBINATION OF SYMPTOMS AND OXYGEN DESATURATION INDEX IN PREDICTING CHILDHOOD OBSTRUCTIVE SLEEP APNEA

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Objective: To develop a screening process of obstructive sleep apnea (OSA) in children based on a combination of symptoms and oxygen desaturation index (ODI). Design Retrospective study Setting Sleep lab of Capital Institute of Pediatrics Participants 141 children aged 21 months to 12.8 years with suspected OSA. Main outcome measures An apnea-hypopnea index (AHI) greater than five was defined as OSA. The occurrence ratio of sleep problems were compared between the OSA and non-OSA groups by the chi-square test. ODI and items that indicated statistically significant differences were tested with non-parametric Spearman correlation tests and binary logistic regression. ODI cut-off point was determined through ODI receiver operating characteristic analysis. Sensitivity, specificity, positive predictive value (PPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and negative predictive value (NPV) were calculated.
Results and Conclusions: Among the 141 patients, 78 (55%) had OSA. Median of ODI and occurrences of observable apnea, mouth breathing, and restlessness were significantly different between two groups. These four items and ODI were correlated with AHI and were important diagnostic factors of OSA in children determined by non-parametric Spearman correlation tests and binary logistic regression. Presence of observable apnea had 95% specificity, 84% PPV, and 4.31PLR. When combined score = 3 was used as cut-off point, specificity, PLR, and PPV were 0.86, 4.22, and 0.84, respectively. When combined score =2 was used as the as cut-off point, sensitivity, NLR, and NPV were 0.92, 0.2, and 0.80, respectively. Observable apnea during sleep was an independent positive predictive factor for OSA in children. A child with observable apnea during sleep should be referred to a special sleep laboratory for PSG diagnosis. When the total score is 3 or 4 based on a combination of symptoms and ODI, OSA can be diagnosed and the child should be referred to a sleep pediatrician for appropriate intervention. When the total score is 0 or 1, the child can be considered normal but should be monitored. When the total score is 2, the result cannot be determined and the child should be referred to a special sleep laboratory for PSG diagnosis. Thus, a screening process is developed based on a combination of symptoms and ODI.

CLINICAL PREDICTORS FOR HOSPITAL ADMISSION IN CHILDREN WITH ACUTE LOWER RESPIRATORY TRACT INFECTION: A PROSPECTIVE OBSERVATIONAL STUDY

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Introduction: Acute lower respiratory tract infections (ALRI) are the most common cause of under-5 mortality and morbidity in children worldwide. It is difficult to decide at presentation whether any particular child with ALRI requires hospitalization, as there is no predictive score available. The definitive diagnosis and hence the child's admission may get delayed, especially in settings where investigative workup is not readily available including resource constraint settings. We designed this study to develop a clinical scoring system for prediction of hospitalization among children with ALRI.
Patients And Methods: This Prospective observational study was conducted over 1 year in Pediatric emergency department (PED) of a tertiary care referral teaching hospital in North India. Children 2 months-5 years with ALRI were included. ALRI was defined as follows: 1) Presence of tachypnea (>40/min for children >1 year and >50/min for children between 2-12 months) and/or chest retractions, 2) one or more of fever >37.8C, wheeze, cough, cyanosis, poor-feeding, lethargy, 3) Duration of symptoms >14 days, 4) No obvious alternative explanation for symptoms. Thirty ‘a priori' identified putative risk factors were prospectively recorded. Our primary outcome was hospital admission. Cases were children who got admitted during hospital stay and controls were those who got discharged from PED within 24 hours. Association between each independent risk factor and hospitalization was tested by calculating OR and 95% CIs. Risk factors with p>0.05 on univariate analysis were excluded. Of the remaining factors, we included factors which were easily measurable at bedside, objective in assessment and related to cardinal signs of respiratory system into binary logistic regression analysis for their independent association with hospital admission, for score generation. To adjudge the model with the best fit, we used goodness-of-fit. Scores for each independent predictor were assigned in proportion to the magnitude of the ß-coefficient derived from logistic regression model. We constructed a receiver operator characteristics (ROC) curve using the total score as the predictor variable and hospital admission as the dichotomous outcome. The p value of the model, and c-statistic were also calculated.
Result: A total of 269 children (75% infants, 2/3 males) with ALRI were analyzed for outcomes. Of them, 144 were admitted. Among all ‘clinical' risk factors, Age <9 Months, RR >50/min, chest retractions, grunt, temperature >37.8C, SpO2 <92%, and oxygen requirement at admission were significantly associated with hospital admission. Out of these seven factors, four factorsâ€”SpO2 <92%, Temperature >37.8C, retractions, and RR >50/ minâ€”emerged as independent predictor variables for model generation. Based on values of beta-coefficients, our model consisted of SpO2 <92% (score of 2), Temperature >37.8C (score of 1), retractions (score of 1), and RR >50/ min (score of 1). The total score was 5. The area under the ROC curve was 0.72 (95% CI 0.66 to 0.78, p<0.001).
Conclusions: Initial SpO2 <92%, temperature> 37.8C, chest retractions, and RR >50/ min mi were independent risk factors for hospitalization among children presenting with ALRI. (CTRI Reg No. CTRI/2012/04/002598)

CHILDREN WITH ASTHMA IN THE EMERGENCY DEPARTMENT; WHAT DID THE CHEST X-RAY CHANGE?

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Background: The Expert Panel Report 3 'Guidelines for the Diagnosis and Management of Asthma' (EPR3) does not recommend the routine use of a chest x-ray (CXR) in the evaluation of children with asthma exacerbations unless they are in severe respiratory distress or have not responded to treatment. However, many children who come to the emergency department (ED) with an asthma exacerbation receive a CXR. Along with unnecessary radiation exposure and increased medical costs, these children many times receive antibiotics since the CXR findings in asthma can be interpreted as pneumonia. We hypothesize that the CXR does not usually alter the management of their asthma exacerbation. Objective: To assess the use and utility of CXR in the evaluation of children with asthma in the ED.
Design/Methods: Retrospective chart review was performed including patients, already diagnosed with asthma, aged 1-18 years with asthma exacerbations who were evaluated in the ED and received a CXR between 2010-2012. Patients with an indication for CXR other than respiratory symptoms were excluded. The subjects were grouped based on their CXR findings and were compared with regards to their disposition status, the use of antibiotics and their clinical course (vital signs, oxygen saturation, response to treatments) in the ED based on the EPR3 guidelines for CXR. The CXR readings by the ED physician and the radiologists were compared. Results were analyzed using frequencies and ?2.
Result: Data of 561 patients were analyzed and from those, 16% (n=91) were admitted. The children who were admitted and met the EPR3 criteria for CXR (31%, n=29), 51% had normal CXR and 49% had pneumonia. The admitted children who did not meet the EPR3 criteria for CXR (69%, n=62), 50% had normal CXR and 50% had pneumonia. Out of the 561 patients, 30.1% (n=169) received antibiotics and, from those patients, 50% had normal CXR and 50% pneumonia. There was no significant difference between the CXR findings, the antibiotic therapy, the disposition status and the fulfillment of the EPR-3 criteria for CXR ($p>0.1$). There was no significant difference between the radiologists and the PED physicians CXR reading, ($p>0.1$). Almost 68% (n=381) of the patients had received =3 previous CXR.
Conclusions: The data show that the CXR did not alter the management and thus should not be a part of the routine evaluation of children with asthma exacerbation.

GENOMIC ABNORMALITIES IN EXTREMELY PREMATURE INFANTS WITH INTELLECTUAL DISABILITY

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Gestational age at delivery is a strong predictor of intellectual disability (ID), being highest at extremely low gestational ages (24-26 weeks); in this group up to 2 in 3 will have special educational needs. Genomic abnormalities are commonly associated with fetal loss during pregnancy. We hypothesised that similar abnormalities may influence outcomes at extremely low gestations and that there is a genetic contribution to the poor intellectual development in surviving children. We performed a genome-wide survey of large (>100kb) and rare copy number variants (CNV, frequency <1%) in a case-control sample using a high-density SNP microarray. 165 extremely preterm children and 5278 population controls were genotyped using Affymetrix 6.0. CNVs were inferred from the SNP data and analysed using established methodology. Data were combined with the results of IQ testing performed at 11 years of age. The burden of CNVs in extremely preterm children was not increased compared with controls (table), nor among 55 children with ID (IQ<55) in whom CNV loci previously implicated in the aetiology of ID were not enriched. EP Children [n=165] Controls [n=5278] ‘p' * Number CNVs Per case Number CNVs Per control Deletions 93 0.56 2173 0.41 0.01 Duplications 125 0.76 4473 0.85 0.32 Totals 218 1.32 6646 1.26 0.56 * Empirical 2-sided P Value based on 10000 permutations We conclude that large and rare CNVs do not significantly contribute to ID in extremely preterm children. This provides support to the hypothesis that ID following extremely preterm birth is more likely to be due to complications of preterm birth and the challenges of supporting continuing neurological development.
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GENETIC INFLUENCE ON SLEEP EEG COMPOSITION IN THE FIRST THREE MONTHS OF LIFE: A TWIN STUDY

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Background: Sleep is a predominant behavioral state in neonates and its quantity and quality is assessed by measuring brain electrical activity with the electroencephalogram (EEG). Since the EEG patterns during sleep change predictably depending on postmenstrual age (PMA), EEG serves as a neurophysiologic marker of brain organization and maturation in healthy neonates but also in those that may be at risk for later neurodevelopmental compromise. The search for the causes of brain injury in neonates indicates that brain damage should be seen in the context of the interplay between genes and environment. The genetic factors underlying individual variability of sleep electroencephalogram (EEG) structure in neonates are largly unknown. Genetic influence on neonatal sleep microarchitecture has yet to be determined. Classical twin studies comparing the phenotypic resemblance of monozygotic (MZ) and dizygotic (DZ) twins are able to provide an estimate of the genetic influence on EEG sleep measures. In this twin study we compared differences in the spectral power composition of AS/REM and QS/NREM sleep among MZ and DZ twins at 37th, 46th and 52nd week PMA.
Methods: Polysomnographic (PSG) recordings were obtained in 10 MZ and 20 DZ twin pairs in 37th, 46th and 52nd week of postmenstrual age (PMA). The EEG power spectra was generated on the basis of Fast Fourier transformation. Genetic influence on AS/REM and QS/NREM sleep composition was estimated by calculating within pair concordance and the intraclass coefficient correlations (ICCs) for d (0.5-3.5 Hz), ? (4-7.5 Hz), a (8-11,5 Hz), s (12-14 Hz) and ß (14,5-20 Hz) at central derivation.
Result: MZ twins show higher ICC correlations than DZ twins for a, s and ß spectral powers during QS/NREM sleep in 37th, 46th, and 52nd week PMA. However, there was no significant difference ($P > 0.05$) between the two types of twins in the mean absolute differences of a, ß and s power values in the 37th, 46th and 52nd PMA. The greatest mean absolute difference between MZ and DZ twin pairtners and also between MZ and DZ twin groups was identified in the delta frequency range.
Conclusions: Our results indicate less within pair similarity for delta power spectra not only in DZ but also in MZ twin groups, while a greater similarity was shown for alfa, sigma, and beta frequencies in both zygosity groups during all three time periods of measurement. Substantially higher ICCs in MZ than in DZ twins identified for alpha, sigma and beta frequency ranges during QS/NREM sleep state in all three periods of measurements (37th, 46th and 52th week) gave an indication of genetic influence in these frequencies. However, the results must be interpreted with caution because higher ICC values were not complemented with higher within-pair resemblance (shown as mean absolute difference in absolute spectral powers) of alpha, sigma and beta frequency ranges in MZ than DZ twins.

NEURODEVELOPMENT EVOLUTION AFTER MODERATE AND SEVERE HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Background: Although the severity of neonatal hypoxic-ischemic encephalopathy (HIE) has been associated with the magnitude of neurodevelopment sequelae, some diversity of the neurodevelopment outcome has been reported. Moderate HIE appears to represent a heterogeneous group with a variable prognosis. Patients and
Methods: We did a retrospective study and analysed the evolution and the neurologic sequelae at 18 months follow-up, and the association of these outcomes with neurodevelopment predictors and cerebral MRI, in a cohort of infants born from 2007-2011 with HIE in one Hospital. Selection criteria: either metabolic acidosis or perinatal complications, and resuscitation at birth, and moderate or severe encephalopathy according to Sarnat and Sarnat's staging system, and gestational age = 36 weeks.
Results: We identified 18 eligible infants, 10 were female. The main risk factors for HIE were: late or variable decelerations on cardiotocography (n=6), meconium fluid (n=4), cord pathology (n=3), placentae pathology (n=2), maternal epilepsy (n=2), maternal thyroid pathology (n=2) and previous fetal death (n=2). HIE was moderate in 7/18 patients and severe in 11/18 infants. Multiorganic failure was identified in 13/18 infants. Cerebral MRI was suggestive of acute ischemic injury in 12/18 infants. The EEG showed abnormal patterns of brain activity in 12/18 infants. At 18 months follow-up, the following sequelae were documented on the severe HIE group: 2/11 died, 6/11 evolved with cerebral palsy, 1/11 evolved with minor deficits and 2/11 had a normal neurologic exam. On the moderate HIE group: 1/7 infant evolved with cerebral palsy, 2/7 with minor deficits and 4/7 showed a normal neurologic exam. Overall 7/16 of the survivors developed important neurodevelopmental sequelae (7/16 cerebral palsy, 6/16 epilepsy, 2/16 blindness). The presence of 3 or more neurodevelopmental predictors (failure to establish breathing by 5 minutes, Apgar score of 3 or less at 5 minutes, onset of seizures within 12 hours, refractory seizures, inability to establish oral feeds by 1 week or abnormal EEG or neuro-imaging) was strongly associated with poor outcome at 18 months ($p=0,008$). The severity of cerebral MRI was associated with negative outcome (cerebral palsy or death), ($p<0,05$).
Conclusions: The presence of three or more neurodevelopmental predictors was associated with poor neurodevelopment outcome at 18 months. Brain MRI findings such as the pattern and severity of brain injury were associated with the neurodevelopmental outcomes. Moderate HIE appears to represent a heterogeneous group with variable prognosis and even severe HIE can have a favourable prognosis. A systematic follow-up, concerning motor and cognitive domains, may help defining interventions in order to improve neonatal outcomes.

NEURODEVELOPMENT OF NEONATES WITH BIRTH INJURY DURING FIRST YEAR OF LIFE

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Children can be injured even in the earliest period of life such as neonatal period,. Unfortunatlly, in spite of modern health care system that excludes birth delivery at home in order to obtain the best medical care to mother and baby, birth trauma is even nowadays one of the main problems in neonatal practice At first glance we can recognize physical birth trauma as kephalhaemathoma, fracture of claviculae, plexus brachialis paresis or paralisis, fracture of ribs or even long bones (humerus and femur) We can detect haemorrhage in brain or suprarenal glandula than can induce such severe health problems that can present real danger toward babies survival using radiological assesment (ultrasound, CT, MRI). If medical support is sufficient to solve this situation just at the beginning of life, main problemthat can occur during first year of life is adverse psychomotor development

Methods: Prospective clinical study was proceeded in 100 term neonates hospitalized at the Institute for children and youth health care of Vojvodina, neonatal department, due to birth injury(AS 5-7 in 1.st minute) Follow up study was prepared by regular check ups at 6 weeks of life and later on in 3 months intervals till 1.birthday by neonatologist , neurologist, physiotherapist and psychologist

Results: and discussion Hypotonia was the most fequent patologic sign of motor development during the first year of life and it was found in over 50% of our patients Due to early neurostimultative treatment in early in children who required it according to their neurological problems,mat the end of our study there were no cases of cerebral palsy . Psychotest revealed normal psychomotor development in all cases but at the bottom range for age of 12 months /RQ 91,66 normal 90 - 125/, slightly dyscharmonic development specially in speech skills.

Conclusion: Although birth injury can be assumed as mild problem if there are no severe consequences in first month of life, it is our duty to follow up psychomotor development in these children as it can become adverse in later period of infancy. Only with preventive check ups and early treatment, severe late consequences as cerebral palsy and mental retardation can be prevented

PRE-ECLAMPSIA - AN ADDITIONAL RISK FACTOR FOR COGNITIVE IMPAIRMENT AT SCHOOL AGE AFTER INTRAUTERINE GROWTH RESTRICTION AND VERY PRETERM BIRTH.

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Objective: To explore the possible influence of pre-eclampsia on cognitive outcome in children born very preterm after intrauterine growth restriction (IUGR) and abnormal umbilical artery blood flow.
Methods: Cognitive function was evaluated at 5-8 years of age with Wechsler scales in 34 children born before 30 gestational weeks after IUGR (PT-IUGR) (11 children were exposed to maternal pre-eclampsia (PE), 23 non-exposed) and in 34 children with no maternal pre-eclampsia and birth weight appropriate-for-gestational age (PT-AGA) matched for gestational age at birth, gender and age at examination.
Result: The subjects in the PT-IUGR group exposed to maternal PE had lower mean verbal IQ (VIQ) (mean±SD 74±16) and lower full scale IQ (FSIQ) (70±19) in comparison with both the non-exposed PT-IUGR (VIQ 89±15; p=0.013; FSIQ 83±14, p=0.029), and, the PT-AGA group (VIQ.96±15, p<0.001; FSIQ 90±14, p=0.001). The differences remained significant after adjustment for known confounders. VIQ and FSIQ did not differ between the non-exposed IUGR and PT-AGA children.
Conclusions: Fetal exposure to maternal pre-eclampsia seems to have an additional negative impact to that of IUGR on cognitive function in children born very preterm.

ELEVATED NEUTROPHILS IN FIRST WEEK OF LIFE AND NEURODEVELOPMENTAL OUTCOME IN PRETERM INFANTS

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Background: To investigate, is there any association between haematological indices in first week of life in preterm, very low birth weight (VLBW) infants and neurodevelopmental outcome at 2 years of age.Recent studies suggest that very low birth weight infants who develop neonatal infection have a significantly increased risk of hypoxia. Perinatal infections are associated with cerebral palsy3. Early warning signs and symptoms are often minimal, subtle and non-specific. We postulate that elevated neutrophil levels in first week of life are associated with poor neurodevelopmental outcome. In neonates, approximately 30 minutes of cerebral ischemia elicits an immediate innate immune response,. This phenomenon may hold important clues for the understanding of the inflammatory response to stroke and its potentially detrimental consequences.4 Studies has shown that Neonatal encephalopathy is associated with altered perinatal systemic neutrophil apoptosis5. In recent studies elevated normoblast count is observed in preterm infants with cerebral white matter injury6. Recent studies showed combining early EEG and normoblast count to predict HIE severity and neurological outcome7. However there is significant disagreement as to association of elevated normoblasts to poor neurodevelopmental outcome Patients and
Methods: In a retrospective study, the neutrophil and other haematological indices were collected from laboratory database on day one and highest count during first week of life. A single neuropsychologist carried out Bayleys scale of infant development (BSID-III) at 2 years corrected gestational age.
Result: 279 infants with birth weight = 1500grams were born in national maternity hospital. 28 infants died in neonatal period. 21 babies were born below 23 weeks gestation and did not survive to NICU admission. 102 VLBW infants had follow up at 2 years and were included in the cohort, 19 infants had below average neurodevelopmental outcome with mean composite score<90 and 83 had normal outcome with mean composite score=90. Those infants who were followed up in other centers by different psychologist were not included in the study. The median(IQR) for highest neutrophil count in first week of life for infants with mean composite score<90 was 8.6(11.6) X 109 and for infants with mean composite score=90 was 4.9(6.4) X 109 (p= 0.022). These were statistically significant. The median(IQR) for highest normoblast count in infants with mean composite score<90 was 17(81) and 34(63) in infants with mean composite score=90. There was no statistically significant difference in these medians (p=0.437)

Conclusions: We demonstrated an association between high neutrophil count in first week of life and mild to severe neurodisability at 2 years corrected age in very low birth weight infants. Elevated levels of neutrophils in first week of life are associated with below average neurodevelopmental outcome This is first study on this topic. We also demonstrated that there was no statistical difference when comparing high normoblast count in first week of life with Total bayleys score at 2 years corrected age, which showed no association between normoblast count in first

RISK PREDICTORS FOR DELAYED PROCESSING SPEED IN 5-YEAR OLD CHILDREN BORN PRETERM

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Introduction: Preterms are at high risk for the development of motoric and cognitive disorders accounting for numerous intellectual problems in further life. Delayed processing speed is an important predictor therefore. Little is known concerning the etiological factors underlying this phenomenon. This study aims to identify risk factors for delayed processing speed in children born before 32 weeks of gestation.
Methods: Within a time period of 3.5 years (January 2003 to August 2006) all infants born before 32 weeks of gestation in Tyrol, an area of Austria, were prospectively enrolled in our study. Processing speed was assessed with the HAWIWA III- test. A total of 161 out of 223 preterm infants (participation rate 72.2%) had a detailed examination at 5 years of age including cognitive assessment (Hannover Wechsler Intelligence Test for pre-school children, third edition (HAWIVA-III) or Snijders-Oomen nonverbal intelligence test (SON-R)). The association between pre- and postnatal factors and delayed processing speed was analyzed. RESULTS: Of 161 tested children, 55 showed delayed processing speed (34.2%). Smoking in pregnancy ($p=0.015$) was highly significant to account for delayed processing speed, in contrast to other perinatal factors (e.g. maternal age, maternal education; n.s.). Furthermore, grade 3 and 4 of retinopathia of prematurity ($p=0.02$), intracerebral hemorrhage ($p=0.008$) and chronic lung disease ($p=0.031$) as well as steroids for chronic lung disease ($p=0.034$) all proved as risk factors. Multivariate analysis identified smoking in pregnancy, steroids for CLD and intracerebral hemorrhage to be associated with consecutive delayed processing speed at the age of 5 years.
Conclusion: We identify smoking in pregnancy as an independent perinatal risk factor for delayed processing speed at the age of 5 years. Furthermore typical postnatal complications of extreme prematurity are associated with delayed processing speed and can therefore lead to consecutive cognitive disorders in former preterm children. We recommend increased emphasis on anti-smoking campains in pregnancy. Cognitive testing of preschool infants and special educational care are warrantable.

SINGLE -NUCLEOTIDE POLIMORPHISMS (SNPS) OF MBL2 GENE OF MANNOSE BINDING LECTIN (MBL) AND MBL SERUM LEVELS AS BIOMARKERS PREDICTIVE OF ADVERSE NEUROLOGICAL OUTCOME IN PRETERM INFANTS.

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Background: Studies on animal models have shown that MBL-mRNA is expressed in brain tissue and MBL may play a role in the brain dysfunction secondary to ischemia-reperfusion injuries.Serum MBL levels vary widely between individuals, due to the presence, in the exon 1 and in the promoter of the MBL2 gene, of Single-Nucleotide Polymorphisms (SNPs), that influence the expression and the stability of the circulating protein. SNPs of the gene MBL2 and circulating MBL, influencing the activation of the lectin pathway of the complement in the brain tissue, could affect the severity of histopathological lesions of the brain during ischemia-reperfusion events in preterm infants and predict the risk of adverse neurological outcome.
Objectives: To evaluate the association between SNPs of the MBL2 gene, MBL serum levels on admission to Neonatal Intensive Care Unit (NICU) and the neurological outcome, assessed during two years follow up, in preterm infants.
Methods: 74 infants born at a gestational age = 32 weeks were studied for MBL2 genotype.Genomic DNA was extracted from blood samples, using the QIAmp DNA Blood kit (Qiagen, Hilden, Germany). Exon 1 of the human MBL2 gene (mutant codons 52, 54 and 57) and its promoter region mutations (codons -221 and -550) were genotyped by polymerase chain reaction (PCR) and restriction fragment length polymorphism (PCR-RFLP) assay. For exon 1, the wild type was designated as allele A and mutations (B as the mutant in codon 54, C in codon 57, and D in codon 52) were pooled and designated as allele 0. For promoter region mutations, the wild type was designated as allele L (position -550) with H as the mutant and allele Y (position -221) with X as the mutant. In a subgroup of 45 infants serum MBL levels had been measured on admission in NICU, using an immunoassay (MBL oligomer ELISA, Antibody Shop, Copenhagen, Denmark). 0,75 µg/ml was the cut-off to discriminate MBL deficiency. Children were subsequently evaluated by clinical exams, brain imaging, auditory brainstem response, eyes examinations during a two years follow up. All children received the Bayley II scales of infant development at 12 and 24 months of corrected age. The adverse neurological outcome was defined as a Mental Development Index Score = 70 at the Bayley II scales at 24 months of corrected age , associated with one or more sensory or motor severe deficits.
Results: 5/5 (100,0%) children with SNPs of the exon 1 showed an adverse neurological outcome, compared to 27/69 (39,1%) children wild type (p=0,01). We find no associations with SNPs of the promoter region. The risk of an adverse neurological outcome was higher, but not significantly, in infants with low MBL serum levels on admission than in infants with MBL above the cut-off (38,9 versus 25,0; OR 1,91; p=0,3).
Conclusions: SNPs of the exon 1 of the MBL2 gene, seem to be associated with a worse neurological outcome in preterm infants and may be predictive of increased neurological risks.

ASSOCIATION BETWEEN NEUROPSYCHOLOGICAL DEVELOPMENT AND GROWTH IN MODERATELY PRETERM-BORN CHILDREN

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Introduction/Background: Of all preterm children ~85% are born moderately preterm, i.e. between 32 and 36 weeks. Preterm children have higher risks of both developmental and growth delay in early childhood. However, the exact interrelationship is unknown. Our aim was to determine the relationship between growth up to 7 years (7y) and neuropsychological development at 7y in moderately preterm-born children.
Patients and Methods: As part of a community based prospective cohort study (LOLLIPOP) we included 247 moderately preterm-born children, born between January 2002 en June 2003. Neuropsychological development was determined at 7y using standardized tests with Dutch norms. We measured total IQ (TIQ), verbal IQ (VIQ), performance IQ (PIQ), motor skills, memory, attention, and visuomotor skills. Growth was measured at birth, 1y, 4y, and 7y and included height, weight and head circumference. To compare growth and neuropsychological development, we calculated z-scores. We computed correlation coefficients between growth and development, and odds ratios (OR) for the risk of abnormal neuropsychological development by growth delay. For the latter, we used cut-off points at the 10% poorest growth and at the 15th centile regarding neuropsychological tests.
Results: We found no association between growth and motor skills. Regarding height gain, we found significant correlations at 4y with TIQ-scores (r=0.151) and visuomotor scores (r=0.230). Abnormal height gain at 4y increased the risk for abnormal TIQ (OR 8.9 [95%-confidence interval: 1.4-55.1]) and visuomotor skills (OR 4.8 [1.1-20.6]). Abnormal height gain at 7y increased the risk for abnormal TIQ (OR 13.0 [2.3-74.0). Regarding weight gain, correlations were significant at 4y for IQ (r=0.169), attention (r=0.152), and visuomotor scores (r=0.165). Abnormal weight gain at 4y increased the risk for abnormal VIQ (OR 7.3 [1.2-46.6]). Abnormal weight gain at 7y increased the risk for abnormal VIQ (OR 20.6 [3.5-120.1]), TIQ (OR 14.7 [2.3-93.3]), auditory attention (OR 2.8 [1.0-7.9]), and attention control (OR 4.3 [1.5-12.5]). We found no associations between abnormal head growth and neuropsychological test scores.
Conclusion: In moderately preterm-born children, impaired height and weight gains at 4-7 years are associated with abnormal scores in some neuropsychological domains (TIQ, VIQ, attention and visuomotor skills), but not in others (PIQ, memory, motor skills). No associations exist between growth in height, weight or head circumference at age 1y and neuropsychological development at 7y.

SCREENING FOR MENTAL HEALTH PROBLEMS IN EXTREMELY PRETERM CHILDREN: ARE TWO HEADS BETTER THAN ONE?

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Background: Children born extremely preterm (EP) are at high risk for psychiatric disorders later in life. Routine screening for early detection of psychopathology would be beneficial. The Strengths and Difficulties Questionnaire (SDQ) is a screening tool with excellent diagnostic accuracy in community and clinic samples, but its use as a screening tool and outcome measure in an EP population has not been tested. Moreover, it is not known whether single or multiple informants provide the greatest diagnostic accuracy in this population. The aims of this study were to investigate the clinical utility of the SDQ in EP children and to determine whether multi-informant reports are a better predictor of psychiatric disorders than single informants alone.
Methods: 219 EP (<26 weeks gestation) children were assessed at 11 years of age as part of the EPICure Study. Parents and teachers completed the SDQ to assess the prevalence of clinically significant emotional, conduct, hyperactivity and peer problems. Multi-informant ratings were aggregated using 2 methods: (1) combined where either the parent or teacher rated the child with an abnormal screen and (2) pervasive where both the parent and teacher rated the child with an abnormal screen. Psychiatric diagnoses of emotional disorders, attention deficit/hyperactivity disorders (ADHD), conduct disorders and autism spectrum disorders (ASD) were assigned using the Development And Well-being Assessment (DAWBA) semi-structured interview completed by parents and supplemented with teacher information.
Result: Using the SDQ, parents were significantly more likely to rate children with clinically significant problems than teachers in all domains except for hyperactivity. Combined ratings resulted in a significantly higher prevalence of all problems than pervasive ratings. Predicting psychiatric disorders from SDQ screens revealed that pervasive ratings had the greatest diagnostic accuracy for emotional disorders (89% accurately classified), conduct disorders (94%), ADHD (90%) and ASD (94%). However, these yielded low sensitivity ranging 17%-50% for the diagnostic categories. To maximise sensitivity for screening purposes, combined ratings were best for emotional disorders (sensitivity 77%, specificity75%), conduct disorders (83%, 88%) and ADHD (85%, 72%), but parent ratings alone were best for ASD (93%, 66%). Using hierarchical logistic regression, an abnormal teacher SDQ significantly improved prediction over an abnormal parent SDQ for conduct disorders (??2 9.3, p=0.002) and ADHD (??2 24.1, p<0.001) only.
Conclusions: Two heads are generally better than one when assessing mental health outcomes. Pervasive ratings have the best predictive accuracy when using the SDQ as an outcome measure, but for first line screening where sensitivity is important, combined ratings should be used for emotional disorders, conduct disorders and ADHD, and for ASD parents know best. The SDQ has excellent diagnostic accuracy when completed by parents and teachers of extremely preterm children and provides a psychometrically sound outcome measure for use in this population.

INATTENTION AND HYPERACTIVITY IN CHILDREN BORN VERY PRETERM: IMPLICATIONS FOR SCREENING AND DETECTION

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Background: Very preterm (VP) birth is associated with an increased risk for psychiatric disorders, particularly Attention Deficit/Hyperactivity Disorders (ADHD). Recent studies have suggested that the risk for ADHD in this population is specific to symptoms and disorders associated with inattention rather than hyperactivity. As inattention is not typically associated with disruptive behaviours, we hypothesised that VP children with inattention may not be detected as easily in the classroom as other children with ADHD, and inattention difficulties may thus go unidentified. Aims. (1) Explore the impact of VP birth on inattention vs. hyperactivity. (2) Determine whether inattention difficulties are identified in school.
Participants and Methods: 117 VP (<32 weeks) children aged 8-10 years in mainstream schools were recruited with a control group of 78 term-born classmates. Parents and teachers completed the Du Paul ADHD Rating Scale IV to assess symptoms of inattention and hyperactivity; higher scores indicate greater difficulties. Combined parent and teacher scores >90th percentile were used to identify clinically significant difficulties. Information was obtained about Special Educational Needs (SEN) from teacher questionnaires.
Results: VP children had significantly higher parent and teacher inattention scores than controls (parent mean difference 3.4, 95%CI 1.7 to 5.1, p<0.001; teacher 3.5, 1.7 to 5.2, p<0.001), and significantly higher parent hyperactivity scores although the effect size was smaller (1.7, 0.2 to 3.2, p=0.022). Among the VP group, both parents and teachers rated children with significantly higher inattention than hyperactivity scores. More VP children than controls had clinically significant levels of inattention (20% vs. 4%, RR 5.1, 95%CI 1.6 to 16.5, p<0.001), but not hyperactivity (10.4% vs. 6.5%, 1.6, 0.6 to 4.4, p=0.346). 40 (42%) VP children and 13 (18%) controls had SEN. After these were excluded, VP children still had significantly higher teacher inattention scores than controls (mean difference 2.1, 95%CI 0.6 to 3.6, p=0.007) and marginally significantly higher parent inattention scores (1.7, -0.0 to 3.4, p=0.056). In contrast, there was no significant excess of hyperactivity among VP children after those with SEN were excluded.
Conclusions: VP birth poses a significantly greater risk for inattention vs. hyperactivity/impulsivity, in terms of both symptoms and clinically significant difficulties. VP children without SEN had significantly higher levels of inattention than controls indicating that, unlike hyperactivity, these problems may go undetected in school. This has important implications as inattention is a key predictor of long-term school performance. Screening for inattention in VP children may aid in detecting those with potential academic difficulties and targeting intervention.

EARLY DEVELOPMENT OF SMOOTH PURSUIT EYE MOVEMENTS IN VERY PRETERM CHILDREN IN ASSOCIATION TO THEIR COGNITIVE DEVELOPMENT AT 2½ YEARS

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Background: The ability to smoothly follow a moving object (smooth pursuit eye movements=SP) develops in mutual dependency with cognition, as you need to predict the velocity and direction of the object to keep it in focus. Children born very preterm (VPT), i.e. <32 w gestational age, are at risk for impaired perception and cognition, and have previously been shown to have a lower gain of smooth pursuit, i.e. proportion of smooth pursuit following a moving object. Strand Brodd et al (2011) showed that at 2 and 4 months corrected age (CA) infants born VPT showed lower gain than term infants (0.27 vs 0.52, $p<0.001$ and 0.46 vs 0.63, $p = 0.001$, respectively). At 4 months CA, the gap was smaller than at 2 months, suggesting some catch-up effect. A significantly larger share of the infants born VPT reached the 10th and 50th percentile for the term group at 4 months CA. Aim: The aim of this study was to investigate any association between early smooth pursuit eye movements and cognitive development at 2 ½ years CA in children born VPT. Method: The study group, comprised of 113 infants born in 2004-2007, with a gestational age of 22 to 32 weeks and a birth weight between 520-2030 g. The infants' head- and eye movements were recorded twice, at 2 and at 4 months CA, while they were looking at a happy face moving horizontally back and forth. The proportion of SP in relation to (head movements, saccades) the objects movement was calculated. At 2½ years CA the children were examined with the Bayley Scales of Infant Development III (BSID III).
Result: At 2 ½ years CA 100 children were available for examination with the BSID III. Of the study subjects, 50 had had their eye movements recorded at 2 months and 67 at 4 months CA. The results showed a significant correlation between the cognitive subscale of the BSID III and SP at 4 months CA ($p=0.027$) but not at 2 months CA. There was no significant difference between BSID III scores for the children examined at 2 months compared to the children at 4 months.
Conclusions: Early smooth pursuit eye movements at 4 months CA, but not at 2 months CA, were significantly correlated with cognitive capacity at 2½ years CA. In normally developing children SP are very close to adult levels at the age of 4 months. This implies that in some children with impaired SP at 2 months CA a rapid development of SP takes place. The ones who improve their proportion of SP have higher score on the BSID III cognitive subscale, resulting in a significant correlation. It remains to be investigated if children born prematurely can develop their SP capacity beyond this age of 4 months CA. If the deficit persists it might have a negative effect on cognitive development.

MATHEMATICS ATTAINMENT IN VERY PRETERM CHILDREN: THE CONTRIBUTION OF GENERAL COGNITIVE SKILLS.

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Background: Very preterm (VP; <32 weeks) birth is associated with general cognitive deficits in IQ, executive functions, working memory, visuo-spatial skills and processing speed. Children born VP are also at higher risk for academic underachievement compared with term-born peers, especially in mathematics. VP children's difficulty with mathematics appears to be specific and persists even after controlling for IQ. Previous studies have investigated isolated or a small number of general cognitive skills to assess their contribution to academic performance. In this study we concurrently assessed a wide range of domain-general skills to quantify their relative contributions to VP children's attainment in mathematics and to determine whether these differ from term-born peers.
Design: 117 VP children aged 8-10 years in mainstream schools were recruited with a control group of 79 term-born classmates. Children completed two half-day assessment sessions comprising a variety of tasks. Standardised measures assessed mathematical attainment, non-verbal IQ, speed of processing, fine motor skills and a number of executive functions including visuo-spatial working memory, visuo-spatial skills, inhibition and switching. Effect sizes (Cohen's d) were computed for comparison across standardised and experimental tasks. All variables were entered into two separate multivariable linear regression models to assess the contribution of these general skills to mathematical performance among VP children and control children, respectively.
Results:. Group differences. VP children had significantly lower scores for non-verbal IQ (mean difference -7.2; 95%CI -13.0 to -1.3; d=0.4) and attainment in mathematics (-12.3; -18.0 to -6.6; d=0.6) compared with controls. VP children also had poorer speed of processing (d=0.4, p=0.007), visuo-spatial working memory (d=0.4, p=0.015), visuo-spatial skills (d=0.6, p<0.001), inhibition (d=0.4, p=0.014) and switching (d=0.4, p=0.004) than their term-born peers. No differences were observed between groups in fine motor skills. After adjusting for IQ, significant group difference were only observed in speed of processing (p=0.025), visuo-spatial skills (p=0.003) and switching (p=0.038). Predicting mathematical attainment. The general cognitive skills described above explained 52% of the variance in both VP and control children's mathematical attainment, however the pattern of predictors differed between groups. Whilst speed of processing, inhibition and switching were significant independent predictors for both groups, visuo-spatial skills were a significant predictor only for VP children, and visuo-spatial working memory was a significant predictor only for control children.
Discussion: General cognitive skills affected by VP birth account for a substantial portion of the variance in mathematical attainment. Similar skills were important for attainment in both VP and term -born children, but visuo-spatial skills were a unique predictor of VP children's attainment. Visuo-spatial skills have previously been reported as a specific area of weakness for this group. Therefore, it may be suggested that interventions focusing on improving these skills may be pertinent for improving mathematics skills in VP children.

PEER VICTIMISATION OF VERY PRETERM CHILDREN AT SCHOOL AGE AND THEIR EMOTIONAL CONSEQUENCES

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Background: Peer victimisation (i.e. being bullied) in childhood has been found to predict a range of physical and mental health problems such as depression, psychotic symptoms, self-harm and schooling difficulties in childhood and adolescence and throws a long shadow over mental health into adulthood. Very preterm or very low birth weight (VP/VLBW :<32 weeks gestation or <1500g birth weight) adolescents are at increased risk for mental health problems including emotional and self-esteem problems. AIMS We investigated whether VP/VLBW adolescents have more often emotional problems because they are more often victimized by peers than full term children.
Methods: In a prospective geographically defined population sample in South Germany, we investigated VP/VLBW children and full term controls from birth to 13 years of age. Peer victimization was assessed by parent report at 6;3 (preschool), 8;5 (elementary school) and 13 years (secondary school). The primary outcome was emotional problems and adolescents' self-esteem at 13 years. Potential confounders controlled for included socio-economic status, child cognitive and language abilities, attention and emotional problems and physical growth assessed preschool.
Results: Of 448 VP/VLBW survivors and 350 full term controls, 263 (59%) VP/VLBW and 293 (84%) had complete datasets. VP/VLBW were not more likely to be bullied at preschool but more often victimized at school age (OR: 1.63 (1.16-2.28)), in particular, chronically in primary and secondary school (OR: 2.35 (1.38-4.01). Children of lower cognitive abilities, with attention or emotional problems in preschool and who were shorter were more often victimized. As VP/VLBW children had more of these problems compared to full term controls they were more often targeted by bullies. When peer victimization was included in prediction functions, it was peer victimisation, in particular chronically victimised children that were at highest risk and not just those who were born very preterm.
Conclusions: Our findings strongly suggest that preventing or dealing with peer victimization could reduce emotional problems and increase self-esteem in all children and in particular those who are vulnerable. While all children have a right to grow up in a safe environment, very preterm children are a highly vulnerable group for peer victimisation and some of the long term psychological adjustment problems attributed to very preterm birth are secondary consequences that could be prevented. Preterm children are often in contact with primary and specialist health service providers. Health providers should routinely ask about peer relationships. Many victimized children do not tell their teachers or parents and just being aware of bullying may reduce prolonged peer victimization. The results suggest that new innovative interventions that increase competence in peer interactions may reduce long term adverse consequences of preterm birth.

EMOTION, ATTENTION AND EFFORTFUL CONTROL AT 24 MONTH-OLD IN VERY PRETERM AND FULL-TERM CHILDREN

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Objective: Literature reports behavioral and socio-emotional problems in children born very preterm that persist throughout adolescence and early adulthood. This study aims to investigate emotion, attention and effortful control in very preterm and full-term children.
Methods: 49 children born very preterm (<29 wks GA) and 27 children born full-term were evaluated at 24 months of age. The Early Childhood Behavior Questionnaire (ECBQ) was completed by parents. Four episodes of the Laboratory Temperament Assessment Battery (assessing joy, anger, fear and attention) and 3 episodes of the Effortful Control Battery (assessing inhibition) were administered to the children
Result: Results on the ECBQ indicate that very preterm children are rated as having higher level of negative affect (discomfort, fear, motor activation, perceptual sensitivity) (p .003) and lower sustained attention (p .024) than full-term children. The higher prevalence of negative affect in preterm children was not confirmed by the experimental tasks. Nevertheless, a trial after trial analysis highlighted specific dysfunctions in the very preterm group such as a distinct attentional pattern with an unchanged level of attention during the tasks and greater difficulties in maintaining inhibitory control compared to the full-term group (p .006)
Conclusions: Taken together, these different results reinforce the existing literature showing the importance of considering both questionnaires and experimental assessments when evaluating populations at risk for developmental disorders. These results were particularly informative bringing new informations about specific dysfunctions in children born very preterm, which may be predictive of later behavioral difficulties.

PERSISTENT PATENT DUCTUS ARTERIOSUS (PPDA) IN VERY PRETERM INFANTS: HIGH RATE OF SPONTANEOUS CLOSURE AFTER HOSPITAL DISCHARGE

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Background: The indication for pharmacological and/or surgical closure of haemodynamically significant Patent Ductus Arteriosus (HSPDA) is highly controversial. Furthermore limited information is also available on how to treat PPDA after failure of pharmacological closure.
Patients and Methods: A retrospective evaluation was conducted in a cohort of preterm infants admitted to the Neonatal Intensive Care Unit (NICU) of Ancona, Italy, between Jan-2004 and Dec-2012. Inclusion criteria were: gestational age (GA) between 24+0 to 29+6 weeks or birth weight (BW) < 1250 g, admission within 48 h from birth and discharged alive from hospital. All infant received routine heart ultrasound between 48 and 72 h of life. HSPDA was defined as a duct diameter > 1.5 mm, a left atrium-to-aorta ratio > 1.4 and an end-diastolic reversal flow in aorta. First line treatment for HSPDA was intravenous ibuprofen (IBU). Intravenous indomethacin (INDO) was used if IBU failed. Surgical ligation was considered in case of persistent HSPDA after failure of IBU and two courses of INDO. If PPDA was not haemodynamically significant, it was followed twice a month by routine ultrasound.
Result: Three hundred and fifty infants met the inclusion criteria (GA 27.4±1.5 w, BW 907±189 g) and PDA was diagnosed in 227 (64.8 %). Two-hundred and nine (92.1%) had HSPDA and 18 (7.9%) non haemodynamically significant PDA (NO_HSPDA). Pharmacological closure of HSPDA was achieved in 168 (80.4%), surgical ligation was performed in 17 (8.1%) and a PPDA was diagnosed in 24 (11.5%) patients. No treatment was given to the 18 NO_HSPDA, with failure to spontaneous closure PPDA in 2 (11.1%).Median age at IBU start was 3.5d (interquartile range IQR 2.8-4.6d). After IBU, PDA closure rate was 43.6%. Median age at 1st INDO was 8.4d (IQR 6.7-11.8) and closure rate was 40.3%. Median age at 2nd INDO was 12.6d (IQR 9.3-20.6) with a closure rate of 53.1%. Surgical ligation was performed at a median age of 28d (IQR 22-37).The 24mo follow-up was available for 15 (83.3%) of the 18 infants born from 2004 to 2010 with PPDA. Thirteen (86.4%) underwent spontaneous PDA closure and only 2 (13.3%) required surgical ligation.
Conclusions: The information that PPDA undergoes spontaneous closure in a vast proportion of patients is of importance and should be taken into account when considering surgery or additional attempts of pharmacological closure.

CAN B-TYPE NATRIURETIC PEPTIDE ASSAYS PREDICT RESPONSE TO MEDICAL TREATMENT FOR SYMPTOMATIC PATENT DUCTUS ARTERIOSUS IN PRETERM INFANTS?

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Introduction/Background: A hemodynamically significant patent ductus arteriosus (PDA) in preterm infants is a common and an important problem associated with significant morbidity and mortality including: intraventricular hemorrhage, necrotizing enterocolitis and bronchopulmonary dysplasia. Therefore, optimal management of PDA is important for improving the clinical outcomes of preterm infants. However, there is no clear evidence of effect on long-term outcomes of PDA treatment in preterm infants. And also there are insufficient data to conclude whether surgical ligation or medical treatment with cyclooxygenase inhibitors is preferred as the initial treatment for symptomatic PDA in preterm infants. There is a risk of failure to close PDA with cyclooxygenase inhibitors. Early medical treatment is associated with more renal side effects and there is not any evidence of respiratory advantage or any difference in other clinical outcomes. The aim of this study is to determine to determine whether plasma BNP levels can predict the failure of the pharmacological closure with cyclooxygenase inhibitors for symptomatic PDA in preterm infants.
Patients and Methods: Seventy five preterm infants with symptomatic PDA were enrolled in this study that underwent plasma BNP measurement before the medical treatment and treated with the first cycle of cyclooxygenase inhibitor (indomethacin or ibuprofen). Of the 75 infants, 57 infants (Responder group, 76.0%) responded to the first cycle of cyclooxygenase inhibitor, indicated by reduced the diameter of PDA and disappeared symptomatic PDA. 18 infants (Non-responder group, 24.0%) did not respond to the first cycle of cyclooxygenase inhibitor, needed additional treatment such as the second cycle of cyclooxygenase inhibitor (16 infants) or surgical ligation of PDA (11 infants).
Results: There was no significant difference in the BNP levels before the medical treatment between the responder group and the non-responder group (2,522±1,288 vs. 3,088±1,519 pg/mL, P = 0.118). But BNP levels were significantly correlated with the magnitudes of the ductal shunt, such as the diameter of PDA, the ratio of left atrium to aortic root diameter and the diastolic flow velocity of left pulmonary artery. The area under the ROC curve of BNP levels for prediction of no response to the first cycle of cyclooxygenase inhibitor for symptomatic PDA in preterm infants was 0.554. At the cutoff BNP level of 2,640 pg/mL and 4,000 pg/mL, the sensitivity was 66.7% (12 of 18) and 35.3% (6 of 17) and the specificity was 59.6% (34 of 57) and 87.9% (51 of 57).
Conclusions: Extremely high BNP levels before the first cycle of cyclooxygenase inhibitor were useful for the prediction of subsequent non-response to the medical treatment for symptomatic PDA. In preterm infant with symptomatic PDA, a BNP level above 4,000 pg/mL can be used as a guide for consideration of initial surgical management for the early therapeutic response to hemodynamically significant PDA and the avoidance of the unnecessary use of cyclooxygenase inhibitors in some preterm infants.

HEMODYNAMIC INSTABILITY FOLLOWING DUCTAL LIGATION IN THE VERY LOW BIRTH WEIGHT INFANT

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Purpose: To identify preoperative risk factors predicting hemodynamic instability, investigage clinical features and effect on the neonatal morbidity of hemodynamic instability after patent ductus arteriosus (PDA) ligation in very low birth weight (VLBW) infants.
Methods: This retrospective study enrolled 45 VLBW infants who underwent bedside PDA ligation at Asan Medical Children's Hospital (Seoul, Korea) from May 2008 to May 2011. Hemodynamic instability was defined as systemic hypotension (mean blood pressure < 10percentile) within 24hrs after PDA ligation and use of inotropics and/or bolus infusion. The patients were divided into hemodynamic stable (HS, n=29) and hemodnamic instability (HI, n=16) groups. Indices of cardiorespiratory stability were recorded before and 1, 6, 12 and 24h following ligation.
Result: The incidence of hemodynamic instability after PDA ligation in VLBW infants was 36%. There were no differences in birth weight, weight on operation day, postnatal age at ductal ligation, use of prostaglandin inhibitors, preoperative B type natriuretic peptide (BNP), PDA size, preoperative FiO2 and oxygenation index. In univariate analysis, HI group had lower gestational age (27+8±2.4 vs. 26+0±1.4 weeks, P=0.033), preoperative pH (7.32±0.07 vs. 7.22±0.15, P=0.034), preoperative base excess (-0.2±4.6 vs. -6.7±8.5 mmEq/L, P=0.002), urine output for 24hrs before ligation (2.5±1.1 vs 3.0±0.8 mL/kg/hr, P=0.09) and higher preoperative creatinine (0.71±0.37 vs. 1.08±0.69 mg/dL, P=0.021) than HS group. Preoperative base excess was a significant risk factor predicting hemodynamic instability in multivariate analysis. HI group had more severe bronchopulmonary dysplasia (0 vs. 3, P=0.011) and longer duration of mechanical ventilation including continuous positive airway pressure (CPAP). Hemodynamically significant patent ductus arteriosus (PDA) is a common problem in premature infants. After PDA ligation, unexplained postoperative hypotension requiring vasopressor is reported
Conclusions: Metabolic acidosis, associated with decreased renal function, was preoperative predictors of hemodynamic instability after PDA ligation. Hemodynamic instability was associated with severity of chronic lung disease and duration of hospitalization.

REPEATABILITY OF ECHOCARDIOGRAPHIC PARAMETERS TO EVALUATE THE HEMODYNAMIC RELEVANCE OF PERSISTING PATENT DUCTUS ARTERIOSUS BOTALLI (PDA) IN PRETERM INFANTS

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Introduction/Background: Echocardiographic and dopplersonographic parameters are routinely used to estimate the magnitude of the left-to-right-shunt (LRS) through a PDA and to define the need for PDA closure in preterm Infants; yet there is insufficient data about the inter-observer repeatability of these parameters.
Objective: To evaluate the inter-observer repeatability of these echocardiographic parameters.
Methods: In preterm infants <34 weeks gestational age (GA), in whom a PDA was suspected based on clinical examination, 2 of 3 investigators prospectively and independently determined the following set of echocardiographic parameters within 30min: Left Atrium / Aortic root diameter-ratio(LA/Ao-ratio), Left Ventricular Pre Ejection Period / Ejection Time-ratio (LVPEP/LVET), Velocity Time Integral (VTI) at Aortic Valve / VTI at Pulmonary Valve-ratio (VTI_AoV/VTI_PV), resistence index (RI) in truncus coeliacus (TC) and arteria cerebri anterior (ACA), diameter of PDA on 2D-echo and maximum systolic und minimal diastolic flow velocity through the PDA at its narrowest point. Repeatability coefficient (RepC) and repeatability index (RepI) were determined according to Bland & Altman and a confidence-step-analysis (CSA) was performed. The RepC (= 2 times the standard deviation of the differences) represents the smallest difference between 2 measurements that, with 95% probability, is not allegeable to inter-observer variability. The RepI is the ratio of RepC/ the arithmetic mean of all measurements. A high value of RepC or RepI indicates poor repeatability. A high CSA value (CSA = difference between lowest and highest value / RepC) indicates a high sensitivity to identify differences not caused by inter-observer variability. Outlier were identified by Dean & Dixen outlier test and excluded from statistical analyses. Data are depicted as median (interquartile range).
Result: 25 repeated measurements were analysed in 18 infants (GA 29 (28-31)weeks; birth weight 1316 (1130-1550)g; postnatal age 16.5 (5.5-18.9)d and weight 1531 (1098-1878)g at the time of echocardiographic assessment). A LRS was identified by color-dopplersonography in 15/25 measurements. PDA-diameter and flow velocities could rarely be measured. Parameters sorted from highest to lowest repeatability: RI_TC (RepI=9%; RepC=0.07; CSA=7.9), RI_ACA (15%; 0.12; 3.8), LA/Ao-Ratio (21%; 0.31; 4.2), VTI_AoV/VTI_PV (28%; 0.31; 5.1), LVPEP/LVET (30%; 0.09; 2.9).
Conclusions: The repeatability of echocardiographic parameters in preterm infants is poor. The best repeatability was found for RI_ACA, RI_TC and the LA/Ao-Ratio. Because of their high RepC, VTI_AoV/VTI_PV and LVPEP/LVET should not guide therapeutic decisions. Supported by â€žElse Kröner-Fresenius Stiftung'.

N-TERMINAL PRO-B TYPE NATRIURETIC PEPTIDE AND TROPONIN T AS MARKERS OF PDA SIGNIFICANCE AND BRONCHOPULMONARY DYSPLASIA IN VERY PRETERM NEONATES

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Background: N-terminal pro-B type natriuretic peptide (NT-proBNP) and Troponin T (TnT) appear to be associated with the severity of patent ductus arteriosus (PDA) shunting as assessed by echocardiography. However, the interpretation and application of NT-proBNP and TnT in the evaluation of PDA and any relationship to adverse outcome needs further exploration. In neonates born before 32 gestational weeks we investigated the association between NT-proBNP and TnT and the following endpoints; (i) newborn characteristics and immediate disease (gestational age at birth, gender, Apgar score, inotropes, mechanical ventilation, and sepsis) (ii) PDA diameter and ratio of left atrium to the aorta (LA:Ao-ratio) and (iii) bronchopulmonary dysplasia (BPD).
Patients and Methods: A cohort study of 134 neonates. PDA diameter and the ratio of the left atrium to aorta (LA:Ao-ratio) were measured on echocardiography postnatal day three. Plasma samples was collected the same day, NT-proBNP and TnT were measured by routine immunoassays. We assessed BPD at 36 weeks of corrected gestational age.
Result: We found that gestational age at birth was inversely related to both NT-proBNP and TnT. There was an incremental association between PDA diameter and NT-proBNP and TnT and the LA:Ao-ratio and NT-proBNP, but not TnT. We found that the risk of BPD increased 1.6-fold with one unit increase of natural log NT-proBNP when adjusted for gestational age (OR=1.6, 95%CI 1.2; 2.2). Adjusting for the presence of a PDA day three, LA:Ao-ratio, and gender did not change the estimate.
Conclusions: NT-proBNP and TnT were associated with gestational age at birth and echocardiography markers of PDA significance. We found NT-proBNP to be associated with BPD and speculate if NT-proBNP may add to the early identification of preterm neonates at risk of BPD.

LARGE PATENT DUCTUS ARTERIOSUS IS NOT ASSOCIATED WITH REDUCED CEREBRAL OXYGENATION IN VERY PRETERM INFANTS??

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Background: Patent ductus arteriosus is associated with adverse outcome in the preterm infant, including an increased incidence of intraventricular haemorrhage. Previous studies have suggested that preterm infants with PDA have lower regional cerebral oxygenation (rCSO2) values, indicating reduced cerebral blood flow.
Objective: To determine if there are differences in rCSO2 values between preterm infants with large patent ductus compared to preterm infants without a large PDA.
Design/Methods: This was a prospective, observational study of preterm infants less than 32 weeks in the first 48 hours of life. rCSO2 values were measured using NIRS INVOS 5100C. All patients had echocardiograms performed during this time period and these were analysed at a later date by an investigator blinded to rCSO2 values. Cranial ultrasound was performed at enrolment, within the first 3-7 days and at 1 month. Statistical analysis was performed using SPSS.
Results: 40 preterm infants were enrolled in the study. The median (range) gestational age for the group was 28 (24 - 31) weeks and median (range) birth weight 1035g (470-1840g). 11 patients had a large PDA identified within the first 48 hours. Patients with a large PDA were more immature (26.6 vs 29 weeks, $p<0.01$), had lower birthweight (920 vs 1170g, $p=0.03$) and were more likely to be ventilated (92% vs 45%, $p<0.05$). The mean rCSO2 was lower in the large PDA group (75.2% vs 81%, $p=0.08$). In a binary logistic regression model with PDA as the dependent variable, gestational age was the only significant variable present {exp (B), 0.6 (CI 0.38-0.93, $p=0.026$)} in the model.
Conclusions: The presence of a large PDA was not statistically associated with lower rCSO2 values in very preterm infants.

TIMING OF PHARMACOLOGICAL TREATMENT OF PATENT DUCTUS ARTERIOSUS (PDA) AND RISK OF SECONDARY PDA-SURGERY, DEATH OR BRONCHOPULMONARY DYSPLASIA- A POPULATION-BASED STUDY OF EXTREMELY PRETERM INFANTS

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Background: Earlier pharmacological treatment of PDA is associated with a higher closure rate than later treatment. However, few clinical trials involve infants born below 27 weeks of gestational age (GA). We hypothesized that timing of treatment is associated with risk of secondary surgery or death, or bronchopulmonary dysplasia (BPD) in extremely preterm infants.
Patients and Methods: The hypothesis was investigated in the population-based, prospective cohort study EXPRESS (Extremely Preterm Infants in Sweden), including all infants born at less than 27 weeks of GA in 2004 to 2007. Among those, 590 were still alive at 24 hours and had complete data on PDA-treatment. Of these, 296 (50%) were treated with ibuprofen or indomethacin and included in the study. Cox proportional hazards regression was used to estimate the hazard ratio (HR) of surgery or death (as a composite primary outcome) in relation to timing of treatment. Age at start of pharmacological treatment was categorized as early (0-2 days), intermediate (3-6 days), or late (7 days or older). Follow-up started on the first day of PDA-treatment and ended 90 days later or on day of secondary PDA-surgery or death, whichever occurred first. Analyses were stratified on GA (in completed weeks) and clustered on region of birth. Among survivors, the risk of BPD (secondary outcome), defined as O2 treatment at 36+0 weeks of GA, was estimated in relation to timing of PDA-treatment by conditional logistic regression stratified on GA, adjusted for sex, duration of respiratory support and small for date (SGA).
Results: The median age at start of PDA-treatment was 4 days (interquartile range 2-6). Ninety-six infants (32%) were treated early, 127 (43%) had intermediate start of treatment, and 73 (25%) late. Twenty-seven infants (9.1%) died after start of pharmacological treatment and 104 (35%) infants had PDA-surgery. The proportion undergoing surgery was lower among those treated early (27%), as compared to those treated at 3-6 days of life (41%) and at 7 days or later (36%) (p=0.10) However, since mortality is high in the first week of life, the HR (95% confidence interval) for the composite outcome -PDA-surgery or death- did not differ between the treatment time points. The HRs were 0.91 (0.59-1.40) for surgery/death after intermediate, and 1.10 (0.53-2.25) after late start of treatment, as compared to early. 167 infants (64%) had BPD. The adjusted odds ratio (OR) for BPD did not differ between early and intermediate PDA-treatment. Late PDA-treatment was associated with lower risk of BPD, OR 0.35 (0.16-0.75), as compared to early treatment.
Conclusion: Timing of pharmacological PDA-treatment among infants born at less than 27 weeks is not associated to risk of secondary surgery or death. Moreover, expectant management is not associated with a higher risk of BPD.

COMPARISON BETWEEN DIFFERENT PHARMACOLOGICAL TREATMENTS FOR PATENT DUCTUS ARTERIOSUS CLOSURE IN VERY LOW BIRTH WEIGHT INFANTS

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Patent ductus arteriosus (PDA) is diagnosed in 40% of very low birth weight (VLBW) infants. There is an inverse ratio between the incidence of PDA and gestational age. In premature infants, the hemodynamic instability that is caused by massive blood flow through the PDA, generate a left to right shunt; increase the risk for major morbidity like: Intraventricular hemorrhage (IVH), Bronchopulmonary Dysplasia (BPD), Necrotizing Enterocolitis (NEC) and high mortality. Therefore, it is important to close the PDA.
The methods for PDA closure consist of medical and surgical treatments.
The main medical treatments are: fluid restriction, diuretics and prostaglandins inhibitors. The major prostaglandins inhibitors in clinical use are intravenous (IV) indomethacin and ibuprofen. The surgical solution is reserved for those who fail medical treatment or with contraindication for such treatment. The aim of this study was to compare different pharmacological treatments for PDA closure (IV Indomethacin, IV Ibuprofen and oral Ibuprofen). We studied 706 VLBW infants with hemodynamic significant PDA. Of those 165 did not received any treatment, 153 treated with IV indomethacin, 95 IV ibuprofen and 247 oral ibuprofen.
The basic characteristics of the 3 groups were similar. The main results of the study were that surgical closure was needed the least at the oral ibuprofen group (only 1.2%), with higher incidence at the IV indomethacin and IV ibuprofen (6.5% and 24.2%, $p<0.0001$). More than this there was no increase incidence of spontaneous perforation in the oral ibuprofen group (2.4%, 3.3%, 0% accordingly) (p=NS). This is the largest cohort of VLBW treated for PDA closure with oral ibuprofen. The differences between the groups lowered after multivariable analysis.
In conclusion, it seems that oral ibuprofen is effective as IV indomethacin or IV ibuprofen with the same incidence of serious side effects. Because the major difference in the price and availability the oral solution can be an alternative for the IV preparation.

CLINICALLY HEMODYNAMIC RELEVANT PATENT DUCTUS ARTERIOSUS IN VERY LOW BIRTHWEIGHT (VLBW) INFANTS DOES NOT CAUSE HYPOPERFUSION-ASSOCIATED CEREBRAL DAMAGE

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Background and aims:: Patent ductus arteriosus (PDA) is the most common functional cardiovascular disease of preterm infants. Hemodynamic relevance for the circulation system and for organ perfusion is difficult to substantiate. The aim of the present study was to non-invasively quantify potential parameters of cerebral hypoperfusion which might reflect perfusion-associated brain damage in immature preterm infants.
Methods: Urinary levels of S100B, neuron-specific enolase (NSE) and myelin basic protein (MBP) were measured and correlated with the status of the ductus arteriosus. In a group of 50 preterm infants with a birth weight of less than 1500g, protein concentrations in urine were tested on day 0-1, 2-4, and 6-8 by Elisa methodology. 26 of the 50 preterm infants had a PDA on day 2-4. 6 of those 26 infants required therapeutic interventions according to current clinical treatment standards.
Result: Levels of S100B and NSE in urinary samples were not different between infants with and without PDA on all three time points. The t-test was calculated after transforming the outcomes with the natural logarithmic transformation. Descriptive statistics are reported in the original scale of measurements. S100 showed no difference between the two groups (S100 day 0-1: p=0,5868, infants without PDA: Mean ± SEM: 587,5 ± 181,2 pg/ml, n=19, infants with PDA: Mean ± SEM: 553,5 ± 170,7 pg/ml, n=25, day 2-4: p=0,7884, infants without PDA: Mean ± SEM: 499,4 ± 182,5 pg/ml, n=22, infants with a PDA: 391,0 ± 68,68 pg/ml, n=25, day 6-8: p= 0,8274, infants without PDA: Mean ± SEM: 479,2 ± 101,6 pg/ml, n=22, infants with PDA: 442,5 ± 85,82 pg/ml, n= 22). NSE showed no difference between the two groups either. MBP was different in the two groups on day 0-1 and day 2-4. There was no significant difference on day 6-8 anymore (MBP day 0-1: p=0,0041, infants without PDA: Mean ± SEM: 223,1 ± 55,9 pg/ml, n=21, infants with PDA: Mean ± SEM: 85,22 ± 14,5 pg/ml, n=25, day 2-4: p=0,0054, infants without PDA: Mean ± SEM: 197,7 ± 43,18 pg/ml, n=22, infants with PDA: 68,98 ± 8,965 pg/ml, n=25, day 6-8: p=0,9578, infants without PDA: 159,9 ± 43,18 pg/ml, n=22, infants with PDA: 152,4 ± 30,89 pg/ml, n=24). Medical interventions for PDA (ibuprofen and ligation) did not affect urinary protein levels.
Conclusions: There is a maturity-associated increase in urinary MBP levels during the first few days of life as described previously. Clinically hemodynamic relevant PDA in VLBW infants does not cause cerebral damage as measurable by urinary levels of S100B, NSE or MBP.

CHANGES IN TREATMENT OF THE PATENT DUCTUS ARTERIOSUS IN VERY LOW BIRTH WEIGHT INFANTS.

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Background: Patent Ductus Arteriosus (PDA) is a common clinical event in very low birth weight infants (VLBW). PDA has been traditionally associated with increased morbidity such as intraventricular hemorrhage, necrotizing enterocolitis and chronic lung disease. It remains unclear whether active treatment is necessary to improve the outcome of these patients. Still, after medical approach has failed, many centers go for surgical ligation. This is associated with some morbidities, including thoracotomy, postoperative hypotension, vocal cord paralysis, etc. Several studies have suggested that surgical ligation could be delayed or even avoided if the baby is clinically stable and certain cardiorespiratory distress criteria are not met. Objectives: 1. To evaluate if changes in the management of PDA in two different periods of time have been associated with changes in the rate of surgical ligation for PDA 2. To examine if changes in the management of PDA in two different periods of time have led to changes in survival and morbidity of VLBW patients with PDA
Patients and Methods: Retrospective analysis from the clinical chats of all the VLBW patients with clinical and echocardiographic PDA admitted in the Neonatal Intensive Care Unit of our Hospital between January 2008 and December 2012. In April 2010, we changed the approach to VLBW patients with PDA from an early surgical approach to a more conservative one. In the first period, patients who failed medical treatment underwent PDAs surgical ligation; After April 2010, PDAs were ligated only if cardiopulmonary compromise developed mainly when patients could not be weaned from ventilator due to PDA. In the first period of the study, from January 2008 to April 2010 period 1 (P1), 93 patients VLBW were included. In the second period (period 2 (P2): April 2010 to December 2012, 40 patients were included.
Results: Both periods had similar averages in patients characteristics; gestational age P1: 26.4 w (+/-2.4) , P2: 26.6 w (+/-0.9); birth weight P1: 836 gr. (+/- 327), P2: 879 gr. (+/- 181. The conservative approach (P 2) was associated with similar rates of medical treatment: P1: 68/93 (73%) vs P2: 32/40 (80%) but decreased rates of ductal ligation P1: 29/93 (31%) vs 8/40 (20%). Rates of survival P1: 24/93 (74%) vs P2: 32/40 (80%); Bronchopulmonary dysplasia P1: 34/93 (36.6%) vs P2: 11/40 (27.5%); Retinopathy of prematurity stage >3 P1: 12/93 (13%) vs 5/40 (12.5%) and Necrotizing enterocolitis 19/93 (20%) vs 5/40 (12.5%) where similar in both periods of time.
Conclusion: Waiting for spontaneous closure of PDA in patients with clinically no significant PDA is a possible treatment strategy that can avoid surgery in some cases and is not associated with significant changes in mortality or morbidities in preterm babies under 32 weeks.

COPEPTIN INDICATES PERINATAL STRESS REACTION IN HUMANS AND IN RATS

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Background: Copeptin is a stable by-product of arginine vasopressin (AVP) synthesis and serves as a plasma surrogate marker of AVP secretion. It has been demonstrated that birth stress strongly induces copeptin/AVP release in newborns. Additional determinants of copeptin in perinatal medicine are barely known.
Methods: Copeptin concentrations were investigated in umbilical cord blood of singleton newborn infants delivered after 34 weeks without birth stress, caesarean section in the absence of uterine contractions. Matched-pair analysis of 12 fetuses with significant intrauterine growth restriction (IUGR) and 42 healthy appropriate for gestational age (AGA) controls was performed. Using an in vivo infant ventilation model (Wistar rats, 14 days old), the impact of commonly occurring stressors in critically ill newborns were studied systematically on circulating copeptin.
Results: Umbilical cord plasma copeptin levels (median [range]) were 4-fold higher in IUGR than in matched AGA controls: 23.2 (6.7-449) vs 5.1 (2.5-53) pmol/L ($p<0.001$). Multivariate regression analysis revealed an association between copeptin and umbilical artery resistance index z-score ($P = .034$). In unstressed ventilated rats basal median copeptin concentration was 22 pmol/L. In response to respiratory alkalosis copeptin increased 5-fold, whereas exposure to hypoxemia, high PEEP, haemorrhage, and psycho-emotional stress produced a more than 10-fold increase ($p<0.05$ for all changes).
Conclusion: High copeptin in IUGR fetuses indicates chronic activation of the AVP system supporting the fetal programming hypothesis. The finding of high copeptin in infant rats upon certain commonly occurring stressors in critically ill newborns, shed light on the cumulative stress young patients may suffer from. Additional studies are necessary to quantify early life stress of infants on neonatal intensive care units.

SEXUAL DISPARITY OF COPEPTIN PLASMA CONCENTRATIONS IN NEWBORN INFANTS

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Background and aims: Arginine vasopressin (AVP), also known as anti-diuretic hormone, regulates water balance and blood pressure, and plays a role in social cognitive processes. Healthy adult men as compared to women have higher plasma level of AVP and its surrogate marker copeptin, the C-terminal portion of the AVP precursor (CT-proAVP). We set out to investigate the association between gender, gestational age, delivery mode, and copeptin levels in newborn infants at birth.
Methods: In a prospective cross-sectional study at two tertiary university hospitals plasma copeptin was determined using the CT-proAVP-Luminescence-immunoassay in venous umbilical cord blood of 354 newborn infants at birth.
Result: In the group of newborn infants born by primary caesarean section (n=126), i.e. without preceding uterine contractions, rupture of membranes, or cardiotocographics signs of fetal stress, umbilical cord blood copeptin concentrations were higher in males than females (median 5.9 [5-95% range 3.0-211] pmol/L vs. 4.5 [2.5-23] pmol/L, $p<0.01$). In the group of infants born vaginally (n=115) a significant sexual disparity of copeptin was found in healthy term infants (males median 944 [6.4-4905] pmol/L vs. females 349 [7.2-2678] pmol/L, $p<0.01$). In infants born after secondary caesarean section (n=113) copeptin did not differ with respect to gender.
Conclusions: Sexual disparity of copeptin is already present in cord blood indicating increased activation of the AVP system in newborn boys as compared to girls.

ASSESSMENT OF COMFORT AND PERSISTENT PAIN IN NEONATES IN THE ABSENCE OF A VALIDATED CLINICAL TOOL

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Background: Although there are many tools for the assessment of acute pain in pre-verbal infants, there is a paucity of validated clinical tools to assess persistent pain in neonates. However, the evaluation of a baby's on-going comfort levels during neonatal intensive care is a crucial concern for both parents and staff. Without an objective tool, it is likely that subjective measures are often used to assess levels of pain or comfort in sick and preterm neonates. Objective: To determine (i) the level of difficulty perceived by staff and parents in assessing persistent pain or comfort in babies (ii) strategies used by staff on a day-to-day basis to assess levels of comfort or persistent pain in neonates in the absence of a clinical tool and to what degree these strategies were similar or variable between individuals.
Methods: Semi-structured questionnaires, with options for free text reporting, were developed and administered to parents of infants undergoing neonatal care and to neonatal unit nursing and medical staff. Both parents and staff were asked to report the degree of difficulty they experienced in assessing pain and comfort in sick and preterm neonates. Members of staff were also asked which specific factors they believed to be valuable indicators of babies' levels of comfort or persistent pain.
Result: 47/50 (94%) parents and 83/91 (91%) staff completed the questionnaire. (i) 50% of staff reported that it was either moderately or very difficult to determine whether a baby was comfortable or had persistent pain; 13% reported that they found it very easy. In contrast, 75% of parents reported that it was either very easy or moderately easy to know whether their own baby was comfortable; 23% said it was difficult for them. >75% of parents believed that their baby's pain/comfort levels were regularly assessed. Only 15% of parents thought that staff would experience difficultly in assess babies' comfort or pain. (ii) Staff described a total of 94 different factors they felt were indicative of a baby's comfort and 139 factors that they believed indicated persistent pain. Terminology differed widely and many factors were non-specific, eg. stable heart and respiratory rates, which were cited by >65% as indicators of comfort, and excessive crying or moaning, which 90% of staff thought indicated persistent pain. 67% of staff also described the importance of simply forming a general impression of babies' comfort levels.
Conclusions: Neonatal unit staff perceive that the assessment of comfort and persistent pain in babies is difficult. Most parents feel confident in assessing their own babies' comfort or pain but they may overestimate the ease with which staff can do so. Indicators of persistent pain have not yet been clearly defined and staff currently use widely disparate and sometimes highly subjective means of assessment. This may present challenges in communication with families and involvement of parents in clinical care, as well as in communication between staff and continuity of care during handover of care.

EFFICACY, APPLICABILITY AND ACCEPTABILITY OF BREAST FEEDING AND BREAST MILK CUP FEEDING VS NO TREATMENT IN PAIN REDUCTION DURING NEWBORN SCREENING TEST: RANDOMIZED CLINICAL TRIAL

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Attention needs to be paid to the management of pain in newborns as pain may not only have serious consequences but also a primary concern of parents. A systematic review documented that breast-feeding is effective in providing analgesia during minor invasive procedures. Despite evidence, breastfeeding has not been adopted nor practiced. This study addresses the gap between research findings and clinical practice. Objectives The objective of the study was to determine the efficacy, applicability and acceptability of breast feeding and breast milk feeding via cup versus no treatment (usual care) in reduction of pain among healthy term neonates undergoing heel lance procedure for newborn screening.
Methods: This was a randomized controlled trial conducted in the Level I Neonatal Intensive Care Unit of the Manila Doctors Hospital on term neonates undergoing heel lance for Newborn Screening test. Newborn infants were randomly allocated to breast feeding, breast milk feeding via cup or no treatment. All infants were being held in their mother's arms until the recovery period (period of no cry). Both the intervention and the recovery phase were audio-video recorded for outcome assessment. The primary outcome of the study was to evaluate pain using the modified COVERS scale and duration of cry. Three assessors independently evaluated the outcomes using the audio-video recordings. To determine applicability, the proportion of 'failure of implementation' were compared and interviews were conducted among the parents and phlebotomists to determine the factors that may have contributed to the 'failure'. A validated global satisfaction scale was used to compare the acceptability of the interventions among the parents and the phlebotomist.
Results: A total of 56 patients were included in the study. Sixteen (16) were randomized to the breastfeeding group, 24 to the breastfeeding via cup and 16 to no treatment. There was a significantly lower COVERS score (3.4 ± 2.4 vs 5.3 ± 2.6 vs 6.3 ± 2.9, p=0.023) and shorter duration of cry in seconds (57.2 ± 50.3 vs 108.0 ± 67.7 vs 113.6 ± 63.2, p=0.0049) in the breast feeding group compared to either of the two comparison groups. The proportion of babies whose cry exceeded 2minutes was lower in the breastfeeding group but this was not statistically significant (18.75 vs 50 vs 54, p=0.068). There was a significantly higher proportion of implementation failures in the breast milk via cup group (79%) compared to the breast feeding group (25%) (p=0.007). The most common reasons for implementation failure in the breastfeeding group were poor attachment to mother's breast (n=2), followed by irritability (n=1) and baby sleepiness (n=1). The main reason for implementation failure in the breast milk via cup group was insufficient or no breast milk (n=19). The overall satisfaction of parents and phlebotomists for both the breast feeding and the breast milk via cup groups were the same (6~very satisfied).
Conclusion: Breastfeeding is an effective intervention for the alleviation of pain among healthy term newborns undergoing heel lance procedures. It is easily applicable and parents and phlebotomists are extremely satisfied about its implementation.

ANALGESIA WITH BREASTFEEDING IN ADDITION TO SKIN-TO-SKIN CONTACT DURING HEEL PRICK: A RANDOMIZED, CONTROLLED TRIAL

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Introduction: Nonpharmacological interventions are important alternatives for pain relief during minor procedures in neonates. The purpose of this study was to compare the efficacy of different non-pharmacological procedures in reducing pain response during blood sampling through heel lance. Furthermore, the influences of non-pharmacological methods on crying time, percentage of crying while sampling, heart rate and number of attempts of sampling were studied.
Methods: This randomised controlled trial was performed on 136 healthy term newborns in the maternity ward of a tertiary hospital. The inclusion criteria were as follows: healthy term neonates (37-416 weeks of gestation), wish to breastfeed and absence of feeding during the previous 60 minutes. Exclusion criteria were as follows: maternal use of opioids, birth in general anesthesia, artificial feeding, previous capillar or venous sampling, and previous admission to the neonatal unit. Participating neonates were randomly assigned to four groups: Breastfeeding + skin-skin-contact (BF+SSC) Group (n=35); Sucrose+SSC Group (n=35); SSC Group (n=33); or Sucrose Group (n=33). Randomisation was by closed envelopes and nurses and parents were masked to the randomization group but not blinded to the treatment assignment. Throughout the duration of the test, babies were continuously recorded with a video camera. The heel was warmed up by a glove with lukewarm water. Heel lance was made with an automated piercing at 48 hours of life. Heart rate was monitored by a pulse oximeter (Radical MasimoSet Datascope, Masimo Corporation, Irvine, CA) set on the infant's hand or foot. It was measured continuously but special attention was given to three time points: t0 (two minutes before sampling); t1 (the highest value of the first 10 seconds after heel prick); and t2 (two minutes after the procedure). Three observers watched the videos and measured pain by Neonatal Infant Pain Scale (NIPS). Intraclass Correlation Coefficient was >0.60 between observers. A inform consent was given to parents before including in the study. Data were analysed per intention to treat. This study was approved by Local Ethical Committee.
Results: During baseline, infants in BF+SSC group had significantly lower NIPS score than Sucrose+SSC group (p=0.002) and Sucrose group (p=0.04). During heel prick, NIPS score was also significantly lower in the BF+SSC group than in other groups (p=0.01). Two minutes after the procedure, NIPS score in Sucrose+SSC group was lower than Sucrose group (p=0.02). For the secondary end point (percentage of crying during blood sampling) both BF+SSC and Sucrose+SSC groups achieved significant lower percentages compared with SSC group (p=0.03). There were no differences in heart rate during heel prick and attempts of heel lances. No adverse effects were noted in any infant.
Conclusion: This study suggests that breastfeeding in addition to skin-to-skin contact provides superior analgesia than other kinds of non-pharmacological analgesia in healthy term neonates during heel prick. . This result is clinically relevant as it shows that in otherwise healthy term neonates, analgesia for minor invasive procedures can be provided by a natural, worldwide available method, i.e. breastfeeding in addition to SSC.

8-YEAR AUDIT OF A SIMPLIFIED GENTAMICIN EXTENDED INTERVAL HIGH-DOSE REGIMEN

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Introduction/Background: Gentamicin, in combination with a beta-lactam antibiotic, is commonly used for treatment of neonatal sepsis. Neonates have a high volume of distribution. It is a paradox that most neonatal dosing regimens still recommend lower gentamicin doses (4-5 mg/kg) than in older children (≥7 mg/kg). Our objective was to audit a simplified gentamicin extended interval high-dose (6 mg/kg) regimen.
Patients and Methods: Over an 8-year period we identified 440 infants with postmenstrual age < 50 weeks who received gentamicin (6 mg/kg over 30 min) and had at least one trough serum concentration (TSC) measured before the third dose. During first week of life the dosing interval was 24 h for term babies (Group A), 36 h for GA 29-36 weeks (Group B) and 48 h for GA < 29 weeks (Group C). After first week of life the dosing interval was 24 h if corrected age (GA + postnatal age) was ≥ 29 weeks (Group D) and 36 h if corrected age < 29 weeks (Group E). TSCs were evaluated for each treatment group. A detailed hearing evaluation was performed to assess potential ototoxicity.
Result: Some patients received more than one treatment episode. Thus a total of 498 treatment episodes were included. Mean±SD gentamicin TSC (mg/L) for the five different groups were: Group A (n=247) 1.2±0.6, Group B (n=58) 0.9±0.4, Group C (n=47) 0.9±0.5, Group D (n=134) 0.8±0.6 and Group E (n=12) 1.1±0.7. Thirty-one (6%) of all TSCs were > 2 mg/L. Of these, 22 were observed in group A and predominantly in children with perinatal asphyxia and renal failure. Thirty-eight infants failed the transient evoked otoacoustic emission screening, but only 5 had confirmed permanent hearing loss. One of the patients with permanent hearing loss had TSC of 2.5 mg/L, but also perinatal asphyxia and a congenital CMV infection. The other four had normal TSCs. Medical staff prescription error was identified in 37 cases (8%), mainly a too long dosing interval. Nursing staff administration error, defined as administration > 3 h earlier or later than scheduled, was identified in 60 episodes (12%), but not leading to elevated TSCs (> 2 mg/L).
Conclusions: This gentamicin high-dose (6 mg/kg) regimen was associated with low number of elevated TSCs (> 2 mg/L), low numbers of prescription errors and we found no evidence for ototoxicity. Further studies are needed to define appropriate gentamicin doses and dosing intervals for neonates across all gestational ages in the neonatal period.

AN OBSERVATIONAL STUDY OF A VALIDATED, SEMI-QUANTITATIVE MOLECULAR ASSAY FOR THE DIAGNOSIS OF LATE ONSET NEONATAL SEPSIS IN VERY LOW BIRTH WEIGHT INFANTS.

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Background: Late onset neonatal sepsis is a condition that is best prevented. If this is not possible, accurate diagnosis is essential. Blood culture is currently the ‘gold standard' diagnostic tool. Molecular techniques have the potential for improved identification and quantification of pathogens. We present the validation and clinical application of a novel semi-quantitative 16S rRNA assay for the diagnosis and quantification of bacteria in late onset neonatal sepsis.
Methods: A molecular based assay was tested under laboratory settings against a range of common neonatal bacterial pathogens. The assay was then applied clinically in the NICU, Royal Maternity Hospital Belfast. Over an 18 month period, all very-low-birth-weight infants greater than 48 hours of age, were eligible for inclusion. When an infant was suspected of sepsis by the clinical team, blood was sent for haematology, inflammatory markers, blood culture and molecular (16S rRNA) analysis. The infants were assessed using the NEO-KISS infection criteria (a clinically based, validated scoring system) and determined whether septic or not. This was compared with the blood culture at presentation. Performance statistics were produced for each test. Quantitative measures including mean bacterial copy number were also produced. Copy numbers were compared with patient characteristics, haematological and inflammatory data.
Results: 86 episodes of sepsis in 60 babies (33 males) were recorded and sampled. The median gestation was 26.7 weeks (Interquartile range (IQR) 26 - 29 weeks).The median weight was 0.98kg (IQR - 0.77 - 1.19kg). The test performance data are presented below. Blood Culture 16S rRNA Sensitivity 0.57 0.76 Specificity 0.45 0.96 Positive Likelihood Ratio 1.04 16.8 Negative Likelihood Ratio 0.96 0.25 Mean bacterial copy number in infants positive by molecular analysis was log10 7.09 (Standard Deviation 1.26) copy no. per ml, with a range of log10 5.07 - 10.71 copy no. per ml. The bacterial copy number had a significant negative correlation with gestation ($p<0.05$), i.e., the smaller the infant the greater the bacterial load.
Discussion: The performance statistics for this molecular assay compare favourably with those of blood culture Clinical use of 16S rRNA assay could improve the diagnosis of sepsis at ‘point of presentation' in these babies. The quantified data shown here give some impression of bacterial numbers present at the time of diagnosis of neonatal sepsis. It has been long accepted that children have higher bacterial counts than adults and that infants have the highest of all. The negative correlation with gestation may reflect immaturity of immune function allowing greater bacterial growth. Molecular diagnosis in neonatal sepsis may have qualitative and quantitative advantages over currently available tests.

COST COMPARISON OF TWO CAFFEINE PREPARATIONS USED FOR PRETERM BABIES

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Background: The tertiary NICU in Belfast has been using a caffeine preparation from Martindale Pharma for the treatment of primary apnoea in premature babies and this preparation comes in packs of 10 vials containing 1mL of 10mg/mL caffeine citrate and costing £48.82. Peyona is an alternative caffeine product manufactured by Chiesi® which comes in packs of 10 vials containing 1mL of 20mg/mL caffeine citrate costing £43.80.
Objective: To compare costs of two caffeine citrate preparations used in the treatment of primary apnoea of prematurity within the NICU setting.
Methods: We retrospectively collected data on all preterm babies (< 32 weeks') treated with caffeine citrate from 1/1/2012 to 31/12/2012 in our unit. This included the loading dose of 20mg/kg and maintenance dose of 5mg/kg of caffeine citrate, increased in some cases up to 10 mg/kg at clinician's discretion, given both intravenously and orally. Number of vials for each dose was calculated. The cost of caffeine citrate per baby per admission was derived and compared against calculated costs if Peyona® had been used.
Results: There were 79 babies < 32 week's who received caffeine therapy in the 12 month study period. The total annual budget for Caffeine in NICU was £15525. The calculated costs if using Peyona® was £10448. Total cost difference for the 79 babies over a year was £5076.
Conclusion: There is a significant difference in the cost of the two caffeine preparations. There is a potential cost benefit of Peyona® product over Martindale preparation amounting to nearly 33% of the total caffeine cost incurred annually by our unit.

SERUM LEVELS OF PERFLUORINATED CHEMICALS IN PREGNANT WOMEN AND FETAL GROWTH: PRELIMINARY RESULTS

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Background: Perfluorinated chemicals (PFCs) are widespread environmental toxicants that accumulate in the human organism. In pregnant women, PFCs cross the placenta thereby exposing the fetus. Based on previous animal and human studies, fetal exposure to PFCs is suspected to cause impaired fetal growth, but studies have shown conflicting results and have not included all PFC compounds. The main objective of this study is to investigate the association between all measurable maternal PFC levels and fetal growth.
Patients and Methods: 1350 participants (250 per year in 2008-2010 and 200 per year in 2011-2013) will be randomly selected from the Aarhus Birth Cohort Biobank from pregnant women who gave a blood sample before 14 weeks of gestation, were nulliparous and provided a time to pregnancy if the pregnancy was planned. A total of 17 PFCs are measured by high performance liquid chromatography - tandem mass spectrometry. Data on gestational age, birth weight and length are provided by the Aarhus Birth Cohort Database. Information on various covariates is available in the Aarhus Birth Cohort.
Result: Preliminary results from 499 participants (2008 through 2009) are presented. The median serum concentration of perfluorooctanoate (PFOA) was 2.4 ng/ml (interquartile range (IQR) = 1.9 - 3.0 ng/ml), while the median serum concentration for perfluorooctane sulfonate (PFOS) was 9.7 ng/ml (IQR = 7.3 - 12.8 ng/ml). Linear regression analyses will be used to estimate the association between levels of PFCs, particularly perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), and proxy estimates of fetal growth while adjusting for covariates (Maternal age, prepregnancy BMI, maternal smoking and alcohol intake during pregnancy, maternal education, maternal diseases, parity, infant sex, and gestational age at birth).
Conclusions: This study investigates the association between fetal exposure to PFCs and impaired fetal growth. Levels of PFOS and PFOA are within the expected range. The data analyses are ongoing and results will be presented.

TWO YEAR INFANT AND MATERNAL OUTCOMES FROM THE SNAP TRIAL: A RANDOMISED CONTROLLED TRIAL INVESTIGATING NICOTINE REPLACEMENT THERAPY FOR CESSATION IN PREGNANCY

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Background: Nicotine replacement therapy (NRT) is widely prescribed for smoking cessation in pregnancy, despite little evidence for its effectiveness and safety; the expert consensus is that NRT should be safer than smoking for the unborn infant. SNAP, a randomised controlled trial comparing nicotine patches with placebo in 1050 pregnant smokers, found a doubling of cessation rates due to NRT at one month. However, at delivery no statistically significant effects of NRT either on maternal smoking or birth outcomes were observed. The study also investigated effects of NRT on infants' development and respiratory problems and on maternal smoking abstinence rates at 2 years after delivery.
Methods: All randomised women, apart from those with documented fetal deaths (n=14), were eligible for follow-up until their infants were aged two. Outcomes were collected by questionnaire sent to participants (PQ2). This asked about maternal smoking and infant health and included items from the ‘Ages and Stages' questionnaire (ASQ-3) evaluating infants' development. If participants did not respond, their general practitioner was sent a short questionnaire to assess the child's development and general health (HPQ). The primary outcome was ‘survival with no impairment' which was a composite of normal scores for all ASQ-3 domains plus no reported problems amongst either remaining PQ2 items or HPQ responses. Only singleton live births were used in the analysis of infant outcomes. For maternal smoking outcomes, non-responders were assumed to be smokers.
Results: From 1036 trial participants, we obtained outcome data for 87% (900; 448 NRT, 452 placebo) at 2 years. 12 women had twins and 14 had no birth data recorded, leaving 1010 singleton infants (891 of these provided outcome data: 445 NRT, 446 placebo); within this group 323 of 445 respondents (72.6%) of NRT group infants survived with ‘no impairment' compared to 290 of 446 respondents (65.0%) in the placebo group (OR 1.41, 95% CI 1.06-1.88, p=0.0198). In NRT and placebo groups, infants' respiratory symptoms were reported in 132/445 (29.7%) and 111/446 (24.9%) of infants respectively (OR 1.28, 95% CI 0.95-1.73, p=0.1049), and, amongst all 1050 women randomised (i.e. including women whose pregnancies did not end in live births), 15/521 (2.9%) allocated NRT and 9/529 (1.7%) allocated placebo had abstained from smoking since a quit date set in pregnancy (OR 1.71, 95% CI 0.74-3.94, p=0.2036).
Conclusion: We believe that this is the first trial of a smoking cessation intervention delivered in pregnancy to investigate the impact on infants' outcomes after delivery. Our findings suggest that NRT used for smoking cessation in pregnancy results in better infant outcomes than placebo. We speculate that this occurred through impacts on maternal smoking behaviour earlier in pregnancy and is the first evidence that a smoking cessation intervention delivered in pregnancy can affect infant outcomes. Longer term follow-up of infants in the trial cohort and trials of higher dose NRT in pregnancy are both now indicated.

CYTOLOGICAL EVALUATION OF THE NASAL MUCOSA IN THE NEONATES EXPOSED TO TOBACCO SMOKE DURING FETAL LIFE.

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Introduction: The objective of this study was to assess the cytological images of the nasal mucosa of the neonates born to mothers active smokers, passive smokers and non-smokers. Patients and
Methods: This was a prospective study conducted in a group of 86 neonates born between 23 and 41 week of gestation. Neonates were assigned to one of three subgroups: babies of mothers who were active smokers, passive smokers and non-smokers based on a questionnaire concerning exposure to tobacco smoke and on the concentration of cotinine in maternal urine. The cytological specimens of the nasal mucosa were obtained from the neonates during the first three days of life. The cytological examination was performed using the methods of the exfoliative cytology. Semi-quantitative evaluation of the cells present in the specimens was done. Haematological summation equipment was used to assess the number of neutrophils, eosinophils, cylindrical, goblet, basal and squamous cells out of five hundred cells counted. The specimens were assessed in the light microscope under the magnification of 400 times. The examination was a double-blind trial. The number of particular cells was shown as a percentage - cytograms were created.
Results: The most common types of cytograms contained neutrophils, cylindrical and squamous cells. There are no significant differences in the number of each type of cells in the cytograms in the assessed subgroups. (p=0.88). Similarly there is no correlation between the median of each type of cells and the cotinine concentration in the mothers' urine.
Conclusion: There is no correlation between cotinine concentration in the mother's urine and the cytograms of the nasal mucosa in neonates. Prenatal tobacco exposure does not influence the image of the nasal mucosa of the neonates.

A HOLISTIC NMR BASED METABOLOMICS STUDY OF TERM INFANTS WITH NORMAL, RESTRICTED AND INCREASED FETAL GROWTH

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Introduction/Background: The major cause for Large for Gestational Age (LGA) infants is gestational diabetes. Fetal macrosomia is associated with significant perinatal and long-term complications, including higher risk for later development of insulin resistance/metabolic syndrome. The associated obesity reflects the imbalance between energy intake and expenditure. Intrauterine Growth restriction (IUGR), characterized by failure of the fetus to reach his/her intrinsic growth potential, is also linked with nutrient and energy metabolism disorders. Metabolomics is a relatively new field with great perspectives in the early diagnosis of infant diseases, thus development of suitable treatment strategies using minimally invasive procedures. Furthermore, metabolomics is applied to discover new knowledge regarding biological processes and systems. In this holistic study, we aimed to detect possible alterations in the profile of various metabolites between LGA and appropriate for gestational age (AGA) fetuses. We also studied metabolic differences between LGA and IUGR fetal blood samples, since both may result in permanent adverse effects on postnatal growth and development.
Patients and Methods: Nuclear magnetic resonance (NMR) based metabolomics were employed on mixed arteriovenous cord blood (UC) samples from LGA (n=6), IUGR (n=7) and AGA (n=15) singleton full-term infants. Samples were used without any prior treatment, using D2O phosphate buffer and TSP as internal standard. NMR spectra were acquired on a Varian-600MHz NMR spectrometer at ambient temperature. The CPMG pulse sequence was applied with 64 transients collected with 64K data points. All NMR spectra were phased, baseline corrected, aligned, reduced into spectral buckets of 0.001 ppm and normalized using commercial software.
Results: PCA and OPLS-DA statistical analysis (SIMCA) of acquired NMR spectra separated the serum metabolite profiles into distinct clusters, representative of the LGA and AGA arteriovenous cord blood samples. Secondary metabolites, responsible for the discrimination were identified from loading plots after assignment with metabolomics software and subsequent 2D NMR techniques. Several metabolites' alterations played a discriminant role for LGA versus AGA (indicatively glutamate and lactate), while higher concentrations of metabolites including LDL, HDL, creatinine and lactate characterize IUGR versus LGA cord samples.
Conclusions: This holistic NMR metabolomics approach has discriminated between LGA and AGA as well as LGA and IUGR samples. IUGR and LGA infants are characterized by an altered metabolic profile affecting lipid and aminoacid metabolism from liver and muscle tissues. These disorders probably account for their metabolic deviation compared to the AGA controls. The differences in levels of various metabolites between IUGR and LGA samples possibly reflects poor energy expenditure of the former, due to intrauterine nutrient deprivation, in contrast to the latter.

NMR BASED METABOLOMICS, HIGHLIGHT METABOLIC PROFILE ALTERATIONS FOR IUGR VERSUS AGA CORD BLOOD SAMPLES

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Introduction/Background: Intrauterine growth restriction (IUGR) characterized by failure of the fetus to reach his/her intrinsic growth potential, is linked with nutrient and energy metabolism disorders, resulting in permanent adverse effects on postnatal growth and development and adult diseases such as hypertension, cardiovascular disease and insulin resistance. Metabolomics have been recently applied in perinatal medicine with great perspectives in the early diagnosis of infant diseases, thus could lead to the development of suitable treatment strategies using minimally invasive procedures. We aimed to investigate possible alterations in various metabolites affecting nutrient balance and placental dysfunction, along with lipid and glucose metabolism between IUGR and appropriate for gestational age (AGA) fetuses.
Patients and Methods: Nuclear Magnetic Resonance (NMR) Spectroscopy with CPMG and 1DNOE pulse sequences was employed on mixed arteriovenous cord blood (UC) samples from IUGR (n=7) and AGA (n=15) singleton full-term infants.
Results: Multivariate data analysis of acquired NMR data, separated the serum metabolite profiles into distinct clusters, representative of the IUGR and AGA UC samples. 2D (two dimensional) NMR techniques were employed together with commercial -omics database software in order to identify secondary metabolites responsible for the discrimination. Biomolecules related to muscle, renal and lipid metabolism (indicatively 2-hydroxybutyric acid, glutamine, creatinine, HDL, LDL) tend to be increased in UC IUGR samples compared to the AGA controls.
Conclusions: The altered insulin sensitivity characterizing IUGR is known to affect lipid metabolism -by increasing LDL production and dyslipidemia- enhancement of oxidative stress mechanisms and deviation in amino acid metabolism from liver and muscle tissues. The aforementioned energy metabolism disorders probably account for the altered metabolic profile in IUGR fetuses compared to AGA controls found in our study.

PROTEOME ANALYSIS OF HUMAN INTRA UTERINE GROWTH RESTRICTION PLACENTAS BY ITRAQ : IDENTIFICATION OF NEW BIOMARKERS

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Background: Intra-uterine growth restriction (IUGR) is a frequent complication of pregnancy that leads to a newborn with a birth weight and/or size below the 10th percentile for a given gestational age. IUGR represents a major public health problem associated with both a neonatal increased morbidity and mortality and an increased risk to develop cardiovascular pathologies and diabetes in adulthood. Human IUGR is a complex and multi-factorial pathology with an incompletely characterised physiopathology in up to 30-40% of cases. Objective: The objective of our study was to analyze the proteome of human placentas from pregnancies with IUGR with a very sensitive technology : iTRAQ (isobaric tags for relative and absolute quantitation).
Design/Methods: We compared proteome of placentas from pregnancies with IUGR of 32 weeks of gestation or more versus proteome of placentas from normal pregnancies, obtained after caesarian section before labor. We collected 12 placentas from normal pregnancies and 4 placentas from pregnancies with vascular IUGR. For the iTRAQ experiment, comparative analysis was done between each four IUGR placentas and four pools of three normal placentas.
Result: A total of 4942 peptides and 391 proteins were identified with a confidence level of 95%. Principal component analysis and functional clustering enabled us to select 40 proteins among the most modified with calprotectine, calréticuline, chorionic somatomammotropin hormone 1, alpha foeto-protein and serpin A1. Validation by immunohistochemistry, Western-blot and RT-PCRq allowed to check protein's expression in individual level. Calcium's pathway seems to play an important role in IUGR. We also found a good correlation between severity of the IUGR and proteins expression pattern.
Conclusions: Our present study is, at the best of our knowledge, the first comparative proteomic analysis of human placenta in IUGR versus normal pregnancy using the iTRAQ technology. Thanks to this work we have been able to identify news pathways involved in IUGR, like calcium's pathway. Soluble proteins markers, like alpha foeto-protein, could be detected in maternal serum from the first term of pregnancy, allowing an earlier diagnosis of IUGR and thus an optimal management of this pathology.

EFFICACY OF EARLY EXPERIMENTAL THERAPY IN LEIGH SYNDROME

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C.B.,secondborn full-term from normal vaginal delivery, from first cousins parents, Egyptians Christian Coptic, was recovered at the Pediatrics Department of San Carlo Borromeo Hospital in Milan, 20 months-old,following an access in Emergency due to occasional vomit and growth deficiency. Baby's medical history,included pregnancy,delivery and perinatal period was normal. Breast feeding until 5th month; regular growth on the 25th%. Weaning at 5 months. From the 7th months periodical vomits and inappetence,growth deficiency without intercurrent acute pathologies. At the admission to the Pediatrics Department the child was dystrophic with mainly axial hypotonia associated to muscle hypotrophy,hyporepresented subcutaneous tissue, coarse down spread on torso and limbs with roseola in the middle of the back, thick hair and eyelashes. Inadequate motorial activity, good interaction in the medical setting. No neurological focal signs, lively tendon reflexes. Periodical tachypnea without respiratory distress. W 6,9 kilos; L 69.5 cm; hc 47 cm (all <3%). Blood exams revealed light metabolic lactic acidosis with traces of ketonuria. Encephalous MR spectroscopy showed evidences of Leigh syndrome with symmetrical wounds on the brainstem. A ex adiuvantibus therapy was began with thiamine, carnitine, riboflavin and biotin with sodium bicarbonate by oral administration. Considering the medical features and MR imaging, we search for gene mutation SURF 1. It was confirmed (homozygousity c.870delT) At the age of 22 months the child started a multicenter experimental trial with EPI-743 therapy with the end point to reduce the serum level of oxidized glutathione, with excellent results and progressive clinical improvement, (Newcastle Pediatric Mitochondrial Disease Scale, the Gross Motor Function Measure and PedsQL Neuromuscular Module) A gain in weight: 2 kilos/4 months. After ten months of experimental treatment, during an acute intercurrent febbrile viral infection, the patient developed an acute respiratory distress with bradypnea/apnea, that required mechanical ventilation for 30 days. EPI-743 medication was never stopped. Despite an impairment of brainstem MR imaging, with new symmetrical oliva's lesions, patient's clinical evidences didn't show any impairment.
Conclusions: good results with experimental therapies in Leigh syndrome suggests the importance of early diagnosis in order to guarantee early therapies and best clinical improvement in affected patients.
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RELATIONSHIP BETWEEN C-REACTIVE PROTEIN AND CAUSE OF PNEUMONIA AND MONITORING SUCCESS OF OUTPATIENT THERAPY IN YOUNG CHILDREN

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Background: In children with pneumonia with fever, it is not always to possible to distinguish between bacterial and viral infections. C-Reactive protein (CRP) is nonspecific but sensitive marker for inflammations, infectious diseases and treatment monitoring of pneumonia, too. AIMS: This study was undertaken to determine the association of serum C-reactive protein (CRP) with pneumonia and antibiotics therapy and other markers among young children.
Methods And Materials: In Sarajevo, Bosnia and Herzegovina , all CRP measurements from primary pediatrics healthcare are performed as quantative immunoturbidometric tests at primary settings laboratories of Health Instutution of Canton Sarajevo and its four munipacitalities. This was a mixed prospective- restrospective study of 1000 febrile children 6 months-6 years old with one or two CRP data and x-ray of lungs confirmation during two years period from May 2010 to May 2012.
Results: Severe pneumonia was confirmed in 34 cases (3.4%) in CRP level more than 100mg/L, moderate serious bacterial pneumonia was diagnosed in 90 (9.0%) of 1001 children with pneumonia and higher level of CRP than 50mg/L , moderate milder bacterial pneumonia infections with moderate increasing CRP between 20mg/L to 50 mg/l was in 205 (20.5% cases), milder pneumonia in 343 cases(34.2%) with range 10mg/l to 20 mg/L, a probably viral infections of lungs with milder level of CRP 5 mg/L to 10 mg/L in 259 children (25.9%), and viral infections in 70 cases (7.0%)
Conclusions: CRP does provide help because CRP values are often higher increased in moderate severe and severe bacterial pneumonia , similarly to those found in severe bacterial infections, as confirmed in our study. Well-known laboratory parameters indicating infection such as C-reactive protein (CRP) are either unspecific but sensitive biomarkers useful for the early diagnosis and therefore can be recommended to guide the initiation of empiric antibiotic therapy, but with caution and monitoring other laboratory data and diagnostic procedures and pediatrics experience. KEY WORDS: Children, Pneumonia, Cause, Treatment, Diagnostics.

DETERMINATION OF INTESTINAL FLORA OF NEWBORN USING MOLECULAR METHODS

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It is well known that the fetus can be colonized in contact with the microorganisms after but also before delivery by many ways. Several studies were done that show many factors may affect intestinal flora including of feeding type, mode of delivery, hospitalization, prematurity, administration of antibiotics and the level of development of country. A total of 60-80% of intestinal bacteria consist of uncultured bacteria for which reason the investigators prefer molecular methods to analyze the intestinal flora. The most used methods by the investigators are FISH, 16S rRNA, DGGE, TGGE analysis and sequences after cloning that have advantages compared to cultural methods.
The aim of this study was to analyze the fecal flora of newborn by molecular techniques and determine the dynamics of intestinal bacterial flora during the first week of life. Ten babies were recruited for the present study. Fecal samples were collected at 1, 3, 7. days after delivery. Thirty fecal samples were analyzed by 16S rRNA amplification and cloning. After analysis of sequencing results the bacterial flora was determined. The bacteria defined by molecular method were classified by delivery mode, feeding type, antibiotic use, place of nursery (NICU or mother), life style, and oxygen use and analysed.
The results showed that the colonization started immediately after birth. The number and diversity of microorganisms increased day by day during the study. For all days that samples were taken, the most detectable genus was Streptococcus (%26), the most detectable species was Escherichia coli (%15,4). None of the samples was positive for Bifidobacteia. Pathogen bacteria like Salmonella, Shigella and Clostridium were positive in 10 % of the feces samples of asymptomatic babies, especially at third and seventh days after birth. The most common bacteria were Bacteroides among vaginally delivered babies and Streptococcus among delivered by cesarean section. None of the fecal samples from cesarean section babies was positive for Bacteroides. The breastfed babies had an heterogeneous intestinal flora at the seventh day of life which include Clostridium, E. coli, Veillonella and Lactobacillus.
Our study showed that stay at newborn intensive care unit at first week of life causes decrease in intestinal flora as well as the diversity of intestinal flora. The colonisation of intestin at first week of life affected by antibiotic use especially at first and third day samples. Our study indicated differences between intestinal flora of the babies of mothers who lives in countryside and cities; babies from countryside and low income had anaerobic heterogen flora than babies from city and high income.
We conclude that intestine of newborn is colonized intensively at the first week of the life. The diversity of bacterial flora is affected by alimentation type, stay at hospital, and use of antibiotics. Our study which defined establishment of intestinal flora during first week of life will be a base for further studies on intestinal flora.

THE ANTIBIOTIC TREATMENT DURRING THE NEONATE PERIOD

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Introduction: the neonate has numerous structural and functional particularities, presenting a stereotipical way of reaction to different causes of disease, thus the diseases of different ethiologies have common or simmilar symthomatology. Objectives: the study has the purpose of identifying the clinical forms of infection that the neonates presented at admission, the antibiotic treatment received as well as other factors that influenced the evolution of the disease. Material and metod: the present study is based on the retrospective analisys of cases of newborns with infectious pathology, hospitalised in the Clinic of Neonatology and Puericulture of the Emergency Clinical Hospital for Children 'Louis Turcanu' Timisoara, over a period of 2 years. The necessary data for elaborating the study have been extracted from the clinical charts as well as the bacteriologic lab tests.
Results and discussions: Durring the afore mentioned period 284 neonates were admitted in our clinic presenting infectious pathology, the repartition according to gender, environment, has indicated insignifiant differences. According to age groups on admission, 19 cases were <7 days of age, 78 cases between 7-14 days of age, 108 cases between 14-21 days and 79 cases over 21 days of age. Clinically and paraclinically 14 cases were diagnosed with neonatal sepsis, the rest of 270 cases presenting clinical localized forms of infection as follows: 93 upper respiratory tract infections; 45 digestive tract infections; 21 urinary infections; 32 cutaneous infections; 17 cases of otitis; 14 cases of conjunctivitis and the rest 48 cases associated 2 or more of the previously mentioned localized forms of infection. The initiation of the antibiotherapy was made with Ampicillin +/- aminoglycosides in most cases, and with 3rd generation cephalosporines in the neonates that presented with neonatal sepsis as well as those from the high risk cathegory. For the cases presenting with conjunctivitis, otitis and cutaneous infections only local topical treatment was used. The evolution under the given treatment was favorable in most of the cases, without the need to change the antibiotic durring the therapeutic period. 63 neonates with low birth weight and the ones that associated multiple risk factors necessitated the change of antibiotic due to the slow evolution. 7 cases with with complex pathology and 4 cases with severe congenital malformations presented with poor evolution and death.
Conclusions: 1. At the studied lot of neonates the upper respiratory tract infections and digestive infections were predominant, followed by cutaneous and urinary tract infections, the association of multiple localization infections were seen in 48 cases. 2. The Ampicillin +/- aminoglycoside antibiotherapy in the initial phase of the therapy for neonatal infections continues to be the most popular due to the fact that the antimycrobial spectrum indicates them as efficient with a pharmacodynamic compliance addapted to this age group. 3. The following are imposed in the choice and utilisation of the antibiotherapy in neonates: strictly necessary indications: (in correlation with the bacteriological analysis), antibiotics presenting less toxicity, apropriate dossage, treatment durring short periods of time, monotherapy (preferably).

MATERNAL SNUFF USE AND SMOKING AND THE RISK OF ORAL CLEFT MALFORMATIONS

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Importance: There is an association between the use of maternal oral Swedish snuff, 'snus' in pregnancy, and the risk of oral cleft malformations in the infant. Abstaining from tobacco use before or in very early pregnancy is associated with a reduced risk of oral clefts. This has implications for the use of nicotine substitution as a means of smoking cessation during pregnancy.
Objective: To determine if maternal use of snuff (containing high levels of nicotine, low levels of nitrosamines and no combustion products) increases the risk of oral cleft malformations in the infant and whether cessation of snuff use or smoking before the antenatal booking reduces the risk of oral clefts.
Design, Setting, Participants: A prospective population-based cohort study was conducted on all live born infants, recorded in the Swedish Medical Birth Register from 1999 through 2009 (n=1 086 213). Risks of oral clefts were evaluated by multivariate logistic regression analyses (using adjusted odds ratios, with 95% confidence intervals [CI]).
Main Outcome Measurses And Results: Compared with infants of non-tobacco users, the adjusted odds ratio (95 % CI) of any oral cleft for infants of mothers who continued to use snuff was 1.48 [1.00 -2.21]. The corresponding risk for infants of smoking mothers was 1.19 [1.01 -1.41]. In contrast, in infants of mothers who stopped using snuff or stopped smoking before the antenatal booking, the corresponding risks were not increased. Adjusted odds ratios were 0.71 [0.44 -1.14] and 0.88 [0.73 -1.05], respectively.
Conclusion And Relevance: Maternal snuff use in early pregnancy is associated with an increased risk of oral clefts. The risk of smoking during pregnancy was in accordance with previous studies. Infants of mothers who stopped using snuff or stopped smoking before the antenatal booking had no increased risk of oral cleft malformations. Oral snuff or other sources of nicotine should not be recommended as an alternative for smoke-cessation during pregnancy.

INTRODUCING INTERNATIONAL CHILD HEALTH INTO UNDERGRADUATE PAEDIATRICS.

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Introduction: Worldwide over 6 million children under 5 die annually. The chance of a child surviving to 5 years of age in sub-Saharan Africa is 16.5 times lower than in a developed nation. Ongoing disparities in global child health emphasize the importance that future doctors in developed nations be informed on some of the major issues early in their training. Aim To survey final year medical students and their level of interest and knowledge of key topics in international child health (ICH) and to evaluate the introduction of a clinical module in international child health into an undergraduate paediatric curriculum.
Methods: We surveyed final year medical students via a questionnaire given prior to and after an hour long interactive seminar on ICH. The seminar was given by a pediatric Registrar with recent experience of working in emergency medical projects in developing nations. Problem based learning with real case examples were used as a teaching tool as well as a question and answer session. The cases covered the major contributors to under 5 mortality; childhood pneumonia, neonatology, malaria, diarrheal disease and malnutrition. In the questionnaire students were asked demographic information, perceived relevance of ICH to their degree and future careers and their knowledge of core subjects in ICH. In the post seminar questionnaire they were asked additional questions on the impact of the session on their interest in ICH.
Result: We included 93 medical students with equal gender distribution. 86% of students were aged 18-27 years. There were 18 nationalities and 59% were non-Irish. The majority of students perceived ICH to be relevant to both their degree (80%) and future Career (69%). A high proportion of students rated their knowledge in core topics as poor or fair prior to the seminar but this significantly improved post seminar. Interest in ICH was increased in 57% of students following the seminar. 61% of students plan to work in the developing world for some period once qualified.
Conclusions: This survey demonstrates the interest among final year medical students in international child health but also the gaps in knowledge of some of the major contributors to child mortality. The results suggest that problem based learning with real case examples from developing nations is an effective teaching tool. Clinical training in core topics in International child health should be formally integrated into undergraduate pediatric curricula.

ASSESSMENT METHODOLOGY BUILT IN PARTNERSHIP, WITH STUDENTS AND TEACHERS - ASSESSING THE THEORETICAL PEDIATRIC CONTENTS APPREHENDED BY THE GRADUATING STUDENT OF THE COLLEGE OF MEDICINE OF PETRÓPOLIS - RIO DE JANEIRO - BRAZIL.

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Introduction: Assuming that the medical course structure should focus on the student's active participation in the knowledge construction and the integration between contents, we believe it is essential to prepare the student for the diagnosis and treatment of most common childhood diseases, as well as the development of skills for an adequate performance as health professional based on humanistic and ethical responsibility and the development of critical thinking regarding medical practice. The teaching of pediatrics at the site of this study has as pedagogical proposal the inclusion of students in various practice settings which provide the analysis of the situational context, the introduction of techniques to establish a novel logic on the relations between theoretical and practical knowledge, privileging thus the consolidation the teaching-learning process built throughout the course, including the cognitive, psychomotor and affective aspects of future health professional.
Objective: To evaluate the knowledge learnt regarding the topic clinical relevance privileged on the proposed syllabus of the course and reviewed in pediatric practice by the group of students who are enrolled in the module of Pediatrics at the College of Medicine of Petrópolis, Mountain Region of Rio de Janeiro State, Brazil
Methods: A descriptive, cross-sectional, study of the 5th and 6th-year graduates of the College of Medicine of Petrópolis - RJ - Brazil, who are in the final stage of Pediatrics module and have as requirement the presentation of clinical sessions based on situations experienced in various practice settings. We conducted a pretest prepared by the presenters on the topic of relevance to be addressed under the guidance of teachers. The instrument used was a semi-structured questionnaire with three (3) questions considered to be of low difficulty level on the identification, evaluation and conduction of a clinical case.
Results: The questionnaire was answered anonymously by 42 undergraduates. The level of correct identification as to the clinical situation presented was 23.8% (10) in opposition to the static knowledge of a scale that showed 85.71% (36). As for the need for decision making in regards to the conduct to be established, 28 students (66.7%) answered correctly.
Conclusion: Assuming the graduate must acquire competencies and skills related to health care; in addition to being able to conduct an active search is evident imbalance between the dimensions of knowledge of this group. It is clear that the implementation of strategies and formative evaluation of sequential themes experienced in clinical practice will allow us to fix the deficits of learning during the training process.

ASSESSING THE INTEGRATION OF SIMULATION TECHNIQUES IN THE CURRICULUM OF UNDERGRADUATE EDUCATION OF PEDIATRICS

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Introduction: Through 2011-2012, simulation was integrated in the 5th year medical students Pediatrics curriculum of the Faculty of Medical Sciences, New University of Lisbon. Objective: To evaluate the students opinions and use this assessment as a method of assure the appropriateness of this education tool in the pregraduate training.
Methods: 2 hours simulation classes were included in Pediatrics curriculum and scheduled to all 5th year medical students. Groups of 6/7 students per class were organized on a two times weekly based schedule. An anonymous evaluation form was voluntarily filled focusing on the logistical, educational and motivational aspects. A Psicometric Likert scale was used and each item was rated from 1 (very bad) to 10 (very good) The study period was the 2011-2012school year.
Result: 215 students attended the lecture. 172 Answered the evaluation form. The quality of the facilities of the CSTP was rated as Very Good (8.6 ± 1.2). Phantoms quality rated as Good (8.2 ± 1.3). The evaluation of teachers was Very Good as the content area (9.87 ± 0.39), the clarity and effectiveness in the statement (9.70 ± 0.78) and availability for the individualized teaching (9.35 ± 0 , 89). The scenarios and techniques improved the procedure safety (8.69 ± 1.26) (Very Good). Skills improvement and material handling was also rated Good (8.27 ± 1.19) and the scenarios created were able to approach clinical reality (9 , 05 ± 1.11) (Very Good). The usefulness of the class in the fifth year Pediatrics course, was also classified as Very Good (9.73 ± 0.65).
Conclusions: The integration of simulation techniques in the curriculum of Pediatrics undergraduate education is possible and adapts to training needs and expectations of students. Key-words: simulation, medical undergraduation, pediatrics, curriculum, post-graduation residency, continuous medical education, skills teaching, simulation centre, technical procedures

THE CHILD WITH COMPLEX HEALTH ISSUES: ASSESSMENT & MANAGEMENT TEACHING MODULE FOR MEDICAL STUDENTS

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Introduction: 9-15% of all children and youth are affected by a medical issues involving more than one body system and they experience limitations in normal function, requiring health and health related services way above that of the average child or adolescent. As this specific patient group is growing we wanted to introduce this topic to our undergraduate students.
Method: The module consisted of a one hour lecture and a practical exercise on an example case in small groups. The learning experience was evaluated by questionnaire.
Result: Questionnaires were returned by 63 of 118 students. Females and males were equally represented. 28.57% of the students were considering Paediatrics as their future career. 58 (92%) had some experience with a child with complex health issues prior to the session (50% during this paediatric rotation, 63.8% in other clinical rotations, 17.24% through friends and family and 18.97% outside medical school). 20% of the students felt even that more sessions would be desirable. The knowledge about this subject increased from a mean of 4.72 to 7.14.
Conclusions: As the group of children with complex health issues is growing due to increased survival of children with extreme prematurity and congenital anomalies, all medical professionals will be more frequently involved in their care both in paediatrics and adult medicine. This also is reflected in the students response who felt learning about the child with complex health issues was important. We concluded that introducing the topic into the undergraduate curriculum was welcomed by the students and helped their understanding of the assessment and care of this specific patient group.

AIMING FOR EFFECTIVE NEONATAL INTUBATION - ASSESSMENT OF PROCEDURE PRACTICE AND TRAINEE PERFORMANCE IN TWO CONSECUTIVE AUDITS ON A REGIONAL NICU

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Introduction and background: Neonatal intubation is a skill that should be mastered by every paediatric trainee. It takes significant practical training to develop this competence and tertiary neonatal intensive care units should play an active role in this process while also guaranteeing patient safety. The aim of our audit was to analyse the current procedure practice and trainees performance regarding intubation in order to implement changes to improve the trainees' skills as well as patient safety.
Patients and Methods: Two retrospective proforma based audits were performed independently in 2011 and 2012 to assess the quality of our neonatal intubation practise. In the first audit 38 babies were included who were intubated during October 2011. During the re-audit in 2012, 28 intubated babies were randomly chosen for analysis. Data was obtained from patient files, drug charts and Standardised Electronic Neonatal Database (SEND). Data were collected concerning birth weight, gestation, indication, endotracheal tube diameter, insertion length at lips, practitioner's seniority, the number of attempts required for successful intubation, the use of pre-medication, chest X-ray findings, change of tube position after performing a chest X-ray and possible complications. Microsoft Excel was used to organise and compare the data. Weight-based guideline was used to determine tube diameter and insertion length.
Results: In 2011 79% (26/33) of the babies were intubated with a correct size tube. In 2012 this was 75% (21/28). In 2011 only 10% of the intubations were attempted initially by junior paediatric trainees (Specialty Trainee St1-St3) and of these 28% were successful. In 2012 39% of the intubations were attempted by junior paediatric trainees of which 54% were successful. During both audits the tube position was confirmed in all cases by a chest X-ray. The tube was found as inserted too far and required readjustment after chest X-ray in 46 % (2011) and 61% (2012). The use of premedication, in semi-elective cases, was 100% in 2011 and 75% in 2012.
Conclusion: Our audit demonstrates that offering first intubation attempt to junior paediatric trainees in a supportive environment is a safe practice. Adopting this practice more on our unit resulted in increased success rate of first attempts at intubation by junior trainees. Inserting the endotracheal tube too far was a common practise. Performing a chest X-ray after every intubation, in order to assess the correct position of the tube, is highly recommended. To improve insertion lengths and correct tube size we have added the weight-based tube size and length to our drug calculator sheets.

POINT OF CARE NEONATAL SIMULATION TRAINING

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Background: It is estimated 80% of critical incidents in hospitals involve a human factor cause. Studies thus far show that use of simulation teaching has played an important role in strengthening clinical and non-technical skills such as interprofessional team working and crisis management skills in health care providers2. As a result, quality of patients care is improving. At present, most neonatal simulation is conducted away from clinical areas in designated simulation centres. These are of high fidelity and are expensive. They often involve the education and development of individual personnel, rather than full functional multi-disciplinary teams and might not reliably reflect learner's true working atmosphere. We are keen to investigate whether in-situ neonatal simulation delivered at their own workplace can be effective in achieving similar key learning outcomes. We aim to deliver teaching using lower fidelity mannequins and a full multi-disciplinary team - with greater emphasis on the clinical scenario and targeted learning objectives in neonatal crisis management. We hope that in situ simulation will provide additional benefits of realism in clinical environment and enable identification of latent errors that can compromise patient safety. We aim for the in situ simulation to supplement the existing training which is used to develop skills of clinical acumen and leadership and to provide 'whole team learning' in an environment that the team perform on a day-to-day basis. These sessions will utilise local policies and protocols and will take into account the variations of practice across the region.
Methods: We plan to conduct a pilot in situ neonatal simulation programme targeting district hospitals across Yorkshire and Humber region in United Kingdom. Lower fidelity simulators will be used in training. It will occur on actual work day, utilising on-duty clinical providers and clinical space. Scenarios will be designed based on need assessment, using local policies and protocols where possible. In order to evaluate the acceptability, feasibility and potential impact of our in situ simulation programme, a regional cross-sectional survey is being conducted. A questionnaire with four major components including - need, feasibility, accessibility and sustainability is being used. A lead nurse and a lead doctor from each hospital are interviewed. Both open questions and a 5 point likert scale is used. This survey also intends to identify potential barriers and will enable effective design and delivery of the programme. Once sustained, this programme will help develop local faculty and empower the district general hospitals to integrate simulation based learning into their training curriculum.
Results: show a demand for in situ neonatal simulation and identification of challenges including time and logistics.
Conclusions: Our in situ neonatal simulation programme aims to enable a more accessible form of simulation education. As a new and quickly developing form of learning we are yet to fully use simulation to its potential. In situ simulation offers a technique to train individuals as a whole functioning multidisciplinary team within their normal environment. This will improve and strengthen human factors and allow the identification of latent hazards and environmental issues.

PILOT TRIAL OF VIDEO RECORDINGS TO IDENTIFY NEWBORNS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY. A STRATEGY TO IMPROVE SELECTION OF PATIENTS FOR THERAPEUTIC HYPOTHERMIA

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Competent neurological exam is essential to identify newborns with hypoxic-ischemic encephalopathy (HIE). Most babies with HIE are born at hospitals with very different training at neurological examination skills. We questioned whether video recordings evaluated by experienced observers can help to identify and classify the degree of HIE. Objective. To assess if there is a good correlation between two experienced clinicians when evaluating video recordings of newborns with perinatal asphyxia.
Methods: Newborns > or = 35 weeks´ gestation with perinatal asphyxia (umbilical-cord or in the first hour of life pH < or = 7.00, need of deep resuscitation, or 5-minute Apgar score < or = 5) were prospectively examined by the clinical assistant and video-recorded of at least 5 minutes at different times within the first six hours of life. A specific neurological exam designed for this study was performed and consisted of 13 items: level of consciousness, spontaneous movements, response to stimulus, tone, myotatic reflexes, and brain stem reflexes. All video recordings were blindly assessed by two experienced clinicians trained in neonatal neurology. They classified the degree of HIE (mild, moderate, or severe) and the quality of the record. Interobserver agreement between both observers was assessed by calculating a weighted k statistic.
Results: 114 video recordings belonged to 51 infants with perinatal asphyxia were examined by both blinded observers. Weighted kappa was 0.94 ($p < 0.001$). Both observers differed in the classification of five exams: 1 moderate vs mild and 4 mild vs no HIE. Taking into account all the exams for each child, HIE was assessed for the 51 infants and kappa was 0.90 ($p<0.001$). Both observers agreed on the 4 infants with severe HIE, on 3/4 with moderate HIE, on 7/9 with mild and on 34/37 without HIE. Most recordings were considered of good quality for the purpose of the study, despite more time of spontaneous movements and response to stimulus and better evaluation of myotatic reflexes were desirable.
Conclusion: Video recordings of a structured clinical evaluation could be a useful tool to identify infants with HIE and to establish the severity when examined by experienced clinicians. Use of video recordings may be a valid approach to help clinicians with a low training in neurological exam skills to improve the identification of newborns with HIE who benefit from hypothermia treatment.

PRELIMINARY DATA OF A PROSPECTIVE MULTICENTER STUDY TO ASSESS HYPOXIC ISCHEMIC ENCEPHALOPATHY

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HIE is a disorder of low incidence and prevalence in most of the Spanish Hospitals. Further, most of the babies with HIE are born at hospitals with very heterogeneous training on neurological evaluation. Therefore, early identification of the severity of HIE is not always easy. This identification is essential to start therapeutic hypothermia within few hours after birth and misdiagnosis could reduce chances of survival and it should be avoided.
Objective: We questioned if newborns with HIE are well identified in hospitals with different skills at neurological examination when compared to two experienced clinicians. **Design:** Prospective multicenter study involving 13 hospitals from the area of Castilla y León and La Rioja in Spain between June 2011 and June 2013.
Methods: Newborns > or = 35 weeks´ gestation with perinatal asphyxia (umbilical-cord or in the first hour pH < or = 7.00, need of deep resuscitation, or 5-minute Apgar score < or = 5) were examined by clinicians with different skills on clinical neurological examination at one, three and five hours of age to assess the degree of HIE. Video recordings of the exams were later blindly examined by two experienced clinicians who also determined the degree of HIE The exam was designed for the study and consisted of 13 items which included level of consciousness, spontaneous movements, response to stimulus, tone, myotatic reflexes and brain stem reflexes. Interobserver agreement between the classification of the clinician on call and both experts was assessed by calculating a weighted k statistic.
Results: Preliminary data of 96 video recording exams of 42 newborns belonging to one hospital are presented. Weighted kappa was 0.73 ($p < 0.001$) between clinicians on call and observers´ classification. Clinicians on call classified absent HIE in 75/96 exams (7 of them were mild and 1 moderate by experts), mild HIE in 14/96 (3 without HIE and 1 moderate by experts), moderate HIE in 2/96 (1 without HIE and 1 severe by experts) and 5 severe HIE (5 severe by experts).
Conclusion: Our data suggest that there is a need to improve the identification of infants with HIE. In addition, evaluation of video recordings by experienced clinicians in real time could help to improve early detection of HIE leading to the onset of therapeutic hypothermia and a better clinical management

GRADUATE MEDICAL EDUCATION REFORMS FOR NEONATOLOGY IN SWEDEN IN RELATION TO THE EUROPEAN SOCIETY OF NEONATOLOGY RECOMMENDATIONS

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Introduction/Background: Neonatology was accepted as a pediatric subspecialty in Sweden in 1994. In some European countries it is still not officially recognized. Educational reforms for specialities/subspecialties were delineated in Sweden in 2008 and by the European Society of Neonatology (ESN) in 1996 (Sidarto B. Oetomo), with revisions in 1998 (Michael Obladen) and 2007 (Neil Marlow). The reforms define new required competencies in communicative skills, professionalism and evidence-based medicine besides key medical competencies. A recent database collected and published by ESN compared neonatal training programs in 30 European countries (Breindahl M, 2013). Uniformity for medical knowledge and skills competencies was found, however, there were discrepancies for legal/ethical issues and personal development. Most countries did not implement mentoring and professional evaluation. The ESN has called for national self-reflection and review of national training programmes as the next step towards international harmonization, and we have in Sweden responded with this work.
Methods: We describe the educational reforms pertaining to the new competency areas in neonatology in Sweden and compare them to the ESN curriculum and look at training structure for the new objectives, feedback processes and evaluation of trainees.
Result: Certification in neonatology in Sweden requires fulfilment of 12 medical objectives as well as 9 new objectives, 3 each pertaining to communication/ethics (with patients/colleagues and pedagogic skills), professionalism/leadership (mentorship, team leader and administration) and evidenced-based medicine (research, quality control and community awareness). These are comparable to those outlined in the ESN syllabus. A mentorship system has been implemented. The mentor is responsible for on-going evaluations and feedback sessions with the trainee. Both mentor and trainee are required to document progress. The mentor must have attended a mentorship course and have pedagogic awareness. However, there are no clear guidelines how to assess the trainee in contrast to the Assessment Framework from ESN. Neonatology program directors are being designated at 3rd level units. They will need to council and support the faculty to change and adapt teaching styles. New curriculum development demands new faculty resources and teaching structure in the training programs. Work-place-based assessments and other pedagogic tools need to be incorporated into programs.
Conclusions: Fulfilment of new competencies in communication, professionalism and evidenced-based medicine are necessary for certification in neonatology in Sweden. A mentorship system and obligatory documentation of progress with regular feedback to the trainee are the only official tools for assessment. There is a need for the profession to provide more structure and clear guidelines for assessment of the trainee on a national level. The ESN assessment framework could help catalyze these reforms.

THE DEMAND FOR AN EDUCATIONAL SMARTPHONE APP: A REVIEW OF OUR EXPERIENCE

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Background: Smartphone use amongst the medical profession is becoming more popular with many medical textbooks, medical calculators and drug formularies now available on smartphone platforms. Neonatal intubation is a potentially life-saving skill. Opportunities for trainees to intubate infants have reduced in recent years, as a consequence of reducing indications for this procedure and reducing work hours. The NeoTube smartphone application was developed in 2011 to assist neonatal trainees in learning neonatal intubation. Objectives: To determine the usage of a neonatal intubation application over a two year period.
Methods: This application does not require wireless internet or 3G access after initial download, so full access to all the features of the application is possible following initial download. We evaluated app usage data from Google Analytics. User feedback was encouraged via return email.
Result: The application has been downloaded over 5000 times in 105 countries. These downloads have resulted in the app being used 22500 times. Of these, 17,367 visits were by returning visitors. The application was viewed most frequently in the United States, followed by the United Kingdom and then Ireland. There were over 105, 000 page views with the most popular pages being 'anatomy of the airway', 'calculations' and 'videos and images'. The average duration of usage per visitor was 3mins 33 secs. Whilst user feedback was low overall at 3%, the feedback was positive overall.
Discussion: With recent advances in technology, smartphones are becoming more available and more accessible around the world. Use of medical apps in clinical care is common as evidenced by the number of page views and countries of usage. Regulation and guidance in this area is lacking. We believe that greater physician involvement should be encouraged and national training authorities/specialties should endorse applications prior to their general release.

THE OBSERVATIONAL RATING SCALE OF PARENTAL INTERACTIONS (ORSPI): FURTHER DEVELOPMENT AS A MEASURE OF QUALITY OF FATHERS' INTERACTIONS WITH THEIR PRETERM INFANTS

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Background: Parent-child interactions are particularly important for preterm infants who compared to their full term peers, provide less clear social cues, and are more irritable and difficult to soothe with an increased risk of poor developmental outcomes. Currently, the time-consuming and costly Parent Child Interaction Teaching Scale (PCITS) is widely used to assess the quality of parent-infant interactions. To provide a brief, easy-to-use alternative, the Observational Rating Scale of Parental Interaction (ORSPI) was developed. This study will explore the validity of the ORSPI as a measure of fathers' interactions with their late preterm infants. Method: Video recordings of fathers interacting with their late preterm infants (born 34-36 weeks gestation) at four months (corrected age [CA]; n=109) and eight months (CA; n=42) during a structured teaching task were rated using the ORSPI (higher scores indicate higher quality interaction). Two versions of the ORSPI were used: 'ORSPI- 5' rates seven items assessing paternal support for emotional and cognitive development (e.g. parent gives task related praise, encouragement or comments in a positive tone to infant) during the first five minutes of the interaction, and 'ORSPI- Total' which rates seven items during the entire length of the interaction plus an additional item : ‘time spent teaching'. Discriminant validity was assessed by comparing the ORSPI- Total scores for late preterm father-infant dyads with previously collected scores of five month-old (n=152) and eight-month-old (n=74) full term dyads. Concurrent validity was assessed by correlating ORSPI scores with previously rated PCITS scores.
Result: Interaction time during a structured play task was longer for fathers of late preterm infants than fathers of full term infants at eight months old ($z=-3.29$, $p=0.001$), and longer interactions were associated with higher ORSPI- Total scores ($r=0.36$, $p=0.001$). After controlling for length of interaction, late preterm dyads had significantly lower ORSPI- Total scores compared to full term dyads at eight-months ($F(1,114)=6.39$, $p=0.013$) indicating good discriminative validity. ORSPI-Total scores were significantly positively correlated with PCITS Total Caregiver scores at four-months ($r=0.46$, $p=<0.001$) but did not reach significance at eight months. ORSPI-5 scores were significantly positively correlated with the PCITS Total Caregiver score at four months ($r=0.47$, $p<0.001$) and eight months ($r=0.42$, $p=0.006$) indicating good concurrent validity. The ORSPI showed excellent intra-rater reliability (ICC=0.98) and good inter-rater reliability (ICC=0.80).
Conclusions: The ORSPI has good discriminative validity, differentiating between late preterm and full term dyads, and good concurrent validity, showing promise as a valid and practical measure of paternal interactions. Standardising interactions to five minutes and using the ORSPI-5 further improves ease of use and sensitivity.

MATERNAL DISCIPLINE IS NOT INFLUENCED BY FAMILY STRUCTURE: A STUDY IN THE GENERATION XXI PORTUGUESE BIRTH COHORT

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Background: Abusive parental discipline may compromise children's physical and psychosocial healthy development. In addition, the family structure may influence the parent-child interactive behaviour, including parental disciplinary practices. Therefore, this study aimed to describe disciplinary practices adopted by mothers of 7 years-old children of a Portuguese birth cohort, according to their family structure.
Methods: On a chronological basis, we evaluated 1168 families of 7 years-old children as part of the follow-up of Generation XXI birth cohort (n=8647). Maternal socioeconomic characteristics, including family structure (lone-parent families vs. husband-wife families), were collected by trained interviewers using standardized questionnaires. The Parent-Child Conflict Tactics Scale (CTSPC) was self-completed independently by mothers and it was administered to children in private setting, by trained interviewers. Items were rated according to the original dimensions of the scale into nonviolent discipline (NVD), corporal punishment (CP), psychological aggression (PsyA) and physical assault (PA). Past-year prevalence was computed for each dimension and compared with maternal education using chi-square test. Mothers-child agreement was estimated through kappa coefficients.
Result: NVD was highly reported by mothers in lone-parent and in husband-wife families (100 and 99%, respectively) as it was by their children (83 vs. 89%). CP was as often mentioned by lone-parent mothers and mothers in husband-wife families (95 vs. 93%), the same being observed for the children (72 vs. 75%). PsyA was similarly reported by lone-parent mothers and those in integral families (96 vs. 97%, respectively). Children from lone-parent families identified less PsyA than children in husband-wife families (75 vs. 77%). PA was more often perpetrated by mothers in lone-parent families than mothers from integral families (9 vs. 6%, p=0.31) but children from single-parent families reported a very similar frequency of PA (25 vs. 23%). Parent-child agreement was week, with the highest kappa value observed for corporal punishment (k=0.2). For NVD, the higher the education level of mothers in husband-wife families the higher the prevalence these disciplinary practices (ranging from 15 to 34%, p<0.001).
Conclusions: A high prevalence of harsh maternal discipline was similarly found among Portuguese school-aged children from both lone-parent and husband-wife family structures, with similar differences in mother-child perspectives. These findings provide relevant insights for the lack of impact of family structure in maternal disciplinary practices.

PREMATURITY, SMALLNESS-FOR-GESTATIONAL AGE (SGA) AND LATER HOSPITAL ADMISSIONS: A NATION-WIDE DATAMINED REGISTRY STUDY

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Introduction: Being born premature and/or SGA is known to be associated with several diseases later in life, including gestational diabetes, hypertension & pre-eclampsia among others. In this study we present a datamining model to establish the association between being born premature and/or SGA and all disease-specific ICD-10 codes in a nation-wide registry.
Methods: Using Danish nation-wide registries we created a cohort of 1.348.106 persons born 1974-1996, and compared the odds for all unique diseases registered in the Danish Patient Registry (DPR) for all hospital admissions in the period 1994-2007 (n = 27.910.558), for persons born premature and/or SGA, compared to persons born at term or with appropriate weight for gestational age (AGA).
Result: A total of 15.059 unique ICD-10 codes were present in the DPR in the period. Only codes used at least 100 times were included (n = 4.175), of which 838 showed a statistically significantly increased or, less common, decreased OR for people born premature and/or SGA. After correcting for multiple testing, 250 remained significant. The diseases covered most organ systems, including cardiovascular, endocrinological, infectious, neurological/neurosurgical, obstetric, orthopedic, psychiatric, lung & urological diseases and occurred throughout childhood and early adulthood.
Conclusions: Being born premature/SGA was associated with an increased risk of many diseases later in life, that affects almost all organ systems over a wide range of ages. In total, we identified 250 diesease or conditions with a significantly altered risk. The effect sizes, however, were small for many of them.

BIRTH WEIGHT STANDARDS DEFINED BY HEALTHY POPULATIONS: IMPROVED IDENTIFICATION OF INFANTS BORN SMALL-FOR-GESTATIONAL-AGE AND AT RISK OF ADVERSE NEONATAL OUTCOMES?

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Background: Major discrepancies exist between the diagnosis of growth restriction made in utero, and the neonatal classification based upon birth weight standards. While the association between intrauterine growth restriction and increased mortality and morbidity is well established, the association between small-for-gestational-age (SGA) and adverse outcomes largely depends on the reference used. Current Dutch birth weight references were based on the entire population of live births. From a clinical viewpoint, failure to exclude growth-restricted infants, inappropriately normalises the small size of an infant who might be at increased risk of adverse outcomes. Our aim was to investigate to what extent a birth weight standard defined by a healthy subpopulation (BWShealthy), could improve identification of infants born SGA and at risk of adverse neonatal outcomes, compared to birth weight standards based on the entire population of live births (BWSentire).
Patients And Methods: All infants with gestational age (GA) 24 to 42 weeks, born in the Netherlands from 2000 to 2007. Antepartum stillbirths, multiple births, and records with missing data were excluded. To obtain a healthy subpopulation, inclusion criteria were restricted to infants without congenital malformations, born to healthy mothers, after uncomplicated pregnancies and, in case of prematurity, born after spontaneous onset of labour. The LMS method was used to calculate birth weight percentiles for both the entire population of live births and the healthy subpopulation. We assessed associations between SGA (birth weight below 10th percentile) and selected adverse neonatal outcomes, separately for each birth weight standard. Diagnostic accuracies, in terms of sensitivity and specificity, were compared.
Results: We included 1,339,360 live births, of which 1,070,953 births satisfied the inclusion criteria of a healthy subpopulation. Before 37 weeks the BWShealthy percentiles were higher at each GA, compared to BWSentire percentiles. From 37 weeks onwards, the two standards agreed almost perfectly. The maximum difference between the 10th percentiles was 312g for boys and 362g for girls at 31 weeks gestation. The proportion of premature infants born SGA according to the BWShealthy was 15-45%, much higher than the expected 10% based on the statistical definition of SGA ($P<0.0001$). SGA infants across all GAs were found to be at increased risk of perinatal mortality, low Apgar scores, bronchopulmonary dysplasia, necrotising enterocolitis and retinopathy of prematurity ($P<0.01$). Despite a substantial increase in the total number of SGA infants when the BWShealthy was used, associations between SGA and adverse neonatal outcomes continued to exist. The improved sensitivity of the BWShealthy, caused only a slight decrease in specificity, when compared to the BWSentire. Overall, the diagnostic accuracy of the BWShealthy was significantly better.
Conclusion: Birth weight standards defined by healthy populations could improve the identification of infants born SGA and at risk of adverse neonatal outcomes.

ASSOCIATION BETWEEN NEONATAL WEIGHT CHANGE AND GLUCOSE METABOLISM AT 4 YEARS OLD

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Newborns lose 5.7% to 6.6% of birth weight (BW) during the first 3 days of life. Excessive or insufficient neonatal weight losses (NWL) have been associated with health problems in the neonatal period, such as disorders in hydration, related morbidities and death. Little is known about its medium and long term consequences, including the effect on glucose metabolism.
Our objective was to evaluate the effect of excessive and insufficient NWL, on glucose, insulin and HOMA score (homeostatic model assessment) levels in 4 years old children. Generation XXI included 8647 newborns recruited between 2005/2006 at the public units providing obstetrical and neonatal care in Porto. Information was gathered by face to face interview and additional data abstracted from clinical records, including BW. Neonatal anthropometrics were obtained by trained interviewers and we restricted the analysis to those weighed up to 96 hours of life. Neonatal weight change was estimated as (weight - BW) / BW × 100, adjusted for age in hours. NWL was categorized as excessive (bellow 10th percentile of the distribution of weight change: = -9.5%), normal (between 10th and 90th percentiles: -9.4% to -4.2%) and insufficient (above 90th percentile: = -4.1%). At age 4-5, children were reevaluated according to standard procedures, including a fasting blood sampling. Glucose and insulin levels were measured and HOMA score was calculated according to glucose (mmol/L) x insulin (μU/mL) / 22.5. Life course data for 516 normal term singletons with no congenital malformation were obtained. Adjusted regression coefficients and 95% confidence intervals [ß (95%CI)] were computed using generalized linear models. Children with excessive or insufficient NWL had lower levels of glucose [-0.010 (-0.134; 0.115) and -0.083 (-0.211; 0.044), respectively], insulin [-0.178 (-0.795; 0.440) and -0.528 (-1.147; 0.091), respectively], and HOMA score [-0.034 (-0.164; 0.097) e -0.124 (-0.255; 0.007), respectively], both compared with normal NWL children.
This study is the first one to provide evidence for the effect of weigh changes in the first few days of life on glucose metabolism. It was concluded that neonatal weight changes do not affect the glucose metabolism, at least in young ages.

THE IMPACT OF TWIN PREGNANCY BIRTH AND BIRTH WEIGHT DISCORDANCE ON NEONATAL OUTCOMES

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Introduction: During the last decade the incidence of twins has increased reaching about 3% of all live births. They represent an increasing health phenomenon due to the high rate of perinatal morbidities they suffer and recently the role of intertwin birth weight (BW) discordance has been emphasized as determinant for adverse neonatal outcomes. AIM: to evaluate the role of twin pregnancy birth and BW discordance on perinatal outcomes.
Methods: A hospital-based retrospective study was performed: 2327 inborn twins, born between 01.01.2007 and 31.12.2011, were included and compared with a control group of 2217 randomly selected singletons. The following clinical data were collected from notes: GA, gender, BW, Apgar score, mode of delivery, early neonatal morbidities (RDS, pneumotorax, PDA, NEC, IVH, cPVL, ROP, hypoglicaemia and sepsis), lenght of stay and mortality. The effect of intertwin BW discordance on clinical outcomes was explored. Univariate and multiple linear and logistic regression analyses were used.
Results: During the univariate analysis, younger GA (34.7±2.8 vs 38.6±1.7wks, p<0.001), lower BW (2204±560 vs 3223±488g, p<0.001) and all neonatal morbidities (except for NEC, cPVL and malformations) were more common in twins compared to singletons. In the multivariate regression model, adjusted for GA and gender, the OR for neonatal morbidities was similar in the two groups, but twin birth was significantly associated with cesarean section (OR 14.5, p<0.001), lower BW (p<0.001), lower Apgar score (p<0.001) and need for NICU admission (OR 0.4, p<0.001). At the univariate analysis intertwin BW discordance was linearly associated with a higher risk for neonatal morbidities and mortality. In the multiple regression model, adjusted for GA, BW discordance was only associated only to a higher risk for sepsis (OR 0.25, p<0.001), gastrointeistinal disorders (OR 1.02, p<0.05), need for blood transfusion (OR 1.03, p<0.05) and abnormal cranial ultrasound findings (OR 1.03, p<0.05).
Conclusions: Increased neonatal morbidity in twins appears to be related to prematurity rather than to twin pregnancy birth itself. BW discordance may play a role although lower GA remains the most important risk factor for adverse perinatal outcome. Further analyses are needed to confirm these observations.

MORBIDITY IN NEONATES WITH INTRAUTERINE GROWTH RETARDATION AND APPLICATION OF EPIDURAL ANALGESIA DURING DELIVERY

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Introduction: Intrauterine growth retardation (IUGR) is one of the present problems in neonatology due to high rates of perinatal morbidity and mortality. The incidence of IUGR ranges from 4 to 10% in developed countries, i.e., from 6 to 30% in developing countries. In the last few decades, epidural analgesia (AE) is recommended for labor with high-risk pregnancies because of many advantages which ensure favorable neonatal outcome.
Objective: To examine morbidity in neonates with IUGR after application of AE during delivery.
Patients and Methods: The prospective study included 327 term neonates with IUGR, who were born vaginally from high-risk pregnancies. All neonates were devided into two groups: the first group consisted of 152 newborns from delivery with AE and the second group included 175 newborns from delivery without AE. The diagnosis of IUGR was based on the assessment of gestational age (Negel) and birth body weight according to the national standard growth curve for our population (Nikolic). In both groups of neonates with IUGR was analyzed morbidity: perinatal asphyxia and its sequelae; haematologic and metabolical disorders, and infections.
Result: The study found a significantly lower morbidity in the first group of neonates with IUGR from deliveries with AE (48/31.6% vs. 81/46.3%, $p<0.01$) compared to the second group of neonates with IUGR from deliveries without AE. The analysis found a lower incidence of perinatal asphyxia (37/24.3% vs. 63/36.0%, $p<0.05$) and its sequelae (19/12.5% vs. 37/21.1%, $p<0.05$): hypoxic-ischemic encephalopathy (16/10.5% vs. 32/18.3%); meconium aspiration syndrome (5/3.3% vs. 9/5.1%); persistent pulmonary hypertension (0/0.0% vs. 3/1.7%) and acute renal failure (2/1.3% vs. 4/2.3%) in the first group of newborns from deliveries with AE. In addition, the analysis established a lower frequency of haematologic disorders (32/21.0% vs. 57/32.6%, $p<0.05$) and metabolic disorders (48/31.6% vs. 80/45.7%, $p<0.01$) in the first group of newborns from deliveries with AE. The study did not determine a difference in the incidence of infections between both groups of neonates with IUGR, from deliveries with and without AE (13/ 8.5% vs. 16/9.1%, $p>0.05$).
Conclusions: The application of AE during delivery of high-risk pregnancies has a special clinical importance in order to reduce morbidity in neonates with IUGR. Key words: neonates, intrauterine growth retardation, morbidity, epidural analgesia

GESTATIONAL AGE MODULATES THE EFFECT OF MATERNAL HYPERTENSION AND CHORIOAMNIONITIS ON NEONATAL OUTCOMES IN VERY PRETERM INFANTS

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Introduction: Very preterm infants have a high mortality and morbidity, due to a combination of immaturity per se, and of the underlying pathology causing preterm birth. Scarce data are available to estimate relative risks among different causes of preterm births, and the effect of gestational age (GA) in modulating these risks is unclear.
Aim: To test the hypothesis that hypertensive disorders (H) and chorioamnionitis (C) are associated to different patterns of adverse neonatal outcomes, and study if GA modulates these effects. Methods. A cohort of neonates 23-30 weeks GA, without congenital anomalies, born in 2008-2011 and assisted in 82 hospitals adhering to the Italian Neonatal Network (INN), was analyzed. Infants born of mothers with H (N=2096) were contrasted with those born after C (N=1510). Outcomes were: in-hospital death, severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), mechanical ventilation, pneumothorax, severe retinopathy of prematurity (ROP), and late-infections (> 3 postnatal days). Random-effects logistic regression models, adjusting for GA, hospital, and potential confounders (antenatal steroids, sex, inborn/outborn, mode of delivery, multiple pregnancy) were used. Results are expressed as odds ratios (OR) and 95% CI.
Results: We studied 3606 very preterm infants, with mean GA 27.4 weeks (SD 2.1), and mean birth weight 938 g (SD 281). The frequency of H and C varied across GA weeks, with H increasing its frequency, and C remaining constant in absolute number (decreasing in relative terms). Overall, mortality was higher in H group (OR 1.39, 95%CI 1.08-1.80). However, GA modulated the effect of H vs C: at 23-25 weeks GA, mortality was higher after H than after C, but this difference progressively waned and reversed until 27 weeks GA, and from 28 weeks onwards, mortality was lower for H. For other outcomes, the effects were constant across GA weeks: at all GA weeks, babies born after H had a lower risk of severe IVH and PVL (OR 0.66 and 0.71 respectively), and an increased risk of BPD (OR=2.05), mechanical ventilation (1.62), pneumothorax (1.54) and severe ROP (1.41) (All P<0.05). No difference was seen for late infections.
Conclusions. Mortality and other adverse outcomes in very preterm infants are related both to degree of immaturity (GA) and to antecedent of preterm birth. H and C are associated to different patterns of outcomes; this points to different pathophysiological mechanisms. For mortality, the relationship between 'cause' and outcome is not constant in the GA strata considered in this study: we speculate that chorioamnionitis, by stimulating lung maturity, reduces acute lung injury, and increases probability of survival at very low GA, but this advantage is offset as GA increases, when the absolute risk of death/morbidities decreases. This interpretation is consistent with the stable effects of exposures (H or C) on other outcomes across GA weeks: C is always (relatively) protective against respiratory pathology and ROP, and always harmful for cerebral pathology. Our study also supports the greater importance of the 'vascular hypothesis' over the 'infectious hypothesis' of BPD.

GESTATIONAL AGE, BIRTH WEIGHT, AND INFANTILE COLIC

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Background: Preterm and growth restricted infants may have developmental delays or deviant organ function related to the central nervous system and the gastrointestinal tract. Since both organ systems are hypothesized to be involved in the pathogenesis of infantile colic, a condition characterized by excessive crying during the first months of life, impaired fetal growth and preterm birth may be risk factors for infantile colic. Objectives To investigate the association between gestational age, birth weight, and infantile colic.
Methods: We used maternal interviews from the Danish National Birth Cohort (1996 to 2002) conducted at gestational week 17 and at six months post partum. We included 62 761 live-born singletons with complete information on birth weight, gestational age, and crying symptoms recorded at six months of age. Infantile colic was defined according to Wessel's modified criteria: crying for more than three hours per day for more than three days per week.
Results: A total of 2605 (4.2 %) infants were born preterm, 54 441 (86.7%) at term, and 5715 (9.1%) post-term. A total of 4353 (7.7%) infants fulfilled Wessel's modified criteria. The risk for infantile colic increased with lower gestational age and birth weight after adjustment for several possible confounders. The highest risk (odds ratio [95 % confidence interval]) was observed for infants born before 32 complete gestational weeks (1.5 [1.0-2.2; $p<0.05$], reference: 40 gestational weeks) or with birth weight less than 2000 grams (1.7 [1.3-2.2], reference: 3500 - 3999 grams). Small for gestational age infants (birth weight below 10th percentile) had higher risk for infantile colic in all gestational ages. This was statistically significant for infants born between 37-41 complete gestational weeks (1.2 [1.1-1.3]).
Conclusions: We found an association between infantile colic, and gestational age and birth weight in a large cohort study. This indicates that the aetiology of infantile colic may be found in the prenatal time period.

MATERNAL DISEASE IN PREGNANCY AND FAILURE ON HEARING SCREENING IN SMALL- AND LARGE-FOR-GESTATIONAL-AGE NEONATES.

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Background: Small for gestational age (SGA) status is known to increase the risk for failure on otoacoustic emissions (OAE) hearing test. Maternal disease during pregnancy such as hypertension (HTN), preeclamptic toxemia (PET) and diabetes mellitus (DM) often leads to SGA status or to large for gestational age (LGA) status and might thus affect hearing screening. We evaluated the effect of SGA status, LGA status and maternal disease on OAE failure in infants >35 weeks' gestation.
Patients and Methods: During a 9-month study period, 113 SGA infants (BW<5th percentile) and 131 LGA infants (BW>95th percentile) were born. For each SGA or LGA neonate, two appropriate for GA (AGA) control infants were matched (birth within the same calendar-week and same GA-week) (AGA group; n=488). Excluded were infants who needed intensive care, had significant malformations; congenital cytomegalovirus infection; auricular skin tag/pit; parental hearing loss; 1st OAE performed before 20 hours of age, and apparent hearing loss (failure on OAE and AABR in one or both ears).
Result: Compared to AGA infants, SGA infants' mothers had significantly more HTN/PET. LGA infants' mothers had significantly more HTN/PET and DM. LGA infants were born more by cesarean delivery (CD) without maternal disease (HTN and/or PET and/or DM) or CD with maternal disease, and failed more on OAE test (SGA: 6.2%; AGA: 6%, LGA: 12.2%). Univariate analysis showed that male gender [p=0.03, OR 1.9 (1.1-3.5)], maternal DM [p=0.002, OR 3.3 (1.6-7.1)], LGA status [p=0.017, OR 2.2 (1.2-4.2)], CD without maternal disease [p<0.0001, OR 5.7 (3.1-10.5)], and CD with maternal disease [p<0.0001, OR 9.6 (4.3-21.4)] were significantly associated with failure on OAE test. Multivariate stepwise logistic regression analysis (Table 1) showed that variables independently significantly associated with failure on OAE included male gender [p<0.045, OR 1.9 (1.01-3.4)], CD without maternal disease [p<0.0001, OR 4.6 (2.3-8.9)] and CD with maternal disease [p<0.0001, OR 9.6 (4.3-21.3)]. Our results show that male gender, maternal DM, LGA status, and CD (with or without maternal disease) were significantly associated with higher risk for OAE failure. Maternal conditions (HTN, PET and DM) appear to affect failure on OAE test. According to our results, the following sequence could be drawn: Maternal DM increases the rate of LGA status which increases the need for CD which is known to be associated with a 3-fold higher failure rate on 1st OAE test. Nonetheless, a combination of CD and maternal disease (HTN/PET/DM) further increased the risk for OAE failure up to 9.6-folds.
Conclusions: Maternal disease during pregnancy, mainly DM, contributes to hearing screening failure regardless of mode of delivery. Whether DM itself or LGA status increase hearing screening failure is yet to be investigated.

ACUNA SEN34-36. DATABASE FOR LATE PRETERM BABIES IN SPANISH HOSPITALS. PRELIMINARY DATA.

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Introduction: Prematurity is the first reason of neonatal morbidity and mortality, and it stands as one of the more important problems for community health. Late preterms, born between 34+0 and 36+6 weeks of gestation, mean 70-75 % of all preterm babies. Data regarding late preterms show increased morbidity and mortality compared to term babies. This is due to the relative physiological and metabolic immaturity, even when the weight may be similar to the term newborn. And what is more important, neurological development may also be compromised in later ages.
Objective: To define the current situation of this group of patients in Spanish hospitals attending births. Causes of prematurity. Mortality. Early and late morbidity. Admission criteria. Postnatal evolution with neurological follow-up up to 2 years.
Method: Epidemiological study of this population in the Spanish hospitals, analyzing the data submitted to ACUNA database. ACUNA was designed by the Group SEN34-36 of the Neonatology Spanish Society in order to recruit every late preterm born in the collaborating hospitals, including all their perinatal data as well as a two years follow up.
Results: 90 centers have entered the study. 37 have sent information to the database. 2343 late preterms have been included up to now, most of them only with the perinatal data. The distribution in gestational ages was: 24% 34ers, 30% 35ers and 40% 36ers. The reason for preterm birth was not specified in a third of cases (33'8%). Cesarean section was performed in 46'6% of the births. In nearly half of them (44'4%) C-section was not justified. 1202 mothers received antenatal steroids. No relationship was stablished between them and morbidity regarding lung maturity. Hypoglycemia was observed in 11'8% of the newborns. Exlusive breast feeding rate at discharge was 47'30%. Admission rate was 60'7% overall, with 12% in the NICU
Discussion: It is interesting to remark the high incidence of hypoglycemia in these children (11,8 %), since some authors suggest it as the principal factor for adverse neurological outcomes (JM Kerstjens et to, 2012). Probably, if more systematic glycemia measures were performed in the first hours/days of life, this incidence would be higher. Breast feeding rate at discharge was low, what is probably related to the difficulties for nutrition of these late preterms. In a period when Neonatal Units tend to adopt strategies for a Family Centered Care model, it is surprising the high rate of admissions for these babies. The aim would be to reduce this rate not diminishing, or even improving the level of attention for the newborn and his family. The improvement in morbidity and mortality in this important group of population needs strategies of prevention, which will be better stablished as long as we know the real reasons for these preterm births. The final aim of ACUNA is to include data for two years follow up for late preterms.

IS NEONATAL MORTALITY RATE (NMR) OF TWINS AND TRIPLETS OF VERY-LOW-GESTATIONAL-AGE (VLGA) BETTER THAN SINGLETONS OR SAME GESTATIONAL AGE? A EURONEONET STUDY

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Background: Perinatal and long-term outcome of twins, triplets and higher-order multiples is worst than for single pregnancies, mainly due to an increase in premature birth. However the neonatal outcome of those of VLGA has not been extensively reported and remains controversial. Aim: To analyse the neonatal outcome of VLBW/VLGA infants born to mothers with multiple pregnancy in NICUs participating in EuroNeoNet.
Methods: Perinatal risk/protective factors, early neonatal complications and mortality rate (NMR) were compared in singletons, twins and triplets, born live from 2006 to 2011 in one of the 192 NICUs, from 16 European countries plus Turkey, belonging to EuroNeoNet. Independent comparisons were performed by non-parametric tests to determine perinatal risk factors associated to multiple pregnancies, using a logistic regression analysis. Crude and adjusted associations were described as Odds Ratios (OR) and its 95% confidence intervals (CI). Significance was set at $p<0.05$.
Result: The cohort included a total of 37,371 VLBW/VLGA infants born alive, of which 32.5% were multiples (28% twins, 4.1% triplets and 0.2% of higher-order). In comparison to singletons, twins and triplets had a significantly higher birth weight (BW) and gestational age (GA) but a lower NMR (singletons 14.5%, twins 12.9% and triplets 10.8%). All those percentages remained stable for all the period studied. Other outcomes like BPD, Leukomalacia and Late Onset Sepsis were also significantly higher for singletons (BPD: 18.2%, 13.8% and 12.5%, respectively; PVL: 5.6%, 4.7% and 2.4%, respectively; LOS: 23.8%, 21.0% and 20.8%, respectively). Perinatal independent factors strongly associated with multiple pregnancies were C-section (OR: 1.6, 95%CI: (1.49-1.66)) together with BW; GA, gender, prenatal steroids, absence of major birth defects and 1 and 5-min Apgar scores. After adjusting for those perinatal factors multiples were more likely to die than singletons (OR: 1.33. 95%CI: (1.23-1.45). Other outcomes such us BPD, Cystic Leukomalcia and Late Onset Sepsis had significantly lower probabilities in multiples.
Conclusions: During the 6 year period studied, twins and triplet infant of VLGA had lower crude NMR and BPD rate, but adjusting for perinatal risk factors, those differences disappeared in mortality but remained in outcomes. The better neonatal outcomes of twins and triplet appears to be mainly related to the longer gestation achieved in multiple pregnancies. The authors do not have anything to disclose.
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MAJOR BIRTH DEFECTS IN VERY PRETERM OR VERY LOW BIRTH WEIGHT INFANTS IN EUROPE. RESULTS FROM THE EURONEONET NETWORK.

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Introduction/Background: Both the prevalence of major birth defects (MBDs) at birth, and the increased risk of death associated with MBDs may have an independent impact on the overall mortality of very preterm or very low birth weight infants. The aim of this study is to determine the frequencies and types of MBDs in very preterm/very low birth weight infants in Europe and their impact on NICU mortality, using data recorded in the EuroNeoNet database.
Patients and Methods: EuroNeoNet is a European-wide neonatal network, prospectively collecting data on the characteristics, type of care received, and outcome of very preterm (<32 weeks gestation, VPI) or very low birth weight (<1501 g, VLBWI) infants. During 2006-2010, 30330 babies, cared for in 185 neonatal units in 17 countries, were enrolled. MBDs were coded according to ICD10 and then grouped following the EUROCAT classification, that excludes some minor defects. Infants with single and multiple MBDs were analyzed separately. Other variables taken into account in this analysis were sex, gestational age (GA), birth weight (BW) z score, and death before discharge. Frequencies and rates were calculated, together with relative risks (RR) and 95% confidence intervals (CI) as appropriate.
Results: Two hundred sixty two infants with missing data about birth defects were excluded. MBDs were reported in 2238 out of the remaining 30007 infants (7.5%, CI 7.2-7.8%), but in 323 cases the type of defect was not specified. Thus, complete information about MBD was available for 1915 babies. A single defect was reported in 84.1% of cases, two defects in 11.3%, and three or more defects in 4.6%, with the total number of MBDs summing up to 2334. Congenital malformations of the cardio-vascular system were the most frequent defects (37.6%), followed by malformations of the gastrointestinal system (13.3%), central nervous system (6.8%) and genito-urinary tract (6.8%). A higher proportion of infants with MBDs, in comparison to those without, had a GA >31 weeks (19.5% vs 15.1%; p<0.001) and a BW below -1 z score (21.7% vs 18.4%) and below -2 z score (1.0% vs 2.2%; p<0.001). No difference was found in males/females distribution. In-hospital mortality rates were 13.1% for infants without MBDs. Despite their higher GA, MBDs infants had a mortality higher than non-malformed peers, increasing from 23.0% in case of a single defect (RR 1.75, CI 1.59-1.92) to 38.2% for those with multiple defects (RR 2.90, CI 2.51-3.36). Infants with MBDs accounted for 11.7% of all deaths.
Conclusions: Among the high risk newborn population of VPI/VLBWI, those with MBDs represent a subgroup with further increased risk of short term mortality. Information collected in the EuroNeoNet network can contribute to better clarify the impact of MBDs on the outcome of these infants, and the relationships of MBDs with perinatal variables, different care policies, and special care services at national and regional level.

THE IMPACT OF SMALL FOR GESTATIONAL AGE (SGA) AS A RISK FACTOR FOR RETINOPATHY OF PREMATURITY (ROP) IS DEPENDENT ON GESTATIONAL AGE

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Introduction: Retinopathy of prematurity (ROP) is a potentially blinding disease affecting very preterm infants. Gestational age (GA) and birth weight (BW) have since long been considered as major risk factors for ROP. However the impact of small for gestational age (SGA) has varied in different studies. The aim of this study was to evaluate SGA as a risk factor in the development of treatment requiring ROP, in a large cohort of preterm infants.
Patients and Methods: Data were retrieved from 5 cohorts previously prospectively assembled for WINROP (Weight IGF-I Neonatal Retinopathy of Prematurity) studies (2004-2009). The 5 cohorts were: a Swedish nation based cohort of extremely preterm infants (EXPRESS) (n=510), an US/Canada multicenter cohort (n=1772), a Boston (US) cohort (n=338), a Lund (Sweden) cohort (n=52) and a Gothenburg (Sweden) cohort (n=353), in total 3025 infants were eligible. Data concerning GA, BW, gender and ROP treatment were retrieved from each original study. All infants had a GA < 32 weeks.The infants birth weight standard deviation score (BWSDS) were calculated. Univariate and multivariate analysis modeling were used calculating significance of risk factors.
Results: The infants frequency of SGA increased significantly with additional GA week ($p<0.000$), median BWSDS decreased significantly with GA week ($p<0.000$). In univariate regression analysis of the whole cohort; GA week at birth and BW were found to be statistically significant. There was a difference between infants born before and after 26 weeks GA. For infants born < 26 weeks GA (n=880); GA and BW were significant risk factors for severe ROP requiring treatment while, for infants born ¬> GA 26 weeks (n=2145); GA, BW, BWSDS and SGA were risk factors for severe ROP requiring treatment. For the whole cohort multi regression analysis revealed SGA ($p<0.000$), male gender ($p<0.05$) and GA ($p<0.000$) as independent risk factors for ROP requiring treatment. For infants born < 26 weeks GA; SGA (OR= 1.69, $p<0.05$), male gender (OR=1.37, $p<0.05$) and GA (OR=0.47, $p<0.000$) were independent risk factors for ROP requiring treatment .For infants born > 26 weeks GA; SGA (OR=3.53, $p<0.000$) and GA (OR=0.41, $p<0.000$) were risk factors for ROP requiring treatment.
Conclusions: SGA as a risk factor for ROP treatment is dependent on GA in both univariate and multivariate regression analysis. For infants born after a GA of 26 weeks; SGA has a high significance and is a major risk factor for developing ROP requiring treatment.

INCIDENCE OF DEVELOPMENTAL DYSPLASIA OF THE HIP FOLLOWING ATTEMPTED EXTERNAL CEPHALIC VERSION

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Background: Breech presentation in pregnancy is a risk factor for developmental dysplasia of the hip (DDH). (1) DDH affects 1-3% of all newborns. (2) In 2010 the National Screening Committee UK, updated guidance recommending that all babies breech at 36 weeks gestation should be screened for DDH even if born cephalically. (3) External cephalic version (ECV) can be offered to women in pregnancy to facilitate a cephalic vaginal delivery. One previous study suggests that babies who are breech at 36 weeks gestation have a higher incidence of DDH which they carry with them even if deliver cephalically. (4) However a recent study showed that babies who had undergone ECV and delivered cephalically had a lower incidence of DDH. (5) We sought to study this further with a larger population of infants who had undergone ECV to investigate the incidence of DDH in this group.
Methods: We performed a retrospective review of maternal and baby records for women in whom ECV was attempted in a single centre between June 2008 and December 2010. Data sheets for all ECVs performed during this time period were reviewed and cross referenced with the subsequent baby's records looking for results of hip ultrasound. The data was further checked by reviewing attendance at hip screening clinic and orthopaedic outpatients to ensure infants, who may have missed initial referral, did not attend screening or presented late with DDH were included in the analysis. The data were analysed using Chi squared and Fisher's exact tests.
Results: Between June 2008 and December 2010 there were 24,552 babies born cephalically and 906 born breech in our centre. 270 ECVs were performed, 125 of which were successful. The incidence of DDH in babies born cephalically who did not have an ECV was 0.33% (0.27 to 0.39) %. In babies who underwent successful ECV the incidence was 2.4% (0 to 5.1) % which was significantly different from those born cephalic (p=0.0013). This incidence of 2.4% was also not statistically significantly different from those babies born breech (p=0.46) who had an incidence of DDH of 4.4% (2.97 to 5.83) %. In babies who underwent unsuccessful ECV the incidence of DDH was 4.8% (1.25-8.35)% which was similar to the incidence in babies born breech (4.4%) who did not undergo ECV (p=0.90).
Conclusion: This study confirms that being breech at 36 weeks gestation is associated with an increased risk of DDH even if successful ECV is performed and a baby delivers cephalic.
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WHAT WE TALK ABOUT WHEN WE TALK ABOUT NICUS: RESULTS OF THE STUDIO OSSERVAZIONALE IN NEONATOLOGIA, ASSISTENZA E CURE (SONAR) STUDY

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Introduction: Unlike adult or paediatric Intensive Care Units, that care only for very sick individuals, NICUs often follow their patients from birth to hospital discharge, providing not only 'intensive care' but, rather, comprehensive care of newborns with special needs. While individual infants of very low birth weight (BW) /gestational age (GA) cared for in NICUs are described through network 'cohort' studies, we have far less data on what is the daily work of NICUs through 'cross-sectional' designs. Aim To obtain a representative description of number and acuity of infants admitted and cared for in NICUs in Italy (Studio Osservazionale in Neonatologia: Assistenza e cuRe: SONAR study).
Methods: 60 Italian NICUs participated in SONAR study in 2010-'11. We carried out 12 cross-sectional (1 per month) surveys, on different shifts (morning, afternoon, night, holiday), and collected data on number of nurses, and number and acuity of infants. Infants' acuity was assessed by nurses using 2 methods the BAPM 2001 classification (each infant is classified as intensive, high dependency, or special care, based on 17 characteristics), and a classification in 5 categories of increasing complexity: 1=continuing care; 2=intermediate care; 3=intensive care; 4=multisystem support; 5=unstable, requiring complex critical care (Rogowski, JAMA Pediatrics 2013).
Results: The NICUs participating to the SONAR Study assisted about 60% of all infants in Italy, and were not different from non-participating units, as judged by the Italian Neonatal Network data. In 2010, they admitted (means) 486.1 infants, of which 52.3 were <1501g BW or <30 weeks GA, on 17.5 beds, providing 5963.2 days of care. We collected 703 reports regarding 11082 infant data points, assessed by 3226 nurses. These infants were for the most part of lower acuity, as judged by both classifications: Rogowski 2013 classification: Acuity 1: 42.0%; Acuity 2: 33.7; Acuity 3: 17.4; Acuity 4: 4.8; Acuity 5: 2.2%; BAPM 2001 classification: Special care: 57.2%; High dependency: 20.1; Intensive care: 22.4%. 708 infants (6.4% of those surveyed) were on ventilator at the time of survey, and 10.2% on CPAP. Infants <1501g BW or <30 weeks GA represented 44% of infants surveyed. Their acuity was on average higher than that of more mature infants (mean acuity= 2.2 vs 1.7, P<0.001).
Conclusions: The majority of infants cared for in NICUs are at not 'intensive'. The daily work of NICUs is mainly on stable infants, often not intensive, with few instable ones. Very preterm infants account for only 1/10 admissions, but for about half of patients' days. These results are very similar to those reported in USA (Rogowski 2013). According to Geoffrey Rose ('The strategy of preventive medicine'), most occurrences of a disease do not come from high-risk individuals, but from the majority of (relatively) low-risk persons. Thus, to reduce the burden of disease in sick infants, we should target not only the (relatively rare) acute phases of hospital stay, but also the much more frequent lower acuity phases. Nurses and neonatologists' job organization could also be ameliorated based on these results. The SONAR study was sponsored by a non-restricted grant by Chiesi pharmaceuticals

EFFECTS OF MATERNAL SMOKING IN PREGNANCY ON ADULT NEUROPSYCHOLOGICAL OUTCOME IN SMALL-FOR-GESTATIONAL-AGE (SGA) AND CONTROL SUBJECTS.

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Background: Maternal smoking has been identified as one of the most potent risk factors of intrauterine growth restriction (IUGR). Being born small-for-gestational-age (SGA) is used as a proxy for IUGR in epidemiological studies. Some studies have shown that being born SGA at term is related to increased risk for cognitive problems compared to those born with normal birth weight for gestational age. Objectives: The aim of this study is to see how maternal smoking in pregnancy relates to neuropsychological outcome in term born SGA young adults and controls.
Design/Methods: This is a population-based follow-up study at age 19-20, including 58 term-born SGA (birth weight< 10th centile, mean: 2918g) and 81 controls (birth weight>10th centile, mean: 3707g). At week 17 of gestation, the mothers reported whether they were smoking or not, and the number of cigarettes per day. When the subjects had reached age 19-20, we performed a comprehensive neuropsychological assessment by. Z-scores were calculated for each test in both groups, based on the mean and SD from the control group. We further calculated domain-scores for: attention, executive functions, language, auditory memory, visual memory, visual-motor integration and motor skills, respectively. Full IQ was assessed by the Wechsler Adult Intelligence Scale-III (WAIS-III). We adjusted for gender, age at assessment and socioeconomic status in all analysis.
Result: The SGA group performed poorer than controls on all the neuropsychological domains and obtained lower IQ scores. The percentage of maternal smoking was significantly higher in the SGA group compared to controls (63% vs. 38%, p=0.011). However, there was no significant difference in domain-scores between SGA subjects exposed to smoking in pregnancy and those who were not. In the control group, those who were exposed to smoking in pregnancy performed significantly poorer than non-exposed subjects on Attention (z= -0.18 vs. z=0.17, p=0.004), Executive functions (z=-0.16 vs. z=0.10, p=0.012), Language (z=-0.43 vs. z=0.27, p=0.000) and Memory (z=-0.23 vs. z=0.15, p=0.014). Smoking correlated with Full IQ scores in the control group (r=0.395, p=0.001), but not in the SGA group. Maternal smoking explained 14% of the variance in IQ scores in the control group (B=9.17, p=0.001). There was no difference in birth weight between those who were exposed to maternal smoking compared to non-exposed subjects in neither the SGA group, nor the control group.
Conclusions: Our results suggest that exposure to maternal smoking in pregnancy have a negative effect on neuropsychological functioning only in subjects born with normal birth weight for gestational age. Maternal smoking is known to be related to IUGR, but other factors causing restricted growth may harm the developing brain beyond the effect of nicotine exposure.

EARLY RESPIRATORY INFECTIONS: GENETIC FACTORS, FAMILY ENVIRONMENT AND PASSIVE SMOKING

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Introduction/Background: Early respiratory infections are important risk factors for respiratory disease in adulthood. Objectives of this study were: i) to estimate the genetic and environmental components of early respiratory infections; ii) to test the hypothesis that passive smoking exposure modifies the relative weight of environmental and genetic factors on susceptibility to these infections.
Patients and Methods: Study subjects were about 1000 twin pairs aged 3-17 years and enrolled in the Italian Twin Registry (ITR), a nationwide database comprising pairs of twins who accept to participate in medical and scientific research activities. Study outcomes were respiratory infections before the first 2 years of life- i.e. bronchitis, wheezy bronchitis, pneumonia and bronchiolitis - as reported by parents in a general health questionnaire. Questions on these infections follow the Italian enriched version of the ISAAC questionnaire, that investigates respiratory diseases with a focus on environmental risk factors and family history. The statistical analysis was based on the twin method that compares measures of concordance in monozygotic and dizygotic twins. For each respiratory infection the proportion of variance explained by genetic factors, by environmental factors shared by the twins and by individual environmental factors were estimated. Furthermore, the same analysis was performed stratifying by passive smoking defined as at least one of the parents smoking in the house and /or in the car.
Results: No genetic influence was found on bronchiolitis (prevalence 11%) for which 95% of the total variation was explained by environmental factors shared by the twins; this result did not change when stratifying by passive smoking. For bronchitis (prevalence 40%), genetic factors explained 16% of total variation and again a strong influence of shared environmental factors (83%) was detected; no difference was seen in the stratified analysis. For wheezy bronchitis (prevalence 11%) and pneumonia (prevalence 7%), a considerable contribution of both genetic and environmental factors emerged. Furthermore, the relative importance of these factors changed when stratifying for parental smoking. In detail, the shared environmental component increased for smokers' children while the genetic component became more important in the non smokers' group.
Conclusions: The study found a substantial effect of shared familial environment in the development of early respiratory infections. For pneumonia and wheezy bronchitis, parental smoking was suggested to account for a relevant proportion of the shared environmental component. Furthermore, susceptibility genes for these infections may be more easily detectable in children not exposed to passive smoking.

RELATIONSHIP IN SCREENING OTOACUSTIC EMISSIONS FAILURE IN NEWBORNS AND PREGNANCY ALCOHOL ABUSE IN A HOSPITAL OF SOUTH OF BRAZIL

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Background: The alcohol ingestion by pregnant women crosses the placental barrier, and the fetus is exposed to the same concentration levels of maternal blood. The effects on the fetus occur independently of the quantity consumed. The alterations include growth retardation, malformations, delayed motor and mental development. In some cases, the alcohol usage by pregnant women may be underdiagnosed in the prenatal period by health professionals unprepared to notice signs compatible with drinking habits, and by the lack of search reporting use. Also, the embarrassment of pregnant women to report alcohol usage may contribute. The screening for alcohol abuse can be diagnosed by validated questionnaires. The T-ACE questionnaire assess alcohol tolerance, the existence of nuisance with regard to criticism of relatives and third parties about how the woman drinks, the perceived need to reduce consumption alcohol and persistence and dependence on the substance. This study aims to assess the prevalence of pregnant women, at ULBRA / SSMD Hospital, who used alcohol during pregnancy, identifying possible teratogenic effects and correlating alcohol abuse in pregnancy with the screening hearing test and check the orientation being given on the risk of alcohol usage during prenatal care related to alcohol abuse.
Patients and Methods: We used the T-ACE questionnaire. We interviewed mothers in rooming-in at ULBRA/SSMD Hospital in the period March to August 2012.The newborns were examined in the search for malformations, collecting anthropometric data, Apgar score and were classified according to gestational age and weight. All data were related to the use and abuse of alcohol. The questionnaire was considered positive for alcohol abuse when the score was equal or greater than to 2, with a maximum score of 5. Data analysis was performed with SPSS 18.0, using the Student t test, Mann-Whitney, chi-square test, McNemar and Kappa, with a significance level of 5%.The ethics committee of the institution approved the study.
Result: 296 mothers were included in the study during its period. The T-ACE was considered positive for alcohol abuse in 33.1% of the women. There was no significant difference between the positive group for alcohol abuse and the negative group in relation to anthropometric data and newborn malformations. The T-ACE positive group was higher maternal age (26.3 + - 6.0 years) comparing to the T-ACE negative group (24.9 + - 6.9 years) (p = 0.078). There was no difference in alcohol abuse among mothers counseled on the risk of alcohol use during pregnancy in the 2 groups. The otoacoustic emissions screening (OAE) were altered in 19.4% of infants in the T-ACE positive group and 8.5% for the T-ACE negative group (p = 0.008).
Conclusions: Alcohol abuse is considered high among pregnant women at ULBRA / SSMD Hospital. There was statistical significance in the failure rate for OAE screening among infants born to mothers positive to alcohol abuse. The orientation to pregnant women in prenatal care was not effective in reducing alcohol abuse. This study showed no presence of teratogenic effects in the sample.

PRENATAL EXPOSURE TO ENDOCRINE DISRUPTORS AND BIRTH WEIGHT IN A DUTCH COHORT - PRELIMINARY FINDINGS

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Introduction: Birth weight is a known risk factor for obesity later in life; both high and low birth weights have been associated with increased body mass index (BMI) in children. Several studies investigated whether prenatal exposure to chemicals affects birth weight and may therefore induce obesity later in life, e,g. through disruption of hormones and/or epigenetic modifications. Findings have been inconsistent regarding the association between exposure to endocrine disrupting chemicals (EDCs) and birth weight.
Objective: To assess the association between exposure markers of EDCs in cord blood and birth weight.
Methods: Polychlorinated biphenyl-153 (PCB-153), dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), and four bis(2-ethylhexyl) phthalate (DEHP) metabolites (mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(ethylhydroxy) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethylhexyl) phthalate (MEHP)), were measured in cord blood collected from 118 term newborns of mothers living in the region of Zwolle in the Netherlands. Perinatal data including birth weight was retrieved from medical records and information of lifestyle was collected by means of questionnaires. Associations were analysed by means of linear regression.
Result: All compounds could be detected in 100% of the samples, except for HCB, for which 47.6% was below limit of detection (LOD), and MEOHP, for which 1% was < LOD. Mean (sd) birth weight was 3577.2 (447.7) grams. For PCB-153, DDE, and HCB, significant positive associations were observed in girls, while in boys inverse associations were observed. PFOS was associated positively with birth weight in the overall group, as well as for boys and girls separately. For MECPP inverse associations were observed in the overall group and after stratification for gender, this association became stronger in boys but disappeared in girls. Similar results were seen for MEHHP. No effects were observed for prenatal MEOHP, MEHP, and PFOA exposure.
Discussion: Results for PCB-153 and DDE are comparable to a large meta-analysis of European cohorts, although no stratification for gender was done in that analysis. Current results for PFOS are not in line with what has been reported in other studies, however this may be due to a difference in exposure levels and potential non-monotonic dose-response curves.

DETECTION OF CHILD ABUSE AT THE EMERGENCY DEPARTMENT USING A NEW PROTOCOL BASED ON PARENTAL CHARACTERISTICS

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Background and aims: Identification of child abuse and neglect based on child characteristics leaves many children undetected. We developed a new approach (Hague protocol) based on characteristics of parents who attend the Emergency Department (ED) because of: 1) intimate partner violence, 2) substance abuse, or 3) suicide attempt or other serious psychiatric problems. Aim of this protocol is to rapidly assess family problems and offer voluntary community based support by the Reporting Center for Child abuse and neglect (RCCAN).
Methods: A prospective, before and after study, conducted at 9 EDs in 3 regions in the Netherlands (one intervention region and 2 control regions)
Result: During the period January 2006 to November 2007, prior to the introduction of the Hague protocol, a total of 4 parents out of 385,626 patients attending the ED in the intervention region (1 per 100,000) were referred to the RCCAN. In the period after the protocol was introduced (December 2007 to December 2011), the number rose to 565 out of 885,301 patients at the ED (64 per 100,000). In the control region where the protocol was not implemented these figures were 2 per 163,628 (1 per 100,000) and 10 per 371,616 (3 per 100,000) respectively (OR = 28.0 (95 CI 4.6 - 170.7)). Child abuse was confirmed in 91% of referred cases.
Conclusions: The protocol has a high positive predictive value and can substantially increase the detection rate of child abuse in an ED setting. Parental characteristics are strong predictors of child abuse.

HEALTH EFFECTS OF ALCOHOL CONSUMPTION AND THEIR SOCIAL IMPLICATIONS AS PERCEIVED BY CROSS-SECTONAL SCHOOL STUDENTS IN UNITED ARAB EMIRATES.

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Objectives: Alcohol consumption is an important epidemiological problem among the adolescents affecting their health and social life. Perceptions regarding the social implications and level of health risks with alcohol consumption were assessed among school students in Ajman, UAE.
Materials and Methods: A sample of 411 school students was surveyed on their perceptions of social implications and health related risks with alcohol consumption. A pre-tested, close-ended, self-administered questionnaire was filled in after consenting. The data was analyzed using SPSS version 19; Chi-square test was applied to determine association between variables.
Result: Male students constituted 55.7% of the total and the age ranged between 15-17 years. 'Alcohol consumption is harmful', was indicated by 91.2%. Moderate-severe level of health with alcohol consumption was attributed by 91.7%. Majority of the female students reported moderate-severe health risk with alcohol consumption than the males (96.3% and 87.7%; $p< 0.01$). 81.3%believed alcohol consumption is associated with social problems. The common perceived social implications were frequent quarrel or arguments, accidents, problems with police, parents, friends, and poor academic performance. Female students highly perceived 'decline in academic performance, problems with parents and friends, and accidents as major social implications with alcohol consumption ($p< 0.05$).There was no association between student's age, parents' qualification with level of alcohol related-health risks attributed.
Conclusions: Majority of the students was aware of the negative impact of alcohol use on health and social life. Media and schools can play integral role in imparting awareness regarding the social implications and health effects of alcohol consumption.

NEIGHBORHOOD, FAMILY AND RISK OF CHILDHOOD AND ADOLESCENT EPILEPSY: A NATIONWIDE EPIDEMIOLOGICAL STUDY FROM SWEDEN

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Objective: To examine whether neighbourhood deprivation increases the risk of hospitalisation for childhood and adolescent epilepsy, after accounting for family- and individual-level sociodemographic characteristics.
Design: An open cohort of all children aged 2 to 17 years was followed between January 1, 2000 and December 31, 2010. Children residential addresses were geocoded and classified according to neighbourhood deprivation. Data were analyzed by multilevel logistic regression, with family and individual-level characteristics at the first level and level of neighborhood deprivation at the second level.
Result: During the study period, among a total of 1,020,766 children, 9354 (0.9%) were hospitalized with childhood and adolescent epilepsy. Age-adjusted hospitalized rates for childhood and adolescent epilepsy increased with increasing level of neighbourhood deprivation. In the study population, 8.7 per 1000 and 10.0 per 1000 children in the least and most deprived neighbourhoods, respectively, were hospitalised with childhood and adolescent epilepsy. Incidence of hospitalisation for childhood and adolescent epilepsy increased with increasing neighbourhood-level deprivation across all family and individual-level sociodemographic categories. The odds ratio (OR) for hospitalisation for childhood and adolescent epilepsy for those living in high-deprivation neighbourhoods versus those living in low-deprivation neighbourhoods was 1.15 (95% confidence interval=1.07-1.23). High neighbourhood deprivation remained significantly associated with odds of childhood and adolescent epilepsy after adjustment for family- and individual-level sociodemographic characteristics (OR=1.13, 95% confidence interval=1.05-1.22, p=0.001).
Conclusions: This study is the largest so far on neighbourhood influences on childhood and adolescent epilepsy. Our results suggest that neighbourhood characteristics affect the risk of hospitalization for childhood and adolescent epilepsy independently of family- and individual-level sociodemographic characteristics.

FEATURES OF CLINICAL AND METABOLIC STATUS OF CHILDREN WITH DIABETIC KETOACIDOSIS IN BELARUS IN 2005-2013

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Objective: to identify features of the clinical and metabolic status of children with diabetic ketoacidosis (DKA), depending on the severity and age of the patients.
Methods: retrospective study of 77 children with the DKA was conducted in the University Clinic (Minsk) in 2005-2013 yrs. Patients were divided into 3 groups according to the age: group1 (G1) - 0-6 years, group2 (G2) - 6-11 years, group3 (G3) - 11-18 years. Anamnesis, clinical features, laboratory analysis, the levels of HbA1c were analyzed. Results were processed using Statistic 10.
Result: in 71.4% of cases DKA developed in the manifestation of diabetes mellitus type 1 (DM1), 28.6% - with decompensation of previously established DM1. 17 patients had cognitive disorders of various severity: stunning, stupor, coma grade 1-2. All children had metabolic acidosis of various severity. Indicators of blood acid-basic state with children with DKA: G1 - pH 7,16±0,06; base excess (BE) - 19,93±2,98 mmol/l; bicarbonate (cHCO3) 8,46±1,86 mmol/l; pCO2 19,96±3,15 mm Hg; G2 - pH 7,17±0,06; BE -20,58±3,29; cHCO3 7,90±2,00; pCO2 20,10±2,47; G3 - pH 7,13±0,08; BE -19,57±3,08; cHCO3 8,71±1,97; pCO2 22,54±2,39. Significantly more severe disorders of the blood acid-basic state were noted with patients with consciousness disorders: pH 6,92±0,07 (min 6,66; max 7,10), BE -27,58±0,96 (min -31,30; max -25,60), cHCO3 4,64±1,03 (min 2,00; max 7,20) compared with patients without impairment of consciousness - pH 7,21±0,03, BE -17,90±1,67, cHCO3 9,40±1,15 ($p<0,05$). In 81.3% of cases (61 patients) were observed quantitative and / or qualitative changes of the white blood cells: reactive neutrophilic leukocytosis (with a shift of the leukocyte formula to the left - in 45.3% of cases), toxic granularity of neutrophils with followed by a rapid normalization. All children had severe glucosuria and ketonuria. Reasons of DKA: long progressive development of DM1 until it manifests: clinical (polydipsia, polyuria, weight loss during 0,5-2 months) and laboratory (the levels of HbA1c in hospitalization >6,1%); acute respiratory infections - 48%; stress - 4 children; treatment failure with children with previously established DM1 - 81,8%.
Conclusions: All children had typical for DKA violations of the clinical and metabolic status: signs of dehydration, weight loss, hyperglycemia, decompensation metabolic acidosis. No significant differences were found in the blood acid-basic state according to the age. There was a significant correlation between the severity of violations of the blood acid-basic state and the severity of the neurological status. Most of the children had reactive changes of the white blood cells.

AUDIT OF POSTNATAL ANTIBIOTIC USE IN NEONATES

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Introduction/Background: The August 2012 publication of NICE Guidelines on Antibiotics for Early-Onset Neonatal Infection prompts more aggressive treatment of babies with maternal risk factors for infection, clinical signs and red flag indicators. The new guideline suggests giving antibiotics to more babies (accepting prematurity and rupture of membranes > 18 hours as risk factors), more blood testing (with repeat CRP at 36 hours of treatment) and further investigating of 'abnormal' results, advising lumbar puncture with CRP = 10. With the exceptionally large numbers of babies being born in this amalgamated unit and changing national guidelines, we wanted to assess the numbers of babies currently receiving postnatal antibiotics in this district general hospital, and the potential impact of the lower treatment thresholds on paediatric workload.
Patients and Methods: We carried out a prospective audit in November 2012 of the babies requiring postnatal antibiotics over the four-week period. We charted risk factors, blood results, outcomes and the number of days of treatment, in order to assess the reasons for antibiotic administration and the workload this presents to paediatric staff.
Results: Twenty-four babies of the total 323 livebirths received antibiotics during November 2012. Twenty babies received Benzylpenicillin and Gentamicin, and four Benzylpenicillin and Flucloxacillin where indicated. Seven received a five-day antibiotic course (five for pneumonia / meconium aspiration and two for multiple risk factors and raised CRP) and 17 had just two days' antibiotics while cultures were awaited, all negative. This resulted in 69 "antibiotic days", with an average of 2.3 per day. Maternal indications for antibiotics included temperatures (nine), GBS where intrapartem prophylaxis was not given (four), chorioamnionitis (two), premature rupture of membranes (two) and previously affected baby (one). Many babies were treated because of more than one risk factor or clinical concern; with overlap, infant indications included suspected sepsis (six), raised inflammatory markers (nine), tachypnoea (seven), temperatures (three) and umbilical flare (three). Maximum CRP was 66, in a baby with an infected haemangioma. All blood-letting, line insertion and antibiotic administration (including drug double-checking) was carried out by the junior medical staff, over and above routine clinical work and frequently out-of-hours.
Conclusions: With an average of 2.3 neonates requiring antibiotics daily, postnatal antibiotics currently provide a significant workload. Updated national guidelines advise even lower treatment thresholds and local guidelines are being revised in tandem. On the basis of incident reporting and staff feedback, an outreach nurse from NICU has now been employed in this district general hospital to assist medical staff with lines and antibiotics. However, rising numbers of babies requiring investigations and antibiotics will demand an even greater paediatric presence in postnatal wards, and further changes to the provision for delivery of this service.

IMPACT ASSESSMENT OF IMPLEMENTING THE NEW NICE GUIDELINES - "ANTIBIOTICS FOR EARLY ONSET NEONATAL INFECTION (2012)" IN A LOCAL LEVEL 2 NEONATAL UNIT

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Background: NICE published its 'Antibiotics for early onset neonatal infection' in August 2012. The aim was to reduce variability in practice in relation to sepsis screening and antibiotic administration in neonates. It advocated a risk factor and clinical symptom based approach. The new guidelines aimed to the reduce length of stay through discharging babies if blood cultures are negative at 36 hours, rather than the standard 48 hours used by most hospitals. Furthermore, it advocated performing lumbar punctures if any C-reactive Protein was greater than 10mg/dL. This audit aimed to assess the impact on service delivery on implementing these guidelines in a local neonatal (level 2) unit.
Methods: Forty-Five term Babies were randomly selected from a cohort of babies who had sepsis screens performed on Day 1 of life between 1st October 2011 to 31st March 2012 as per local guideline. Data was collected on maternal risk factors, clinical indicators for sepsis, lumbar punctures and length of stay. The new NICE Guidelines were applied to these patients retrospectively based on their clinical presentation to determine if implementation would alter the decision to perform sepsis screen, lumbar puncture and duration of antibiotic treatment and consequent impact of length of stay.
Result: Out of the 45 babies selected, required data was available in 43/45. Bacteriological screening was performed appropriately according to local guidelines in 40/43 infants. Applying the new NICE Guidelines in these babies would have resulted in a similar number of patients having septic screens (39/43). Implementing the new guidelines did not significantly change length of stay (4.0 vs 4.2 days), however it would result in a higher proportion of babies requiring lumbar punctures (16 vs 27).
Conclusions: Implementing the new NICE guidelines would increase the frequency of Lumbar punctures being performed, without the reducing length of stay.

CONGENITAL SYPHILIS SITUATIONAL ANALYSIS OF A MUNICIPALITY IN THE STATE OF RIO DE JANEIRO - BRAZIL

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Introduction: Despite the commitment shown by the Ministry of Health (MS), the rates reduction of vertical transmission of syphilis has represented a major challenge for public health in Brazil. According to the Millennium Development Goals, the MS is targeting the elimination of congenital syphilis by 2015 (<0.5 / 1000 live births). Being syphilis a millenary disease, which presents simple methods of diagnosis and effective treatment, it becomes imperative to know the reasons why this disease still remains today.
General Objective: To analyze the cases of congenital syphilis reported in the County Health Service (SMS) of Petrópolis - Rio de Janeiro, Brazil, in 2012, identifying vulnerable points of obstetric and neonatal care.
Methodology: A descriptive, retrospective study of cases of congenital syphilis occurred in 2012 through a revision of the epidemiological notification forms from SMS Petrópolis.
Result: During the year 2012 there were 3795 births. In this period 24 cases of congenital syphilis were reported: 6 cases/1000 incidence of live births. Of these, 4 were excluded due to missing data. Two hospitals were responsible for the notifications which occurred on average in the first five days of life, demonstrating a state of surveillance in relation to the problem. The mean maternal age was 26.15 years, six adolescents (30%). As for maternal education, we found only a pregnant woman with high school degree. We identified 16 (80%) mothers who received prenatal care. The diagnosis occurred during the prenatal in 60% of cases and at delivery in 25%. The treatment was considered inappropriate by the criteria of MS in 85% of pregnant women who received prenatal care. Only two partners (10%) pregnant women were treated concomitantly. The diagnosis of the newborn occurred within the first three days of life, with an average of 1.5 days. Of the 20 infants studied, 20% were stillborn, 10% had clinical manifestations at birth and 70% were asymptomatic. Regarding the tests used for screening: 37.5% were CSF investigated and bone 68.75%, both unaltered. As therapy instituted, 68.75% used the recommended regimen by MS, RN others used other schemes.
Discussion: Although it is a reportable disease, information on incidence and quality of data is still unreliable. Access to health services does not seem to be limiting, since the vast majority of pregnant women performed prenatal care, but we observed that the vast majority of treatments were considered inadequate, which shows a lack of care quality. This study found pregnant women who exclusively used the public health service, had poor education and low participation in the working market, 25% of these being adolescents. The approach to the neonate demonstrates little adherence to the protocol established by MS, represented here by the small number of investigated for neurosyphilis and bone alterations, besides the use of therapeutic regimen against the recommendations.
Conclusion: Infection control remains a major challenge for everyone involved in caring for the woman, the pregnant and the child, requiring awareness of the actors involved so that we can meet the goals.

HEART RATE VARIABILITY WITHIN 12 HOURS OF BIRTH IN TERM NEONATES WITH PERINATAL ASPHYXIA

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Background: Hypoxic-ischaemic encephalopathy (HIE) following perinatal asphyxia remains a significant cause of long-term neurological injury. A reliable physiological marker that could ensure early diagnosis and grade the severity of encephalopathy would significantly aid targeted neuroprotection. Heart rate variability is a non-invasive index of the neural control of the heart and can provide information on the functional state of the autonomic nervous system. HIE is associated with altered autonomic nervous system function and HRV measurement may help identify the presence of encephalopathy and severity of injury. The aim of this study was to compare measures of HRV in healthy term neonates and neonates with asphyxia as defined by both clinical assessment and continuous multi-channel video-electroencephalography (EEG), within 12 hours of birth.
Patients and Methods: As part of an on-going EEG study, full-term neonates with perinatal asphyxia (arterial cord pH <7.1, 5 minute Apgar score =6, or requiring intubation at delivery), and healthy controls were recruited. Only those with good quality EEG and ECG data recorded within 12 hours of birth were included. ECG data was extracted and a 1-hour epoch at 12 hours after birth was analysed. Time and frequency domain features of HRV were calculated and included manual correction of R-peaks. The normalised RR interval (NN interval) was estimated and used to calculate - mean NN interval; standard deviation of the NN interval (SDNN), approximate entropy (apEN), Poincare analysis (SD1, SD2), and relative power in high frequency (HF), low frequency (LF) and very low frequency bands (VLF). All EEGs in each of the 3 groups were visually interpreted and graded as normal or abnormal. Kruskal-Wallis statistical analysis was used to identify any significant differences between the three groups followed by Mann Whitney-U post-hoc analysis.
Results: In total the recordings of 60 neonates were assessed (19 healthy, 11 asphyxia only, 30 encephalopathic (14 mild, 7 moderate, 9 severe)). All EEGs in the healthy and asphyxia only groups were normal. EEGs in the encephalopathic group were all abnormal showing varying degrees of abnormality consistent with the clinical grade of encephalopathy. HRV analysis revealed significantly reduced measures in encephalopathic neonates compared to controls; Mean NN interval (526.3 vs 474.0ms; p=0.003), SDNN (41.0 vs 27.2ms; p=0.001), SD1 (9.55 ms vs 5.81ms; p=0.001), and SD2 (224.04 secs vs 150.53 secs; p=0.001). No significant differences were seen in ApEN, HF, LF and VLF measures between groups. There was also a trend for lower HRV measures in the asphyxia only group but this did not reach statistical significance.
Conclusion: HRV shows significant changes in term neonates with HIE within 12 hours of birth when compared to healthy controls. As HR is measured in all neonates in the NICU, quantification of HRV measures may provide useful physiological markers of encephalopathy following perinatal asphyxia.

THERAPEUTIC HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY: A UK SURVEY OF PRACTICE DURING NEONATAL TRANSPORT AND ITS IMPLICATIONS FOR EUROPE

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Background: Therapeutic hypothermia is endorsed as a standard of care by the British Association of perinatal medicine. Therapeutic hypothermia significantly reduced the risk of death or disability at 18 months, (P=0.002) with a number needed to treat of nine. Between 50-73% of neonates are born outside centres with the expertise for providing cooling in the United Kingdom. National recommendations include availability of 24 hour services to transport these babies using a nationally endorsed passive cooling guideline. Are passive-cooling methods effective or should teams be delivering servo-controlled cooling in transit. Services' offering servo-controlled cooling feel it is more efficacious with lower risk of over-cooling especially where geographical regions for transport are large. Methods- A cross-sectional survey of all UK neonatal transport services (n=21) was conducted in December 2011 and repeated in December 2012. Data were collected using a pre-designed proforma and follow-up telephone calls. Response was 100%.
Results: All UK transport services undertake transfers of infants requiring therapeutic hypothermia. Passive cooling methods were used by 15/21 (70%) while 6/21 (30%) used servo-controlled equipment in 2011. All but one of the active cooling services had dedicated ambulances. All services use rectal temperature monitoring in transport and audit their temperature control. Outreach education regarding therapeutic hypothermia to enable early referral is undertaken by 17/21 of services (81 %). The efficacy of passive cooling published by various transport services varies from 20%-67%. The efficacy of active cooling published by the Western team in Bristol is 90%1. 50% of transport teams using passive cooling were exploring whether to use servo-control in December 2011. In December 2012 9/21 of transport services were using servo-control cooling in transport all of whom had dedicated ambulances bar one.
Discussion: Where therapeutic hypothermia is indicated, the key goal is achieving and maintaining target neuroprotective temperature. Servo-controlled cooling during neonatal transport has better efficacy but is linked to the availability of dedicated ambulances and has significant cost and safety implications. It involves modification of existing transport trolley or the ambulance system. This survey could not address the safety of such interventions and only one such system appears to confer to European standards. Irrespective of the method used to cool neonates rectal temperature monitoring for accuracy is universal. The importance of auditing the effectiveness of temperature control and outreach education to encourage early referral is widely practised.
Conclusion: Servo-controlled cooling in neonatal transport is replacing passive cooling in neonatal transport teams around the United Kingdom for enhanced efficacy of neuroprotection. A key limiting step appears to be the availability of dedicated neonatal transport ambulances allowing modification for the purpose. There are no direct comparisons of contemporaneous developmental or thermal outcomes for infants transferred with either TOBY-passive cooling guidance techniques versus transfers with cooling machines. Such work would inform neonatal transport leaders when evolving strategies for cooling infants. The use of servo-controlled cooling needs to be balanced carefully against the cost implications to each service as well as the safety implications to staff and baby during transport.

THE ASSESSMENT AND MANAGEMENT OF HAEMODYNAMIC STATUS IN INFANTS RECEIVING THERAPEUTIC HYPOTHERMIA - AN ADHOC APPROACH.

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Background: Appropriate haemodynamic assessment and management of infants undergoing therapeutic hypothermia following hypoxic insult, is as important as optimising ventilation. These infants are known to be at risk of developing multi-organ failure, including significant renal and cardiac dysfunction.
Objectives: Our aim was to review the current practice for assessment and management of haemodynamic status in term or near term infants, cooled for hypoxic encephalopathy.
Design/Methods: A single centre retrospective audit, completed at University Hospital of North Tees, UK. Data was collected from case notes and discharge summaries for all therapeutically cooled infants, managed and registered according to the TOBY protocol, from 2009 to present. Data relating to blood pressure measurements, echocardiography, blood markers, including cardiac troponins, renal dysfunction, fluid management and the use of fluid boluses was collected. Details on the choice, dose, start times and duration of inotropes for managing haemodynamically 'compromised' infants were recorded, in addition to the demographic and TOBY registry data (completed for every baby cooled in the UK). The project was registered and approved by North Tees and Hartlepool NHS Foundation Trust audit department.
Result: 18 cases met the above criteria - 11 males and 7 females. 13 infants (72%) were identified having had a haemodynamic concern, all of whom received inotropic support. The primary cause for concern was low blood pressure in 54% of cases, as defined by variable parameters. All but one patient had echocardiographic assessment, with 77% of scans showing cardiac dysfunction. Renal dysfunction was prevalent but not exclusive to patients with haemodynamic concerns. Other assessment tools included Toponin 1, serum lactate and LDH, which were variably abnormal in all cases. There was no rationale identified for the use of fluid boluses, nor choice of inotrope.
Conclusions: 1. Multiple assessment 'tools' are available regarding haemodynamic function. 2. These were widely employed, but at inconsistent intervals. 3. Universally elevated Troponin I levels and cardiac dysfunction on echocardiography indicate underlying myocardial injury. 4. Haemodynamic management in this group is inconsistent and varies between clinicians 5. The effects of early intervention to augment haemodynamics before clinical signs or symptoms should be explored in well designed trials. 6. Locally, recommendations are underway to improve assessment and management consistency in this group.

CHANGES IN VISCERAL AND CEREBRAL ARTERIAL BLOOD FLOW VELOCITIES IN NEONATES WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY (HIE) DURING WHOLE BODY HYPOTHERMIA AND AFTER REWARMING

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Background: Hypoxic ischemic encephalopathy (HIE) may be associated with multiple organ failure. Severe alteration of cerebral and visceral blood flow velocities take place following asphyxia. These infants are also at risk for necrotizing enterocolitis (NEC). Mild hypothermia, improves the neurological outcome following HIE and is now standard practice. To date, there is no published data on visceral hemodynamic changes associated with cooling and NICUs have introduced different feeding guidelines.
Objective: To assess changes in blood flow velocities in middle cerebral (MCA), renal (RA), superior mesenteric (SMA) and celiac arteries (CA) as well as cardiac output, among newborns with hypoxic ischemic encephalopathy during whole body therapeutic hypothermia and after rewarming.
Design/Methods: A single center prospective observational pilot study involving twelve cooled newborn infants with HIE. Hemodynamic measurements were made during the study period at 4 time points, [Hypothermia I] within 24 hours after commencement of cooling; [Hypothermia II] between 48-72 hours of hypothermia [Rewarming I] within 24 hours of rewarming at normothermia; [Rewarming II] after starting feeds. Fisher's exact test, Student's t-test and Mann-Whitney U test were used for analysis where appropriate.
Result: Twelve infants were studied at a mean gestational age and birth weight of 40 ± 1.0 weeks and 3435 ± 787g respectively. Therapeutic hypothermia was commenced at a median of 1.5 hours [range 0-4.5 hours]. All 12 patients survived and none developed NEC during their stay. The peak systolic velocities (Vs.) of CA (0.63cm/s to 0.72 cm/s, p=0.002) and SMA (0.45 cm/s to 0.57 cm/s, p=0.039) showed significant increases after rewarming with no significant alterations in the Resistant Indexes (RI). Four babies had absent or reverse end-diastolic flow (AREDF) of CA or SMA during the hypothermia period. They required longer time (beyond 11 days of life) to establish full enteral feedings (p=0.048). There was no significant association between prolonged time to establish full feeds (beyond day 11) and left ventricular output, SMA parameters (Vs, RI) and systolic blood pressure during hypothermia and rewarming periods. However, lower CA Vs between 48-72 hours (p=0.024) and lower diastolic blood pressure at 48-72 hours of life (p=0.048) were found in these infants. 6 out of 12 patients required inotropic support (5 with dopamine or dobutamine; 2 requiring both). They needed longer periods of time to establish full enteral feeding, 11 days of life or beyond; p=0.008, compared to those without using inotropes. The Vs did not differ between the hypothermic and post rewarming periods in RA (p=0.59) and MCA (p=0.1).
Conclusions: Significant changes in visceral hemodynamic parameters before and after rewarming accompany therapeutic hypothermia. Abnormal diastolic flow patterns and lower CA peak systolic velocities during hypothermia period may be associated with a prolonged period of time to establish enteral feeds. A larger sample size is needed to understand the change in flow patterns of major vessels and their clinical significance.

THE RELATION BETWEEN MYOCARDIAL FUNCTION AND CEREBRAL CIRCULATION IN ASPHYXIATED NEONATES DURING THERAPEUTIC HYPOTHERMIA

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Background: Hypothermia has become standard treatment of perinatal hypoxic ischemic encephalopathy (HIE). Myocardial function is depressed in asphyxiated infant and can be measured by tissue Doppler imaging (TDI). Doppler ultrasound can be used to evaluate blood flow velocities in the anterior cerebral artery (ACA). Aim: To assess the relationship between myocardial function measured by TDI and circulatory parameters of the ACA in asphyxiated newborns during and after hypothermia. Hypothesis: TDI parameters of myocardial function are related to changes in cerebral circulation during and after hypothermia treatment.
Methods: Forty-four newborns with HIE were investigated with cerebral and cardiac ultrasound within 12 hours of body temperature of 33.5°C (T1), on the third day of hypothermia (T2) and within 12 hours after rewarming (T3). We measured peak systolic, end-diastolic and mean velocities in ACA and myocardial function by means of TDI.
Result: Peak systolic ACA velocity increased at all examinations ($p<0.001$). There was a moderate correlation between systolic myocardial function and mean velocity in the ACA at T1 ($r=0.416$, $p<0.02$), but not at T2 or T3.
Conclusions: There was a moderate correlation between parameters of myocardial function and cerebral circulation during the early phase of hypothermia treatment. Further studies are needed to explore the role of myocardial function in HIE and hypothermia treatment.

LEFT VENTRICULAR LONGITUDINAL STRAIN AND STRAIN RATE MEASURED BY 2D SPECKLE TRACKING ECHOCARDIOGRAPHY IN NEONATES DURING WHOLE-BODY HYPOTHERMIA

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Background: Therapeutic hypothermia is beneficial to term newborns with hypoxic-ischemic encephalopathy. Hypothermia may also cause changes in cardiac contractility and cardiac output The purpose of the study was to assess changes in cardiac performance in newborn infants with hypoxic-ischemic encephalopathy during therapeutic hypothermia and rewarming with two-dimensional speckle tracking echocardiography.
Methods: For 8 asphyxiated neonates - median birth weight (range): 3038 (2725 to 3253) g; umbilical artery pH: 6.9 (6.8 to 7.18) - undergoing whole-body hypothermia (33 to 34 °C), left ventricular longitudinal strain and strain rate, as well as heart rate, cardiac output, and left ventricular fractional shortening were determined at four points in time: at the start (T1) and end of hypothermia (T2), immediately after rewarming (T3) and at the age of 5 to 7 days (T4).
Result: Mean (SD) of heart rate increased from 93 (12) at T1 to 133 (12) beats per minute at T4 ($p<0.001$). Cardiac output was low during hypothermia (T1: 207 (43) ml/kg/min, T2: 240 (70) ml/kg/min) and increased significantly ($p<0.001$) afterwards (T3: 329 (70) ml/kg/min, and T4: 388 (78) ml/kg/min). Left ventricular fractional shortening remained unchanged. Left ventricular global longitudinal peak systolic strain did not differ significantly between hypothermia and rewarming while the systolic strain rate increased from -1.1 (0.3) s-1 at T1 to -1.8 (0.26) s-1 at T4 ($p=0.001$).
Conclusions: Hypothermia affects peak systolic strain rate, heart rate and cardiac output, with complete recovery after rewarming, whereas peak systolic strain and fractional shortening remain stable.

LASER SPECKLE IMAGING OF REPERFUSION IN CEREBRAL ISCHEMIA DURING THE DEVELOPMENT

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Background: Few studies have characterized cerebral blood flow (CBF) after neonatal or pediatric ischemia and/or hypoxia, and there is variability in reperfusion patterns reported according to the species, the developmental stage and ischemia duration. The aim of this study was to evaluate blood-flow changes in large arteries and microvessels during the first 20 min of reperfusion after ischemia in rats during brain development. Cerebrovascular reactivity and hemodynamic responses against ischemia will determine at what age the switch between immature and mature vascular responses occur in the brain.
Methods: Ischemia-reperfusion was induced in 7-day- (P7), 15-day- (P15) and 21-day- (P21) old rat pups by electrocoagulation of the left middle cerebral artery (MCAo) associated with transient (50 min) left and right common carotid arteries (CCAo) (Bonnin et al., 2011). Relative cerebral blood flow (CBF) changes and images were obtained by laser speckle Doppler monitoring using the moorFLPIâ„¢ (Moor Instruments Ltd, Axminster, UK). Blood-flow changes (mBFVs) were monitored by ultrasound imaging with sequential Doppler recordings in internal carotid arteries and the basilar trunk. Cerebrovascular reactivity was measured in the presence of the 5% hypercapnic gas mixture.
Result: Between P7 and P13, a gradual increase in mean blood-flow velocities (mBFV) illustrated a gradual perfusion during early re-flow in both internal carotid arteries. In contrast, and as early as P14 reperfusion returns to basal values immediately after occlusion release. Speckle images demonstrated a gradual reperfusion in the contralateral hemisphere between P7 and P13, whereas as early as P14-P15 (and at P21) reperfusion immediately returns to basal values. This spontaneous re-flow was associated with a more or less hyperemic episode (middle and posterior territories). In the ipsilateral hemisphere, re-flow returns immediately to basal values in the posterior territory and return to the level obtained after MCAo in the territory of middle cerebral artery. Mean BFVs measured in the internal carotids at P7, P14 and P21, and under 5% CO2 demonstrated vascular reactivity at P14 and 21, but not at P7.
Conclusions: Collectively, these data indicate that 1) vascular tone is different between immature (P7) and mature (from P14) rat brain vessels; 2) early re-flow is gradual after occlusion release in immature (P7 until P13), whereas it is spontaneous with more or less hyperemia as early as P14. Laser Speckle Doppler monitoring represents a powerful design to monitor CBF, and provides useful information. On the basis of these data, the switch between immature and mature vascular responses occurs at P14.
References: Bonnin P et al. Impact of intracranial blood-flow redistribution on stroke size during ischemia-reperfusion in 7-day-old rats. J Neurosci Methods 2011; 198: 103-109.

DYNAMIC SPATIO-TEMPORAL IMAGING OF EARLY RE-FLOW IN A NEONATAL RAT STROKE MODEL

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Background: Few studies have characterized cerebral blood flow (CBF) after neonatal or pediatric ischemia and/or hypoxia, and there is variability in reperfusion patterns reported according to the species, the developmental stage and ischemia duration. The aim of the study was to better understand blood-flow changes in large arteries and microvessels during the first 15 min of re-flow in a P7 rat model of arterial occlusion.
Methods: Ischemia-reperfusion was induced in P7 rat pups by electrocoagulation of the left middle cerebral artery (MCAo) associated with transient (50 min) left and right common carotid arteries (CCAo) (Bonnin et al., 2011). Blood-flow changes were monitored by using ultrasound imaging with sequential Doppler recordings in internal carotid arteries and basilar trunk. Relative cerebral blood flow (CBF) changes were obtained by using laser speckle Doppler monitoring. Tissue perfusion was measured with [14C]-iodoantipyrine autoradiography. Cerebral energy metabolism was evaluated by mitochondrial oxygen consumption.
Result: Gradual increase in mean blood-flow velocities (mBFV) illustrated a gradual perfusion during early re-flow in both internal carotid arteries. Upon ischemia, the MCA territory presented a residual perfusion, whereas the caudal territory remained normally perfused. Upon re-flow, speckle images demonstrated a caudo-rostral propagation of reperfusion through anastomotic connections, and a reduced perfusion in the MCA territory. Autoradiography highlighted the caudorostral gradient, and persistent perfusion in ventral and medial regions. These blood-flow changes were accompanied by mitochondrial respiration impairment in the ipsilateral cortex.
Conclusions: Collectively, these data indicate the presence of a primary collateral pathway through the circle of Willis, providing an immediate diversion of blood flow towards ischemic regions, and secondary efficient cortical anastomoses in the immature rat brain. Furthermore, the use of 3 separate techniques to evaluate blood flow in the brain during and after reperfusion in a neonatal stroke model provides useful information as each of them complements the others.
References: Bonnin P et al. Impact of intracranial blood-flow redistribution on stroke size during ischemia-reperfusion in 7-day-old rats. J Neurosci
Methods:2011; 198: 103-109.

N-ACETYLCYSTEINE-AMIDE REDUCES CEREBRAL IL-1B-LEVELS AND INFLUENCES THE RISE OF BLOOD PRESSURE AFTER PERINATAL ASPHYXIA IN NEWBORN PIGLETS

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Introduction: The WHO estimated in 2010 that approximately 800 000 children died because of the complications of perinatal asphyxia. In many cases of perinatal asphyxia the children survive, but with severe mental or physical handicap. The endogenous antioxidant capacity is challenged after perinatal asphyxia. After asphyxia it comes to reoxygenation and reperfusion and the organism suffers from even more oxidative stress, which may result in a more severe neuronal damage. NACA, a novel anti-oxidant, has indicated some promising results regarding organprotection after hypoxia. Patients and
Methods: Study design: Fifty-four newborn piglets, age 12-36 h, were included. Invasive blood pressure, EEG and ECG were measured continuously. Randomised parallel-group design; one control group (n=6) and 4 experimental groups (n=12), exposed to global hypoxia, until BE was either -15 or -20 mmol/l (moderate/severe asphyxia with or without NACA) The pigs were observed for 9.5 hours. Tissues from brain, eyes, thymus, heart, lungs, liver, spleen, kidneys and ileum were removed and stored until further analysis. During the experiment we sampled blood regularly. We took bloodgases and blood samples for oxidative stress. Statistics: When comparing a continuous variable in two groups, an independent samples t-test was used, with 5% significance level. The statistical analysis was performed by using SPSS version 18.
Result: In piglets exposed to moderate asphyxia and treatment with NACA the mean rise in MABP was significantly lower, 26±10(± SD) mmHg from end hypoxia to 37±7 mmHg after to 30 minutes of reoxygenation (deltaMABP= 11±9),than for the group not exposed to NACA; MABP 34±22 at end hypoxia to 54±25 after 30min of reoxygenation (deltaMABP= 20± 10),p< 0.01). There was also a significant difference between piglets exposed to severe asphyxia and treatment with NACA; MABP 33±17 from end hypoxia to 38±10 after 30 minutes of reoxygenation (deltaMABP=5±12), compared with the group which did not receive NACA, MABP 31±22 mmHg at end hypoxia and 48±25 mmHg after 30min of reoxygenation (deltaMABP= 17±8),(p< 0.01). Between the groups which were treated with or without NACA vs. saline there were no significant differences in heart rate, pCO2, pO2, BE, temperature, pH or Lactate. The activity of cleaved Caspase 3, a protease involved in apoptosis, was measured in the liver. We found no significant differences between the groups.
Conclusions: The pigs in the NACA-groups had a slower rise of blood pressure after hypoxia. Whether this reflects an effect of NACA or underlying compensatory mechanisms is unknown. Further studies of histopathology and injury markers will address possible neuroprotective effects of NACA treatment following birth asphyxia.

TIME-FREQUENCY METHOD FOR NON-INVASIVE ASSESSMENT OF THE CEREBRAL AUTOREGULATION (AR) IN INFANTS

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Background: Frequency-domain methods have been applied to study cerebral AR in neonates using non-invasive surrogates of cerebral perfusion such as near-infrared- derived parameters. The frequency domain analysis uses the very low and ultralow frequencies to explore coherence (COH) between signals. A high COH indicates impaired AR, the range being 0-1. The mean blood pressure (MBP) and near-infrared (NIRS) are not periodical signals therefore spectral density is rather uniform in a given window which has an important impact in the signal-to-noise ratio. In addition, this analysis ignores the trend (positive or negative) and phase of signal. Time domain analysis would overcome these limitations. However, the method relies on true-synchronized data acquisition system. Objective: an alternative cerebral AR analysis is proposed to improve mutual information quantification that measures the mutual dependence of the signals.
Methods: Granger causality method uses linear regression modelling (time domain) to calculate autoregressive polynomials of stationary signals. A signal (X2) 'causes' X1 if knowing the past observations of X2 helps to reduce the prediction error of X1 (1). A spectral (frequency domain) interpretation of Granger causality (spectral G-causality) can be derived by examining the Fourier components of a multivariate autoregressive modelling (MVAR). The spectral G-causality results gives two coefficients. Each of these coefficients indicate the dependence of X2 respect to X1 and X1 respect to X2 in frequency domain. In our case, the spectral G-coeffNIRS?MBP and spectral G-coeffMBP?NIRS.. This allows causal interactions to be analysed by frequency. Impaired AR can be derived from the interaction between both coefficients.
Result: Cerebral AR was analyzed in 30-min windows. Synchronized and time-locked MBP and NIRS-derived cerebral tissue oxygenation index (TOI) traces were obtained in infants below 31 weeks' gestation using a home-made system. The spectral Granger's coefficients(spectral G-coeffTOI?MBP and spectral G-coeffMBP?TOI) and classical COH were applied to evaluate AR in correlated and non-correlated trace changes. Both methods brought similar area under the curve for A and B. The spectral G-causality identified dependency at different frequencies.
Conclusions: Spectral G-causality methods offer additional information on signal dependency that cannot be obtained from classical COH analysis which may improve the accuracy of the method. (1) Granger C. Investigating causal relation by econometric models and cross-spectral methods. Econometrica 1969;37:424-38.

NON-INVASIVE ELECTRICAL CARDIOMETRY IN THE NEWBORN

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Background: Non-invasive assessment of cardiac performance and circulatory status is always a challenging important aspect in the neonatal care. Objectives: The aim was to assess the feasibility and usefulness of electrical cardiometry (EC) by AESCULON mini® in the newborn infants.
Subjects and Methods: Subjects were 15 term and preterm infants admitted to the neonatal care unit of Tokai University Hospital in the four month period between December 2012 and March 2013. Infants with evident congenital systemic and/or cardiac anomalies were excluded. The subject infants were 25-40 (median 36) weeks in gestational age (GA), 774-3042 (median 2500) grams in birth weight (BW), and 0-7 (median 2) days after birth. All measurements were performed with infants in a closed or open incubator in quiet sleep with neonatal electrodes/sensors attached on the skin. Data were sampled and recorded every minute for 15-30 minutes. Analyzed parameters were heart rate (HR), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR), index of contractility (ICON), and thoracic fluid content (TFC). Correlation between values of CO obtained from echocardiography and electrical cardiometry was also studied in 7 infants.
Result: Satisfactory signal detection was achieved in all infants with neonatal sensors by saline-wetting on the skin side. The measured values were: HR 84-155 (median 121)/min,SV 1.11-1.77 (median 1.43)mL/kg,CO 95-273 (median 167)mL/min/kg,SVR 9.2-32.7 (median19.8)x103 dyn·sec/cm5*kg,ICON 43-118 (median 60.6),TFC 24.1-42.3 (median 30). Significant negative correlation was found between GA and HR, and GA and CO; and positive correlation between GA and SVR. There was a good correlation between CO calculated from the echocardiographic Doppler velocimetry and CO obtained by electrical cardiometry ($y=0.81 x +23.36$, $r2=0.81$, $p<0.001$)
Conclusions: Electrical cardiometry with AESCULON mini® was feasible and useful for measuring CO and seemed to be potentially useful for the assessment of circulatory status and cardiac performance in the newborn infants.

BIOMARKERS OF OXIDATIVE STRESS IN THE EARLY POSTNATAL PERIOD: REFERENCE VALUES IN BLOOD AND URINE OF HEALTHY TERM NEWBORNS.

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Background: Oxidative stress is an unbalance between pro-oxidant and antioxidant factors that leads to increased levels of reactive oxygen and nitrogen species, which can cause cellular and tissue damage. Newborns are especially sensitive to oxidative stress, and numerous factors around the moment of birth can interfere in this delicate balance. In the last years this issue has attracted a growing interest, leading to the study of the role of oxidative stress in different neonatal conditions, especially in the preterm, but also in the term newborn (for example, hypoxic-ischemic encephalopathy), and the posibilities of antioxidant therapies. However, to our knowledge, only a few studies have set out to determine the normal, baseline levels of markers of oxidative stress in healthy term newborns. Objective: To determine the baseline levels of markers of oxidative stress and antioxidant defense in the healthy term newborn at birth and within the first 48 hours, in blood and urine. To test if urine is a useful sample for the study of oxidative stress in the newborn.
Patients and Methods: All newborns above 35 gestational weeks born in our institution from October 2012 - March 2013 were elegible for study. Newborns born to mothers with gestational diabetes or arterial hypertension, a prenatal diagnosis of malformation or intrauterine growth restriction, sentinel events during labour, a need for emergency cesarean or deep reanimation, Apgar score below 8 at the 5th minute, cord arterial or venous pH below 7.10, and all those who needed admission to the NICU were retrospectively excluded for the analysis. 236 newborns (106 females and 130 males) met the inclusion criteria. Blood samples at birth (cord arterial and venous blood) and at 48h postnatal life (heel puncture) were collected. Urine from the first and second day was collected. The levels of total antioxidant capacity, malonilaldehyde and carbonyl group in blood and urine, and those of glutathione and nitric oxide in plasma were analyzed (only blood glutathione ratio and total antioxidant capacity by the time this abstract was sent in). The gestational and perinatal evolution were recorded in detail until the time of hospital discharge.
Result: Expressed as mean and standard error of the mean: the mean values of glutathione ratio in venous cord blood 0.15 (standard error 0.06) did not differ from those in arterial cord blood 0.16 (standard error 0.07), or at 48h postnatal life 0.16 (standard error 0.07). Total antioxidant capacity levels were as follows: 1.03 mM (standard error 0.31) in venous cord blood; 1.22 mM (standard error 0.47) in arterial cord blood, and 1.38 mM (standard error 0.39) at 48h postnatal life.
Conclusions: These are data from a large group of newborns, aiming to give an accurate description of the baseline levels of the biomarkers in blood and urine in our population, which could be useful when it comes to making therapeutic decisions in the future.

THE TIMING OF BALLOON ATRIAL SEPTOSTOMY NEEDS TO BE CAREFULLY DECIDED IN NEONATES WITH COMPLETE TRANSPOSITION OF GREAT ARTERIES: A SINGLE CENTER EXPERIENCE.

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Introduction/Background: Balloon atrial septostomy (BAS)is a crucial procedure to survive in neonate with complete transposition of great arteries (TGA) when interatrial communication is not sufficient. As developing of fetal diagnosis and neonatal management, earlier procedure is increasing among TGA neonates. However the first day of life is highly unstable period for those with congenital heart disease so that we investigated on effects and complications according to timing of BAS.
Patients/Methods: From January 2000 to December 2010, 86 consecutive patients who was admitted to Asan medical center, Seoul, Korea for TGA with intact ventricular septum was enrolled in this study. We reviewed retrospectly of their medical records. These patients were divided into those with BAS and without having BAS (non-BAS) and patients of BAS group were divided into those having BAS within 24 hours (early-BAS) and after 24 hours (late-BAS) postnatally. Demographic data of each group, hemodynamic data before and after BAS, and any complication relating procedure were analyzed.
Results: There was trend of early BAS whereas rate (0-25%) of non-BAS group had been steady during past 10 years. BAS rate was 89.6% and mean time to corrective surgery after BAS was 6 days. After BAS, patients are improved in metabolic acidosis, low oxygen partial pressure, and systemic blood pressure. BAS group showed low initial oxygen saturation compared to non-BAS group (60.22±14.81 vs. 70.60±12.44%, p=0.038). 11 complications (14.5%) among BAS group were reported; 3 mortality preoperatively, 3 arrhythmias, 1 injury of valve structure, 2 asymptomatic ICH, and 2 seizures. Early-BAS group was not different in initial oxygen saturation (60.08±15.55%), oxygen partial pressure (26.66±9.96mmHg), systolic blood pressure (63.36±10.01mmHg) and complication rate (11.9%) statistically but they showed high rate of fetal diagnosis (74.6%) and low initial pH (7.21±0.11) compared to late-BAS group.
Conclusion: In neonates of TGA with intact ventricular septum, early-BAS group did not show the differences in hemodynamic parameters compared to late-BAS group except in initial acidosis. For reducing complications of BAS, the indication and the timing of procedure is carefully decided during the first day of life which can be vulnerable by transition to neonatal physiology.

CONGENITAL HEART DISEASE AND MICROCEPHALY AT BIRTH: A POPULATION BASED STUDY OF 2467 CHILDREN

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Background: It is recognized that neurodevelopmental disorders are frequent in children with congenital heart disease (CHD) and these disorders are largely attributed to prenatal factors. Reduced head circumference at birth, a marker of reduced fetal cerebral growth, has been demonstrated in children with CHD, and the relation to impaired neurodevelopment has been shown. However, existing studies, due to small sample sizes and highly selected populations, have largely failed to identify risk factors for impaired cerebral growth. Moreover, genetic syndromes were not sufficiently accounted for in these studies and the focus was on complex CHDs, and the impact of more common CHDs has yet to be evaluated. The objective of the present study was to investigate the correlates of microcephaly at birth in a population based study of children with all types of CHD.
Patients and Methods: 2947 Danish children born 2000-2008 were eligible for validation. A total of 2467 were eligible for genetic testing of the two most common genetic syndromes in CHD: trisomy 21 and 22q11 deletion syndrome. Further genetic, newborn, and maternal characteristics were identified in national registries. We present preliminary results of a matched cohort study. Each child was randomly matched to three children from the general population according to gender and gestational age. The risk of microcephaly (<-2 SD) in non-syndromic children with CHD (n=1535) and syndromic children with CHD (n=241) was compared to healthy children by means of conditional logistic regression. The results were adjusted for birth weight.
Result: Unadjusted measures of head circumference were smaller in both the non-syndromic (-0.2 cm 95%CI -0.3; -0.1) and the syndromic newborns with CHD (-1.3 cm 95%CI -1.3; -1.0) compared to the general population. The risk of microcephaly was higher in both the non-syndromic (OR=1.7 95%CI 1.3; 2.2) and the syndromic newborns with CHD (OR=4.1 95%CI 2.4; 7.2). When birth weight was adjusted for, the difference virtually disappeared in the non-syndromic newborns (OR=1.1 95%CI 0.7; 1.6), whereas the risk remained considerable in the syndromic newborns (OR= 2.4 95%CI 1.2; 5.0). Further results will be presented at the meeting.
Conclusions: Preliminary results from a subset of the CHD cohort support the hypothesis of reduced head circumference and increased risk of microcephaly in children with both syndromic and nonsyndromic CHD. It is further suggested that microcephaly in non-syndromic CHD may largely be explained by a general fetal growth restriction, whereas brain growth in syndromic children with CHD seems even more compromised than overall growth during the fetal period. Further analyses will evaluate the association between head circumference and specific CHDs, specific genetic disorders, maternal anthropometrics, parity, smoking status, maternal medical diseases, sociodemographic factors and placental weight.

DEVELOPMENT AND VALIDATION OF A DIAGNOSTIC PREDICTIVE SCALE URINARY TRACT INFECTION IN FEBRILE INFANTS

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Introduction: Urinary tract infection (UTI) is a bacterial infection, most common in newborns, whose clinical manifestations are nonspecific. Objective: To develop and validate a Predictive Scale febrile UTI without source infants hospitalized in a neonatal unit.
Patients and Methods: A case-control study with 158 febrile infants with UTI and fever without source 346 hospitalized in a neonatal unit. The analysis was performed with Stata ® 11. Associations were determined by odds ratio (OR) with confidence interval of 95%. To find Predictive Scale, we conducted multivariate logistic regression analysis, establishing major and minor criteria according to regression coefficient, while the yield was determined by sensitivity, specificity and area under ROC. New Predictive Scale was validated with 108 new febrile neonates.
Result: In this work included the construction of 504 scale no apparent febrile neonates, found 158 (31.3%) with UTI, 222 (44%) with fever of unknown origin without serious bacterial infection (SBI) and 124 (24.6%) with hypernatremic dehydration. The urine isolates were Escherichia coli (122, 77.2%), Enterobacter cloacae (16, 10.1%), Klebsiella sp (14, 8.9%), Enterobacter aerógenes, Enterobacter aglomerans y Enterococcus sp (2; 1.3% each). Of these, 26 were isolated bacteria simultaneously in urine and blood, Escherichia coli (22; 84.6%) and Enterobacter cloacae (4; 15.4%). The major criteria for diagnostic prediction of UTI were two altered urinalysis = 10 cells / field with or without bacteriuria, nitruria and leukocyte esterase and uncentrifuged urine Gram positive (OR: 49.3, CI 95%: 24.5 to 99.5) and minor criteria were, male sex (OR: 6.7, CI 95%: 2.3 to 11.9), age at time of fever greater than 7 days (OR: 5.2, CI 95%: 2.3 to 11.9), previous neonatal hospitalization (OR: 6.1, CI 95%: 1.9 to 19.4), altering the temperature (38.5 ° C or more, persistent fever, hypothermia) (OR: 2.7, CI 95%: 1.2 to 5.8), and C reactive protein 1.7 mg / dL or greater (OR: 3.6, CI 95%: 1, 7 to 7.7), being positive with one major and three minors. This showed good performance with sensitivity 100% (CI 95%: 98.3 to 100%), specificity 92.3% (CI 95%: 85.8 to 98.9%) and area under ROC 0.962 (CI 95%: 0.932 to 0.991) when validated in 108 new febrile infants without focus. Discussion: UTI in the neonatal period is an extremely serious problem, with high risk of sepsis, complications, sequelae and death. Treatment must be done quickly in the hospital. This work highlights the important contribution they have UTIs in the etiology of serious bacterial infections in neonates admitted to our NICU or another. The absence of clinical and laboratory markers highly sensitive, indicating the likelihood of urinary tract infection in neonates, highlights the important role it can play this scale with confidence to suspect and identify this pathology.
Conclusions: The new scale predictive allows good performance to predict a UTI in febrile infants.

INCREASED SERUM AND URINARY NGAL CONCENTRATIONS IN SEPTIC NEWBORNS FREQUENTLY IS NOT RELATED TO ACUTE KIDNEY INJURY

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Background: Neutrophil gelatinase-associated lipocalin (NGAL) is postulated as a new sensitive diagnostic marker of acute kidney-injury (AKI). Injured epithelial cells of various organs and neutrophiles release NGAL into the circulation. Therefor in septic newborns the usefulness of NGAL in the diagnosis of AKI could be limited.
Aim: The aim of the study was to analyze serum and urinary NGAL levels in septic newborns.
Material and method: 59 newborns admitted to NICU and suspected for infection was enrolled. Serum and urinary NGAL concentrations were assessed during the three subsequent days. 29 newborns served as a control group. 95% CI of the mean serum and urinary NGAL in the control group served as the reference (50-150 ng/ml and 6-67 ng/ml).
Result: At admission the higher than reference serum NGAL values were found in 31 (53%) septic newborns. Similar creatinine and cystatin C values were observed in septic newborns with normal and increased serum NGAL levels during 3 subsequent days. In 2 (6%) patients with increased and in 7 (25%) with normal NGAL values no decrease in serum creatinine level on the third was found. Two (6%) patients with increased serum NGAL and one (4%) with normal serum NGAL developed AKI during the observation. There were significant correlation between serum NGAL and CRP and procalcitonin.
Conclusions: 1. Increased serum NGAL concentration in septic newborns is usually not related to acute kidney injury. 2. Low specificity of serum NGAL measurements limits its usefulness for early acute kidney injury diagnosis in septic newborns.

URINE NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN DOES NOT PREDICT MILD AKI IN PRETERM NEONATES.

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Background: We evaluated urine neutrophil gelatinase-associated lipocalin (uNGAL) as an early acute kidney injury (AKI) biomarker in preterm neonates.
Methods: 35 preterm neonates were prospectively evaluated for serum creatinine (sCre) documented AKI during the first 14 days of life. During the study period, urine samples were collected daily. Of the neonates evaluated, we analyzed 11 developing AKI (cases) and an equal number of neonates without AKI (controls) matched for gestational age and postnatal age. uNGAL was measured at the day of AKI occurrence (day 0) and the preceding two days (day -1 and day -2, respectively) using ELISA.
Result: Cases had significantly higher sCre compared to controls on day 0 (1.21±0.48 vs. 0.83±0.16 mg/dL, p=0.031) but not on days -1 (0.76±0.15 vs. 0.81±0.16 mg/dL, p=0.423) and -2 (0.81±0.31 vs. 0.83±0.22 mg/dL, p= 0.819). sCre increased by 58.5±24.8 % from day -2 to day 0 in cases whereas it decreased by -5.5±17.5 % in controls (p< 0.001). Similarly, uNGAL (ng/mL) was significantly higher in cases compared to controls only on day 0 (19.1±3.5 vs. 13.3±7.3, p=0.017) and not on days -1 (18.8±3.1 vs. 16.3±7.8, p=0.383) and -2 (19.3±1.8 vs. 19.4±0.8, p=0.979).
Conclusions: In preterm neonates, uNGAL may document mild AKI having, however, little predictive value 1-2 days prior to its development.

QUANTITATIVE DETERMINATION OF BIOMARKERS OF PROTEIN, DNA AND LIPID OXIDATION IN URINE SAMPLES OF PRETERM NEWBORNS

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Introduction/Background: Pre-term newborns are prone to oxidative stress related diseases, which unequivocally condition their mortality, morbidity and long-term outcome. In comparison to older infants, therapeutic requirements of the preterm neonate are unique and hence request the development of specific analytical protocols. Sample collection has to be adapted to very limited volumes and pain-causing processes should be avoided. Hence, non-invasive urine analysis has been repeatedly considered to be an alternative to other biofluids such as, for example, plasma.
Patients and Methods: Two quantitative methods based on ultra performance liquid chromatography - triple quadrupole mass spectrometry (LC-MS/MS) for the analysis of urinary biomarkers of both protein and DNA as well as lipid oxidation in newborns has been developed and validated. The suitability of the method to provide a snapshot of the oxidative stress status has been thoroughly demonstrated in a clinical trial (REOX, 2012-2013, EUDRACT 2088-005047-42) including over 200 samples from extremely low birth weight infants.
Results: LC-MS/MS methods were successfully developed and validated based on the FDA guidelines for bioanalytical method development. After successful validation, both methods were applied to the analysis of urine samples from pre-term newborns, which allowed to determine typical ranges of concentrations of biomarkers for protein oxidation (ortho-tyrosine/phenylalanine, m-tyrosine/phenylalanine, 3-NO2-tyrosine/para-tyrosine, 3-Cl-tyrosine/para-tyrosine), DNA oxidation (8-deoxyguanosine/2-deoxyguanosine) and lipid peroxidation (2,3-dinor-iPF2a-VI, 8-iso-15-keto PGE2, PGE2, 5-iPF2a-VI, 8-iso PGF2a and PGF2a as well as total isoprostanes, isofurans, neuroprostanes and neurofurans).
Conclusions: The proposed procedures showed adequate performance in terms of sensitivity, selectivity, accuracy and precision. Furthermore its usefulness could be demonstrated when applied to samples of a clinical study comprising over 200 samples of extremely low birth weight infants. The methods could be applied in other clinical or studies, where the oxidative status of individuals is of relevance. Adapting the sample pre-processing, both methods could be easily adapted to their use in other biological matrices.
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PAIRED ANALYSIS OF NEONATAL SERUM CREATININE SAMPLES: COMPENSATED JAFFE VERSUS ENZYMATIC QUANTIFICATION

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Introduction: Serum creatinine (Scr) in part reflects glomerular filtration rate in neonates, but values depend on the technique used (Jaffe colorimetry or enzymatic quantification)1,2. Compensation (-0.3 mg/dl) of the Jaffe method for interfering 'pseudocreatinines' and traceability of creatinine assays to isotope dilution mass spectrometry (IDMS) should reduce the difference between both assays. However, validation with paired observations in neonatal serum samples are not available.
Methods: A paired analysis was performed in serum samples collected in neonates to quantify the differences between both techniques (compensated Jaffe or enzymatic, both IDMS traceable, Roche Diagnostics and Cobas c702 module) and the impact of clinical characteristics (age, weight, bilirubinaemia) on these differences. Paired analysis, Blant-Altman and (multiple) correlation were applied.
Result: Scr analysis was performed on samples collected in 129 neonates [median gestational age 38 (range 24-41) weeks, postnatal age 17 (1-236) days, weight 3.19 (0.62-4.55) kg, albuminaemia 34.8 (21-67) g/l, total bilirubinaemia 6.8 (0.2-16.1) mg/dl]. Median compensated Jaffe Scr was 0.50 (range 0.14-1.16) mg/dl, enzymatic was 0.48 (range 0.06-1.11) mg/dl. A mean Scr difference of 0.013 (-0.2-0.11) mg/dl was observed (Wilcoxon, $p=0.0039$). Bilirubin (total, free, direct) had a significant correlation on this Scr difference. In a multiple regression model, total bilirubinaemia remained a significant covariate ($r2=0.24$, $p<0.001$).
Conclusions: Scr observations with compensated Jaffe are statistical significantly different (0.013 mg/dl) to the enzymatic measurement. However, these differences are very limited with still an impact of bilirubin on the difference between both techniques.
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MEASUREMENT OF THE INTERNATIONAL NORMALIZED RATIO OF PROTHROMBIN TIME USING A PORTABLE DEVICE FOR COAGULATION SCREENING IN HEALTHY TERM NEONATES

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Background: Neonates routinely receive vitamin K to prevent vitamin K deficiency bleeding, which is associated with a high mortality rate and a high frequency of neurological sequelae. A coagulation screening test might be necessary to detect prophylactic failure. However, drawing blood from neonates for coagulation studies involve 2 major difficulties: the challenge of venous access and the comparatively large amount of blood required. CoaguChek XS (Roche Diagnostics, Tokyo) is a portable device designed to monitor prothrombin time by drawing a very small volume of blood (10μL). Although the device is used in pediatrics, studies have not been performed to evaluate its clinical utility in neonates, and the reference value is unknown in this population. Objectives: To determine the reference values for international normalized ratio (INR) using the CoaguChek XS by capillary puncture in healthy term neonates, and to evaluate the device by assessing its ease of use in clinical practice.
Patients and Methods: This study included 230 healthy term neonates born at a perinatal center between July 2012 and February 2013. The INRs measured on the CoaguChek XS were analyzed in 4-day-old neonates. We used 95% confidence interval (C.I.) to establish the reference value. In addition, factors that could potentially influence the INRs were evaluated.
Result: The enrolled neonates were orally administered vitamin K the day after birth. A reference range for INRs in 4-day-old neonates was established using the CoaguChek XS as the mean value 1.07, with a 95% C.I. of 1.06-1.08. A significant difference in the INR was noted between male (mean value, 1.06; 95% C.I., 1.04-1.07) and female (mean value, 1.08; 95% C.I., 1.07-1.10) participants. The INRs were found to correlate with the hematocrit values ($r = 0.35$, $p < 0.01$) and gestational age ($r = -0.18$, $p < 0.01$). In addition, the INRs demonstrated seasonal variation (INR in summer > INR in winter) and significantly correlated with the outdoor temperature ($r = 0.24$, $p < 0.01$) in spite of the room temperature ($p = 0.07$).
Conclusions: The CoaguCheck XS device is safe, fast, and convenient for performing INR assays in neonates. Our study is the first to establish a reference value for INRs that were measured using the CoaguChek XS in healthy term neonates. This device can be used as a model for coagulation screening tests in neonates.

IS CSF-NEURON-SPECIFIC ENOLASE (NSE) PREDICTIVE OF ADVERSE OUTCOME IN INFANTS WITH HYPOXIC ISCHEMIC ENCEPHALOPATHY? A SYSTEMATIC REVIEW AND METAANALYSIS.

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NSE in CSF appears in excessive amounts in acute brain disorders and is a potential marker of neonatal brain injury.
Objective: To perform a Systematic review of the literature and a comprehensive summarize of the available clinical research performed on this biomarker as an outcome predictor in infants with hypoxic ischemic encephalopathy. Methods. A literature search was conducted via PubMed (1960-January 2013), Medline (1960-January 2013) and Embase (1980-January 2013). Search terms used included 'neonatal', 'hypoxic-ischemic encephalopathy', 'biomarkers', 'cerebrospinal fluid', 'neuron-specific enolase'. The abstracts were pooled and reviewed by two different authors to identify articles that met inclusion criteria. Once the relevant articles were selected, they were reviewed using a standard review form and a composite evidentiary table was constructed.
Results: The search initially identified 85 articles. Of these, only 7 prospective studies of HIE with long term follow up of at least one year after discharge were included and critically reviewed. Two studies were posteriorly rejected because they did not report raw data to be analysed. The five studies included were published after year 1993 and involved a total of 228 patients with HIE (three studies had less than 30 patients and the other two more than 60 patients). CSF-NSE was always determined within 72 hours of life. Four studies combined abnormal neurological outcomes with death as a single variable and one abnormal outcome. There were not conflicting results about the association of NSE with poor outcome or abnormal outcome. However the outcome measures were heterogeneous. A meta-analysis of the studies provided evidence of an association between NSE and adverse outcome (death or long term neurological disability). The positive likelihood ratio was 5.242 (3.159-8.697), and the negative likelihood ratio was 0.124 (0.049-0.314). The diagnostic OR was 49.378 (14.89-163.68).
Conclusion: CSF-NSE determined within 72 hours after birth provides a good discrimination of outcomes in infants with HIE. However the research on this biomarker is limited due to the small sample sizes of the studies, and disparate outcome measures as well as heterogeneous time of determination of NSE within the first 72 hours of life. Future studies require rigorous and more uniform methodology and consistent outcome measures.

CSF-NEURON SPECIFIC ENOLASE (NSE) IS AN ACCURATE BIOMARKER OF BRAIN INJURY IN NEONATAL HYPOXIC-ISCHEMIC ENCEPHALOPATHY TREATED WITH HYPOTHERMIA

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Objective: NSE is a potential marker of neuronal injury. We questioned whether CSF-NSE at 72 hours of life correlated with the degree of HIE established before 6 hours of life and with the brain damage on MRI in infants treated with hypothermia.
Setting: Level III Neonatal Intensive Care Unit in Barcelona, Spain. Design. Prospective observational study.
Patients and Methods: Consecutive near or full-term infants with HIE were assessed with a clinical scale during the first 6 hours to establish the degree of HIE. Infants with moderate or severe HIE received whole-body hypothermia. CSF samples were obtained by LP at 72 hours of life (24-72 h). CSF-NSE was measured by enzyme immunoassay. Two sequential MRI studies (first at 90±31 and second at 303±59 hours) with conventional T1/T2 and proton MRS were performed. MRI scans were reviewed by 2 researchers masked to clinical data and CSF-NSE levels. Images were scored according to the scheme of Rutherford et al.
Results: A total of 51 neonates with HIE were included: 11 infants had mild HIE, 15 moderate and 25 severe. All infants with moderate or severe HIE were cooled. CSF-NSE levels were related to the severity of HIE within the first 6 hours of life: mild: 22.01 ±7.4 ng/mL, moderate: 46.4±27.3 ng/mL; severe: 274.9±251.1 ng/mL ($p<0.01$). NSE levels in CSF (cutoff value, 30 ng/mL) provided a good discrimination of the degree of HIE (AUC: 0.936; IC 95%: 0.864-1.00) and were correlated with the MRI score (Sp 0.886; $p<0.001$). While infants with normal MRI or punctate white matter (WM) lesions had levels of 35.4?22.5 and 30.0?12.5 ng/mL, respectively, infants with deep grey matter injury or with widespread loss of grey matter-white matter differentiation together with damage to the central grey matter had significantly higher levels ($p<0.001$): 94.6 ? 70.5 and 175.5?149.2 ng/mL, respectively. The CSF-NSE levels were associated with the presence of lactate peak in the first proton MRS (228.5±110.6 vs 40.7±24.2 ng/mL abnormal vs normal MRS, $p<0.01$).
Conclusions: Elevated CSF-NSE levels measured at 72 hours in infants with HIE treated with hypothermia are associated with the clinical severity of HIE and with the severity and extent of brain injury. CSF-NSE approximately 72 hours of life accurately reflects the severity of brain damage in the cooled infants.

IMMUNOLOGICAL PARAMETERS OF BLOOD AT CHILDREN AT THE ALLERGY

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Purpose and research problems: Studying of immunological parameters of blood of children suffering various forms of an allergy.
Materials and research methods: 130 children aged from 6 till 14 years, from them with the allergic rhinitis (AR) of-46 patients, the bronchial asthma (BA) of-48 patients, and the food allergy (FA) of-36 patients were subjected to inspection. All patient along with general-clinical, laboratory and functional conducted also immunological researches. The control group was made by 30 healthy children of similar age.
Results of research and discussion: Researches showed that immunological parameters of blood of patients at an allergy differ from parameters of blood of children of control group. In blood of children with FA decrease in level of leukocytes (P<0,05) is found, and children about AR have rather high level of leukocytes 7935,5 ± 204,8 in 1 mcrl. (P<0,05). It is characteristic also reliable increase of level of lymphocytes is observed at allergic diseases that is greatest reflected at children at AR (P<0,05). Change in the maintenance of CD4 of +lymphocytes that was shown by decrease in all groups of children with an allergy (?<0,01) was at the same time characteristic. The deepest deficiency is shown at FA - 476,0 ± 34,5 in 1 mcrl. Level of cytotoxic lymphocytes (CD8+) it is authentically lowered at OH and PAS (?<0,01), and at AR absolute value was authentically raised for the account leucocytos in this group - 578,3 ± 32,4 in 1 mcl. (?<0,05). In our researches at children at the CD20 level of +-cages (?<0,01) BA raises, and absolute size authentically increases at children about AR (?<0,01). In all surveyed groups of children level of relative and absolute CD23 values of +-cages was authentically raised (?<0,001). It became clear that at allergic diseases there is a decrease in synthesis of IgG (?<0,05), IGA and IGE increase, and also multidirectional change of the IGM level. The relative and absolute maintenance of NK cages in blood of sick children with OH below data of control group, on the average twice (P<0,01). In group of children about ARE level both relative, and absolute number of CD16 of +lymphocytes was raised on the average in 2,1???? (P<0,001). The relative and absolute maintenance of NK cages in blood of sick children with OH below data of control group, on the average twice (P<0,01). In group of children about ARE level both relative, and absolute number of CD16 of +-lymphocytes was raised on the average in 2,1???? (P<0,001). The relative number of NK cages in group of children with PAS didn't differ from parameters of control group, however, in absolute values the tendency to increase was observed.
Conclusion: The allergic answer is characterized by formation of antibodies and specifically reacting lymphocytes that provides "armament" of an organism for hypersensitivity. It is explained by the morphogenetic processes, induced at the immune answer which significantly change structure of immune system and promote development of I and the II types of reactions of hypersensitivity.

THE EFFECT OF A CONTINUOUS GLUCOSE MONITORING SENSOR AS A DIAGNOSTIC TOOL ON HBA1C LEVELS IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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Introduction: Type 1 diabetes mellitus (T1DM) is one of the most frequent chronic disorders in children. Most patients check their blood glucose level using the fingerprickmethod and a blood glucose meter (self-monitoring of blood glucose, SMBG). This provides information about the blood glucose value only at the moment the blood was sampled. When using a continuous glucose monitoring system (CGMS) blood glucose levels are measured semi-continuously. CGMS is an additional tool for patients on insulin pump therapy. Literature on the effects of a CGMS on long term diabetes regulation is conflicting and there is little literature on the effects of CGMS for a single, short period only. When patients show an elevation of glycosylated haemoglobin (HbA1c) the question how to improve glycaemic control is challenging and CGMS probably offers a valuable tool.
The aim of this study is to evaluate the effect of a CGMS used for a short period of two to seventeen days on HbA1c levels in children with T1DM on an insulin pump, compared to SMBG. During the GCMS period diaries are kept on food intake and activity. After the CGMS period evaluation of the acquired information by members of the pediatric diabetes team results in adjustments in insulin regimen and education for the patient and his caregivers on how to improve glycaemic control (CGMS+).
Methods: In this retrospective study 109 T1DM patients (age 2-20 years) treated with an insulin pump were divided in a case group that received a CGMS+ for two to seventeen days and a control group that performed SMBG. HbA1c levels at baseline, on short term (< six months after baseline HbA1c) and on long term (> six months after baseline HbA1c) were extracted from patient files. In both groups differences in change in HbA1c levels at baseline and at second and third measurement were analyzed. A subgroup analysis was made between younger children under the age of 12 years and adolescents.
Results: A significant decrease in HbA1c was seen in the overall intervention group in the short term (-2,2 mmol/l), but not in the long term period. In children under twelve years of age a significant decrease in HbA1c of was seen in both the short term (-4 mmol/l) and the long term (-5,6 mmol/l). There were no beneficial effects of a CGMS+ compared to SMBG on HbA1c levels in adolescents.
Conclusion: Our results show that in children with T1DM a CGMS+ leads to an improvement of HbA1c in the short term as compared to SMBG. In the long term only a trend to a beneficial influence of a CGMS+ still exists. CGMS+ is mainly effective in lowering HbA1c levels in children under 12 years of age both in the short term as well as in the long term. In adolescents there was no provable effect of a CGMS+ on HbA1c levels.

CROSS-CORRELATION OF HEART RATE AND OXYGEN SATURATION: A NEW METRIC FOR PREDICTIVE MONITORING FOR SEPSIS AND NEC

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Introduction/Background: Predictive monitoring, or analysis of vital signs to predict potentially catastrophic illnesses, has the potential to improve outcomes of neonatal intensive care unit (NICU) patients. Our group previously showed that continuous monitoring for abnormal heart rate characteristics associated with sepsis reduces mortality among very low birth weight (VLBW) infants. In the current study we expand this work to combined cardiorespiratory predictive monitoring. Increased apnea is a common presenting sign in preterm infants with late onset sepsis (LOS) and necrotizing enterocolitis (NEC). Respiratory pauses may entrain decreases in heart rate and oxygen saturation, and we hypothesized that an increase in their cross-correlation (XC-HR-SpO2) would occur prior to clinical diagnosis of LOS and NEC.
Patients and Methods: All continuous vital sign data from bedside monitors are stored on all infants in the University of Virginia and Columbia University NICUs, including every 2-second recordings of HR and SpO2. XC-HR-SpO2 was calculated in 365 preterm VLBW infants for every 10-minute period for their entire NICU stay, resulting in greater than 4 million measurements or 40 infant-years of data. Maximum XC-HR-SpO2 value was identified within each 10-minute window. We then identified cases of blood culture-positive LOS or Bells stage II-III NEC. Relative risk of LOS or NEC was calculated for each value of XC-HR-SpO2 as the fraction of infants with LOS or NEC diagnosed within 24 hours of the value divided by those without. Calculations were performed using estimated probability density functions and bootstrapping to account for repeated measures.
Results: 71 episodes of LOS or NEC were identified in 58 of the 365 infants for whom XC-HR-SpO2 was calculated (median gestational age 26 weeks, interquartile range 24.0-27.5 weeks). There was a statistically significant near-linear increase in relative risk of LOS or NEC with increasing XC-HR-SpO2. The relative risk for LOS or NEC diagnosis within 24h increased 3-fold with an increase in XC-HR-SpO2 from 0.2 to 0.8. Inspection of cardiorespiratory data from individual patients revealed that the increase in XC-HR-SpO2 was associated, in many cases, with increased respiratory pauses (apnea and periodic breathing).
Conclusions: Cross-correlation of HR-SpO2 increases prior to clinical diagnosis of LOS and NEC, at least in part reflecting increased respiratory pauses. This and other new metrics incorporating multiple vital signs may be useful for predictive monitoring of NICU patients, leading to earlier detection and treatment of potentially catastrophic illnesses.

BIOIMPEDANCE SPECTROSCOPY (BIS) PARAMETERS IN HEALTHY CHILDREN: RELATIONSHIP TO AGE, WEIGHT, LENGTH AND BODY MASS INDEX (BMI)

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Background: Knowledge of fluid status is crucial when evaluating hydration levels in critically ill children. Current reference methods are dilution methods. However, these techniques are invasive, expensive, and require highly trained personnel, and are therefore not suitable for routine paediatric examination. Bioimpedance spectroscopy (BIS) offers an alternative, non-invasive, simple, portable and inexpensive method of measuring hydration levels in children. One BIS approach is to use the physiological values of total body fluid (TBF), extracellular fluid (ECF), and intracellular fluid (ICF), which are based on predictive equations and only proven in adults. Another approach is to use the impedance values of extracellular resistance (RE) and intracellular resistance (RI). RI and RE are the electrical resistances originating from ICF and ECF, respectively. These values are advantageous, since predictive equations are not required. The purpose of this preliminary study was to investigate whether there is a relationship between RE and RI and: age, weight, length or body mass index (BMI).
Subjects and Methods: Whole-body measurements were performed on 119 healthy children (69 boys, 50 girls, ages 2-14 years) with normal weight and length for their age. A BIS device (5kHz-1MHz) was used.
Result: Data for boys and girls combined, showed significant negative correlations between the impedance values of RE and RI, and the following variables: age, weight, length and BMI (see table).
Conclusions: This study demonstrates a change in RE and RI according to: age, weight, length and BMI, and therefore offers promising perspectives for further research areas (e.g. gender influence on RE and RI). Particularly pronounced, was the association between BMI and impedance values. These relationships could be a viable alternative to ECF and ICF, and offer the potential of a new way of monitoring hydration levels in critically ill children. Table: Girls and boys combined, ages 2-14 years (n=119) r p-value Re vs Age -0,4 P=0,0001 Ri vs Age -0,5 P<0,0001 Re vs Weight -0,5 P<0,0001 Ri vs Weight -0,5 P<0,0001 Re vs Length -0,4 P<0,0001 Ri vs Length -0,4 P<0,0001 Re vs BMI -0,6 P<0,0001 Ri vs BMI -0,6 P<0,0001

ULTRASONOGRAPHY IMAGE OF THE THYROID GLAND IN NEONATES BORN TO MOTHERS WITH HYPOTHYROIDISM

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Objective: To estimate the thyroid volume of neonates born to mothers with hypothyroidism. Materials: The prospective observational study of the 54 (male and female) neonates born between 36 and 42 weeks of gestation age from mothers with hypothyroidism. The mean of thyroid volume out of 158 healthy neonates was 1,048 (0,240). Babies were excluded if they have any congenital malformations. The mode of delivery was as well caesarean section as vaginal delivery.
Methods: The infants were scanned with the same ultrasound scanner, HD 11 XE Philips, using a linear L15-7 MHz probe. Babies were examined in the supine position with the neck hyperextended. We performed transverse and longitudinal sections of each lobe of the thyroid gland. The measurements of the maximum length, breadth and depth of each lobe were recorded. The thyroid volume was calculated by ultrasound scanner using the ellipse formula: length x breadth x depth x 0,52 for each lobe of the thyroid gland. Both lobes were measured to give combined volume. Correlation between variables was assessed using the Bonferronie test.
Result: The mean thyroid volume of neonates of mothers with hypothyroidism was 0,964 ml (SD-+/-0,246 ml). Comparison of the thyroid dimensions of healthy newborn and newborn of mothers with hypothyroidism (treated properly) showed no differences except that the left lobe was longer, the depth of the left lobe was grater and volume of the left lobe was bigger in healthy newborn. Although these differences are significance ($p<0.01$), they are not cause significance in total volume of thyroid gland. Screened TSH values were within reference ranges. except TSH of one child.
Conclusions: Correctly treated hypothyroidism during pregnancy seems to have no impact on the thyroid volume of newborns. Unfortunately I presented a patient with elevated TSH and a small volume thyroid gland who was born to a mother with hypothyroidism which weakens my hypothesis. Further examinations on bigger population are needed. Corresponding author: Aleksandra Mikolajczak MD Neonatal and Intensive Care Department, Medical University of Warsaw e-mail: aamikolajczak@wp.pl

COMPARATIVE EVALUATION OF ULTRASONOGRAPHY AND MAGNETIC RESONANCE IMAGING IN ACUTE KNEE INJURIES IN CHILDREN.

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Background: Currently, acute knee injury diagnostics is one of the actual problems of traumatology. The knee joint is a complex anatomo-functional structure. Joint trauma results in severe anatomical abnormalities. Clinical manifestations of acute injury often do not match the severity of the damage. In this report, we compared the diagnostic efficacy of ultrasonography and MRI in the evaluation of damaged knee joint structures.
Materials and Methods: Ultrasonography and MRI were performed in 96 children (68 male, 28 female). All ultrasound studies were performed by standard technique with the use of Philips IU 22, Sonosite Micromax ultrasound machines and linear and convex transducers in the frequency range of 3 - 17 MHz MRI was performed with Philips Achieva 3 Tesla scanner.
Results: and Discussion Ultrasonography revealed damage of knee joint structures in 96 children. In 15 of them avulsions of osteochondral fragments from patella and articular surfaces were revealed. The total number of ligamental injuries was 124, meniscus damages - 36. MRI also revealed damages in the entire group of children, including the presence of osteochondral injuries in 17 cases. The total number of ligamental and menisci injuries was 67 and 104 respectively. Average diagnostic efficiency for MRI was 67% and 64% - for the ultrasonography.
Conclusion: The optimal method for diagnosing injuries of ligaments and menisci in children is MRI. However, the advantage of the ultrasonography is in its availability, low price and the possibility of use as a screening.

COMPARATIVE EVALUATION OF ULTRASOUND AND LOW DOSE CONTRAST ENHANCED CT IN PEDIATRIC BLUNT ABDOMINAL TRAUMA.

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Background: Imaging in acute blunt abdominal trauma include the initial ultrasonography (USG), followed by contrast enhanced computed tomography (CE CT) for further evaluation of parenchymal organs and detection of active bleeding, if the patient was hemodynamically stable. The current standards used in the centers involved in the treatment of acute abdominal trauma, prescribes to assess visceral injury by initial CT, despite the high radiation dose. In this report, we compared the sensitivity and specificity of ultrasonography and low dose contrast enhanced computed tomography for diagnostics of pediatric blunt abdominal trauma. Patients and
Methods: Ultrasound and CE CT were performed to identify damage of parenchymal organs of the abdominal cavity and retroperitoneal space in 57 children (40 boys, 17 girls, mean age 8.9 years, +/- 2.8) with blunt abdominal trauma. A comparative evaluation of the sensitivity, specificity, accuracy of quantity and locations of injuries for ultrasound and CE CT was performed. Low dose CT was performed on a Philips Brilliance 16 scanner. Contrast media was injected intravenously manually without use of automatic injection system. Omnipaque 300 or 350 mg/ml was used in the rate of 1-3 ml/kg - up to 40 ml, depending on the age and weight of the child. Images were obtained immediately after contrast media injection. The study protocol was approved by the ethics committee and written informed consent was obtained from parents.
Results: In 31 patients, CE CT showed no abnormalities. CE CT revealed 30 parenchymal organ injuries in 26 patients. Lesions were located in the spleen (15), liver (9), right kidney (2), the left kidney (3) and pancreas (1). Ultrasound revealed 21 of the 30 lesions diagnosed by CE CT and six injuries (overdiagnosis: left kidney contusion - 1, perirenal hematoma on the left - 2, rupture of the liver - 2, rupture of right kidney - 1) in the group where the CE CT revealed no damages. In addition, ultrasound showed the presence of free fluid in two patients from the group where CE CT showed no abnormalities, and in 22 children with parenchymal organs injuries present at CE CT scans.
Conclusion: The optimal imaging method for acute abdominal injuries detection in children is a low dose contrast enhanced CT. Ultrasound has the same accuracy as unenhanced CT in parenchymal organs injuries and can be used as a screening method.

DEVELOPMENT AND VALIDATION OF A DIAGNOSTIC SCALE DEHYDRATION IN INFANTS WITH FEVER

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Introduction: hypernatremic dehydration has been associated with exclusive breastfeeding, with potentially serious neurologic complications related.
Objective: To develop and validate a predictive scale of dehydration in infants admitted for fever in the first two weeks of life. Patients and
Methods: A case-control study of 240 febrile infants 0-14 days of age, hospitalized in a neonatal unit. The analysis was performed using Stata ® 11. Associations were determined using odds ratio (OR) with confidence interval of 95%. To find the impact of weight loss on sodium, chloride, glucose urine density and linear regression was used for multivariate analysis and logistic regression, while model performance was determined by sensitivity, specificity and area under ROC.
Result: The diagnostic model that best characterized the infants with dehydration were female gender, birth weight> 3200 g, age at = 3 days fever, weight loss> 2% per day, exclusive breastfeeding, serum sodium > 145 mmol / L, serum chloride> 108 mmol / L, urine density = 1025 and blood glucose <60 mg / dL, with sensitivity of 94.2% (95% :89,6-98, 8%), specificity 83.3% (95% CI :76,3-90, 4%), positive predictive value 85% (95% CI :78,5-91, 4%), negative predictive value 93.5% (95% :88,3-98, 6%) and area under ROC 0.888 (95% CI :0,848-0, 927). Validation in a new group of febrile infants had similar results.
Conclusions: A predictive model of dehydration in febrile infants allows us to initiate appropriate therapy, which reduces potential complications of dehydration with or without hypernatremia as well as guidance on the non-initiation of antibiotics or use shortening.

SCREENING FOR DEVELOPMENTAL DELAY IN INFANTS BORN LATE AND MODERATELY PRETERM: VALIDITY OF A PARENT REPORT MEASURE

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Background: Infants born late and moderately preterm (LMPT; 32-36 weeks gestation) are at increased risk for developmental problems compared with term-born peers. Screening in infancy may thus be beneficial for early identification of developmental delays in this population. The Parent Report of Children's Abilities (PARCA-R) has good diagnostic validity for identifying developmental problems in very preterm infants. However, its clinical utility has not been tested in a LMPT population, in which problems are likely to be more subtle and thus difficult to detect. We aimed to assess the concurrent validity and diagnostic utility of the PARCA-R as a screening tool for identifying developmental delay in 2-year-old children born LMPT.
Methods: The parents of 229 children born LMPT (32-36 weeks) aged 24 months (mean 25; range 24-27) completed the PARCA-R questionnaire to assess their infant's cognitive and language development. PARCA-R scores were summed to yield a total Parent Report Composite (PRC) score. Children were subsequently assessed at home using the Bayley Scales of Infant and Toddler Development-III (Bayley-III), the current Gold Standard. Standardised scores were obtained for cognitive and language development from which a mean score (Bayley-CL) was computed to assess overall development. Bayley-CL scores <85 were used to classify developmental delay.
Result: Mean PRC score was 90.14 (SD 35.58). Bayley-III Cognitive scores were mean 96.72 (SD 11.17), Language scores mean 100.10 (SD 16.72), and Bayley-CL scores mean 98.64 (SD 12.60). There was a moderate correlation between PRC scores and Bayley-III Cognitive scores ($r=0.40$, $p<0.001$), and large associations with Bayley-III Language scores ($r=0.69$, $p<0.001$) and Bayley-CL scores ($r=0.63$, $p<0.001$) indicating good concurrent validity. Overall, 32 (15.09%) LMPT children had developmental delay. Using Youden index, the optimum PARCA-R cut-off for identifying children with developmental delay was PRC scores <79 which gave sensitivity 0.81 (95%CI 0.80 to 1.00) and specificity 0.69 (95%CI 0.49 to 0.82), indicating good diagnostic utility.
Conclusions: The results from this study indicate that the PARCA-R is a valid measure of identifying developmental delay in infants born late and moderately preterm at 2 years of age. This provides support for its continued use as an early screening measure for developmental delay in preterm populations.

HOW TERRIBLE ARE THE TERRIBLE TWOS? REFERENCE VALUES FOR THE CBCL AT 2 TO 2.5 YEARS.

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Background: Empirical research of psychopathology in preschool children is limited. Existing studies tend to focus on those aged 3-5 years. Increasing knowledge of the prevalence, presentation and correlates of psychopathology at different age points throughout early childhood is essential given the rapid changes in children's' developmental capacities during this period. Using standardised measures to assess emotional and behavioural problems in childhood has become increasingly popular. The Child Behavior Check List 1.5-5 years, has been extensively reported and is used routinely in clinical practice. Although this measure has been standardised for use in children as young as 18 months, few studies have focussed on younger children (< 3 years). The weight of an abnormal CBCL score at this age is unclear. The aim of the current study is to investigate the use of the CBCL/1.5-5 years in a sample of two year old children and to provide normative data. Design & Method This study uses a cross-sectional design. Participants and their parents were drawn from the population based Cork BASELINE birth cohort study (www.baselinestudy.net). Participants included in this study were born full term (>= 37 weeks) and had completed the Child Behaviour Check List at 2-2.5 years. Data were analysed using SPSS 20.
Results: In total 852 children were scored by their parents (mean age=25.2 months, age range=24-30 months; male 50.6%, female 49.3%). The majority were completed by the child's mother (86.9%) in their own home (93.7%). The mean Total Problem Score (TPS) was 21.78 (SD=14.3; 95% confidence interval=20.82-22.74). The majority of TPS assigned fell within the typical range (96.7%). On the Internal Problem and External Problem scales, 94.5% and 95.4% of scores fell within the typical ranges respectively. Lower TPS were associated with thridthird level (university) education, higher occupations and increasing income. The mean TPS was higher, 23.3 (SD 11.7), when fathers completed the CBCL compared with mothers, 21.6 (SD 14.4). On the five DSMâ€”oriented scales over 96% over participants obtained scores within the typical range.
Conclusions: These data, taken from a 'healthy' sample provide useful normative information for clinicians and researchers. The findings demonstrate that the CBCL/1.5-5 years can be used as an effective screening tool for behavioural and emotional problems for two year old children. Abnormal CBCL scores even at this young age are outside normative behaviour and require further assessment.

TARGETING ZERO INFECTIONS: ACTIVE SURVEILLANCE INTERVENTION TO REDUCE CENTRAL LINE ASSOCIATED BLOODSTREAM INFECTIONS

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Objective: CLABSIs are a significant cause of morbidity and mortality in neonatal intensive care units. CLABSI is defined as a bloodstream infection that occurs with a central line in place or within 48 hours of its removal, when no other source of infection is identified. An active surveillance intervention was conducted to improve the adherence to procedures recommended to reduce CLABSI.
Methods: The intervention targeted clinician's use of the following issues: correct hand washing, full barrier precaution during insertion of the central line, cleaning the skin with chlorexidine in infants > 1500 g, sterile manipulation of the catheter, reducing the number of manipulations of the catheter, prompt removal of unnecessary catheters. Several audits were made to reach all the medical and nurse staff. During a period of 21 months direct surveillance of catheter insertion and manipulation was performed to check the adherence to infection control practices. Number of CLABSI and catheter days were collected from a hospital based infection control practitioner.
Result: From April 2011 to December 2012 the mean CLABSI rate, expressed as the number of infection episodes per 1000 catheter days, decreased from 14,9 to 3,5. The number of bacterial CLABSI decreased significantly whereas the number of fungal CLABSI remained constant over that period of time
Conclusions: The adherence to bundles is the tool to prevent infections from catheter insertion to catheter removal. These interventions have to be implemented to achieve the goal of zero CLABSI.

DOES MICROBIOLOGICAL SCREENING IDENTIFY BACTERIAL RESISTANCES TO BE CONSIDERED IN CALCULATED ANTIBIOTIC THERAPY OF NOSOCOMIAL SEPSIS IN THE NICU?

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Introduction: Colonizing bacteria may cause nosocomial infections in patients of the neonatal intensive care unit (NICU). The infections are mainly caused by gram-positive bacteria, especially coagulase-negative staphylococci (CNS), which colonize the infants´ skin. Most gram-negative bacteria causing blood stream infection (BSI) have been colonizing the infants´ intestine previously. In 2012, the German Commission for Hospital Hygiene and Infectious Disease Prevention recommended a microbiological screening of preterm infants on NICUs, targeting to identify bacteria revealing resistances which should be accounted for in calculated antibiotic therapy in case of nosocomial infection. We analyzed screening results and courses of our patients aiming to identify the spectrum of colonizing bacteria and to check whether the identified bacteria caused observed infections. Patients and
Methods: On a weekly basis we cultured pharyngeal or tracheal and rectal swabs to identify multidrug-resistant bacteria and bacteria causing pneumonia (pharyngeal or tracheal swabs). All patients of the NICU hospitalized at the screening days were included. We recorded nosocomial BSI (diagnosis of BSI due to CNS requested clinical symptoms plus laboratory changes), clinical sepsis with sterile blood culture, necrotizing enterocolitis (NEC), pneumonia, and sterile site infections.
Result: From July 2012 to February 2013, 65 (86%) of 76 infants had positive screening cultures, i.e. either potential pathogenic bacteria in pharyngeal or tracheal swabs or multidrug-resistant gram-negative bacteria. Enterobacter cloacae was found in 15 of the infants during July to October 2012. Enterobacter cloacae has an inducible Amp C resistance gene, which should be accounted for in calculated antibiotic therapy. The other gram-negative bacteria detected by our screening did not reveal multidrug resistances. We observed 17 episodes of infection in 16 patients: 7 episodes of BSI due to CNS, one BSI due to Staphylococcus aureus, which had not been identified by the screening, and 5 episodes of clinical sepsis with sterile blood culture. One infant had an intestinal perforation and peritonitis. Enterobacter cloacae, which had been identified by the screening, was found in the ascites. In 3 infants with NEC, one had a BSI due to Enterococcus faecalis, which had not been a target of the screening.
Conclusions: 1. CNS were the main pathogen in nosocomial BSI in our NICU. Calculated antibiotic therapy already covers CNS. 2. The endemic microflora of our small cohort temporarily comprised a large part of multidrug-resistant Enterobacter cloacae. However, this bacterium had been identified as a pathogen in the observed episodes of infection only once. Enterobacter cloacae vanished during the second half of the study period. 3. The suitability of the microbiological screening to identify bacterial resistances to be considered in calculated antibiotic therapy will have to be evaluated on a larger data base.

AN EVALUATION OF SYSTEMIC ANTIBIOTIC EXPOSURE IN THE MANAGEMENT OF SUSPECTED EARLY NEONATAL SEPSIS

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Background: Guidelines from the UK National Institute for Clinical Excellence (NICE) (1) and from the American Academy of Pediatrics (AAP) (2) were published in 2012 which provide recommendations for the management of suspected early neonatal sepsis. Intravenous gentamicin and penicillin are the first-line antibiotics required by NICE; the AAP recommend gentamicin and ampicillin. Both guidelines advise that serial measurements of serum CRP is of value in guiding the duration of antibiotic treatment, a concentration of <10mg/l within two days of starting treatment having a high negative predictive accuracy for 'proven or probable sepsis'. Neither guideline provides information about the frequency of antibiotic treatment in early neonatal sepsis. Aim The aim of this study was to measure the frequency and duration of systemic antibiotic treatment for early neonatal sepsis and to estimate the frequency of 'proven or probable' sepsis in those who are treated.
Methods:A prospective cohort study was undertaken of babies born in a tertiary maternity unit. Data were collected, from November 2011 - March 2012, concerning the number of inborn births, number screened for early sepsis, number receiving systemic antibiotics, and duration of antibiotic treatment. Blood was taken for culture and for measurement of plasma CRP before starting treatment and blood for CRP measurement was taken again at 48 hours, and subsequently as clinically indicated. Indications for antibiotic treatment were similar to those specified in the NICE guideline.
Results: There were 2642 livebirths; 307 (11.6%) babies were screened for infection and 272 (10.3%) received intravenous (IV) antibiotics. Of the 2469 born at >/= 37 weeks gestation, 172 (7%) received IV antibiotics, compared with 100 of 173 (58%) of babies who were <37 weeks. 65 (38%) of term and 42 (42%) of preterm babies were treated for longer than 72 hours. 3.5% of blood cultures from treated full-term babies and 1% from treated preterm babies grew bacterial pathogens; Streptococcus agalactiae grew in 4 of the 7 positive cultures. Two or more plasma CRP measurements were obtained in 78% of babies and a concentration of >10mg/l was recorded in at least one sample in 89 (33% of all treated babies).
Conclusions: Early systemic antibiotic treatment was prescribed for a relatively large proportion of newborn infants but only a small number had bacteriologically confirmed sepsis. At least 33% of treated babies had a laboratory indicator of 'proven or probable sepsis' and 41% were clinically considered to require treatment for longer than 72 hours. These data indicate that about 2.7% of full-term babies and 24% of preterm babies in our hospital would receive a course of antibiotics incorporating gentamicin for more than 72 hours following birth if the NICE and AAP guidelines were followed. The long term consequences of these recommended regimens require further study. 1. Antibiotics for early-onset neonatal infection: antibiotics for the prevention and treatment of early-onset neonatal infection. NICE Clinical Guideline 49. August 2012. 2. Management of Neonates With Suspected or Proven Early-Onset Bacterial Sepsis. Pediatrics 2012;129;1006 - 1015.

NEONATAL HERPES INFECTION: INCIDENCE RATES, PRESENTATION, AND OUTCOME IN BABIES UNDER 14 DAYS OLD

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Background: Neonatal herpes simplex infection can have devastating outcomes for otherwise healthy babies. In the United Kingdom, the stated incidence is 1.6 per 100,000 live births, which contrasts to an incidence of 31 per 100,000 in the United States. We aimed to discover the current incidence of neonatal herpes simplex infection in our region, to describe the variety of differing presentations seen, and to consider which presenting features could be used for prognostication.
Methods: We retrospectively reviewed the case notes of all neonates presenting with in first 14 days of life to Nottingham University Hospitals from 2006-2013. The cases were identified by database interrogation and laboratory reports.
Result: Fifteen cases were identified with neonatal herpes infection. Two of these cases were transferred from other hospitals for tertiary care and all others were from the local population giving an incidence of about 17.7 per 100,000 live births which is markedly higher than previously quoted. Four cases presented within first 48 hours of life while 7 infants presented in the second week. Six infants were born prematurely and there were six deaths. High vigilance and early recognition of subtle signs can be critical, however, the presence of haemodynamic instability and coagulopathy at presentation were independent predictors of death.
Conclusions: Neonatal herpes infection is much more common in United Kingdom than previously quoted. The clinical presentation can be varied and subtle. As the incidence of reported genital herpes rises we urge greater vigilance and early treatment with antiviral therapy, particularly in neonates presenting with cardiovascular compromise and presumed sepsis.

THE CLINICAL CHARACTERISTICS AND PROGNOSIS OF LATE ON-SET GROUP B STREPTOCOCCUS SEPSIS IN NICU OF OUR HOSPITAL

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Objective: To investigate the clinical characteristics and prognosis of late onset B streptococcus sepsis, therefore to provide reference for better clinical diagnosis, treatment and reduce complications.
Methods:15 patients who diagnosed late onset GBS sepsis at hospital discharge in our NICU (Neonatal Intensive Care Unit) were retrospectively analyzed , from Jan 2007 to Dec 2011. And 34 patients who diagnosed late onset non-GBS Gram-positive bacteria sepsis at hospital discharge were selected as control in the same period.
Results: The common symptoms of late onset GBS sepsis are fever, lower reaction and convulsions. Compared to the clinical menifestations of late onset non GBS Gram-positive bacteria sepsis, the difference of Late onset GBS sepsis in the clinical menifestations such as the shortness of breath, convulsions and apnea , was statistical significance ($P < 0.05$). Laboratory test displayed that the ratio in white blood cell count (CSF) > 100×106/ L, Higher Sensitive C - reaction protein(hsCRP) > 100 mg/L and glucose (CSF) < 3.11 mmol/L of late onset GBS sepsis group are higher than those of late onset non GBS Gram-positive bacteria sepsis group, the difference was statistically significant ($P < 0.05$). The results of drug resistance displayed that GBS were sensitive to penicillin,ampicillin, ceftriaxone, piperacillin/tazobactam, levofloxacin and vancomycin; The resistant rate to erythromycin and gentamycin were 87.5% respectively. ? Compared to the sequela of late onset non GBS Gram-positive bacteria sepsis, the difference of Late onset GBS sepsis was statistically significant ($P < 0.05$); while on the fatality rate, there was no statistically different ($P > 0.05$).
Conclusions: The start of late onset GBS sepsis is hidden, atypical, and with more complications. If not promptly treated, it can cause sequela. Clinical menifestations, such as fever, Refusing milk , and poor mental reactions should be taken into account the possibility of this sepsis. What´s more, it is very important for suspicious patients to early use effective antibiotic treatment.

MYCOPLASMA PNEUMONIAE INFECTIONS IN PAEDIATRIC AGE: CLINICAL VARIABILITY

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Background: Mycoplasma pneumoniae (MP) is an emerging pathogen. It is the most common cause of atypical community-acquired pneumonia, but it is also responsible of determining several conditions, like reactive arthritis, thrombocytopenia, vasculitis, FUO, dermatitis.
Objectives And Study: In our study we want to detect how much role MP has in determining pneumonia, thrombocytopenia and arthritis in pediatric age.
Patients And Methods: In our survey we recruited 102 pediatric patients (male 54, female 48), admitted in our Department of Pediatrics during the last year (gen-dec 2012). All the patients were admitted for low respiratory tract infections, arthritis, thrombocytopenia. They all were screened for MP sierology and tested for specific IgM positivity. We collect also some epidemiological data about the months of admission and grouped them for season of the year.
Results: In 76 (74,5%) out of 102 patients, diagnosis of bronchopneumonia was made; 17 patients (16,7%) were admitted for arthralgia, 4 (3,9%) for rash/dermatitis, 2 (1,9%) for thrombocytopenia, 2 (1,9%) for vasculitis, 1 (0,9%) for FUO. Of the above created groups, IgM serology was detected to be positive in 27 (26,47%) out of 102 patients (15M, 12F), distributed in this way: 19 (70,4%) affected by bronchopneumonia, 5 (18,5%) by arthralgia, 2 (7,1%) by thrombocytopenia, 1 (3,7%) by vasculitis. Patients in which IgM serology was detected to be negative were 75 (73,53%), 39M and 36F; the most common diagnosis was again bronchopneumonia (57 patients, 76%), followed by arthralgia (12 pz, 16%), rash/dermatitis (4pz, 5,3%), vasculitis (1pz, 1,3%), and FUO (1pz, 1,3%). According to the 4 seasons of the year, we found that the most of patients IgM positive was in spring and winter (29% e 26,3%), followed by summer (25%) and autumn (23,5%). About the age of our patients, we found that 62 were under 5 years; of them, 15 (24,2%) were IgM positive(5M and 10F), and 47 IgM negative (75,8%); while 40 pz were over 5 years, 12 (41,6%) IgM positive (9M and 3F) and 28 (58,4%) IgM negative.
Conclusions And Discussion: We found the higher incidence of IgM positivity for MP in winter and spring. The most common clinical form, independently from sex, age and season of the year, was bronchopneumonia. There was no difference in incidence of IgM positivity according to the age of patients. We found, instead, a higher incidence in females among patients under 5 years of age, and in males among the over 5 years ones.

RISK FACTORS OF INVASIVE IRAB INFECTION AMONG COLONIZED PATIENTS IN NEONATAL INTENSIVE UNIT

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Background: Imipenem-resistant Acinetobacter baumannii (IRAB) infection has becoming a serious problem in current neonatal intensive care. Invasive infection could result in increased morbidity and mortality than simple colonization. But there have been few investigations on risk factors of invasive IRAB infection among colonized patients.
Methods: IRAB outbreak was identified in the neonatal intensive care unit (NICU) of Seoul National University Children's Hospital from May 2011 till April 2012. We collected data retrospectively from IRAB-positive 45 patient. They were classified as ‘invasive infection (n=7)' and ‘simple colonization (n=38)'. ‘Invasive infection' was defined as IRAB infection on sterile specimen (bloodstream, cerebrospinal fluid, and pleural fluid), and ‘simple colonization' was as positive results on surveillance cultures of anal swab. We investigated risk factors of ‘invasive infection' and differences of outcomes between ‘persistent infection' and ‘negative conversion' group.
Result: Seven infants developed invasive IRAB infection (15.5%). 1 min-Apgar score (median 4 vs. 1; p=0.018) and patent ductus arteriosus (57.9% vs. 100%; p=0.04) was significantly different between two groups. Clinical risk index for babies II (CRIB II) score (median 8 vs. 14; p=0.051) also was high in II group. Duration of central catheterization, intubation and hospitalization before isolation was not different significantly between two groups. Operation history before isolation has no relationship with invasive infection. Mortality was 15.8% and 42.9% in SC group and II group, respectively (p=0.131). Incidence of all bacterial sepsis was higher in II group than SC group (26.3% vs. 71.4%; p=0.032). Total duration of invasive ventilation (7 vs. 64; p=0.005), central catheterization (31.5 vs. 89; p=0.043) and IRAB isolation (11.5 vs. 68; p=0.035) was significantly longer in II group. Eleven cases had persistent IRAB infection. Prevalence of major anomaly (2 vs. 5; p=0.006), total duration of intubation (5.5 vs. 41; p=0.003), numbers of transfusion after initial isolation (2 vs. 12; p=0.002) and mortality (5.9% vs. 63.6%; p=0.0) was significantly high in persistent infection group. Duration of parenteral nutrition (3 vs. 15; p=0.05) was also was significantly longer in persistent infection group.
Conclusions: The risk factors of invasive IRAB infection were 1 min-Apgar score, patent ductus arteriosus, CRIB II score and the risk factors of persistent isolation were major anomaly, total duration of intubation, transfusion after isolation and duration of parenteral nutrition. Mortality of II group was higher than SC group, although not significant statistically. Close observation and appropriate antibiotic treatment are needed in high risk of invasive infection patients in NICU during IRAB outbreak.

DETECTION OF MARKERS OF HERPESVIRUS INFECTIONS IN FREQUENTLY ILL CHILDREN AND VIRAL EFFECTS ON THE DISEASE COURSE

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Introduction: The role of herpesviruses in the occurrence of acute respiratory viral infection (ARVI) in children has not been studied in sufficient detail. Our objective was to assess etiological validity of herpesviruses (CMV, EBV, HHV-6) in acute episodes of ARVI in frequently ill young children and to study the effects of herpesviruses on the disease severity and duration. Patients and Methods. Seventy frequently ill children (more than 6 ARVI per year) aged 3 months ¬ 3 years (mean 1.8±1.2 years) with clinically manifested disease were examined. DNA of CMV, EBV and HHV-6 was detected by qPCR in blood, urine and saliva. Antibodies were detected by ELISA in blood plasma: IgM to CMV and EBV; IgG to CMV, EBV and HHV-6. Detection of markers of herpesvirus infections and viral load were compared with clinical manifestations and severity of disease.
Results: Markers of CMV-infection were detected in 81.4% (57/70) children. Anti-CMV antibodies were detected in 38.6% (27/70) children. Primary infection (IgM) was revealed in 15.7% (11/70) children under 1 year. IgM and IgG (indicators of aggravation of CMV-infection) were detected in 17.1% (12/70) children. Only anti-CMV IgG (marker of latent infection) were detected in 5.7% (4/70) children. In 37.1% (26/70) children both antibodies and viral DNA were revealed, 4.3% (3/70) out of them suffered from acute infection, as evidenced by the presence of IgM and viral DNA. The presence of IgM, IgG and viral DNA in 14.3% (10/70) children as well detection of IgG and viral DNA in 18.6% (13/70) children may be indicative of CMV reactivation. Markers of EBV infection were revealed in 41.7% (33/70) children. Only anti-EBV antibodies were detected in 20% (14/70) children. Primary infection (only anti-EBV IgM) was not idenified. In 2 children chronic infection was aggravated, as evidenced by the presence of anti-VCA-IgM and anti-NA-IgG. Marker of latent infection (only anti-NA-IgG) was detected in 17.1% (12/70) children. Active EBV infection (anti-VCA-IgM and viral DNA) was revealed in 8.6% (6/70) children. Markers of HHV-6 infection (IgG and viral DNA) were detected in 61.4% (43/70) children. Statistical analysis of the results obtained has shown a higher detection frequency for CMV markers in comparison with makers of EBV: 81.4% vs. 47.1% (?=0.001), and HHV-6: 81.4% vs. 61.4% (?=0.035). Viral load analysis showed that herpesviral DNA concentrations in children with severe ARVI were 10 5.4 ± 10 2.1 copies/ml in comparison with viral load in children with mild course of the disease (10 4 ± 10 1.4), the differences are statistically significant, p = 0.001.
Conclusion: High frequency of markers of herpesvirus infections in children with ARVI was revealed. Detection of CMV, HHV-6 and EBV DNA in high concentrations was associated with the development of disease complications.

EVALUATION AND TREATMENT OF VERY LOW BIRTH WEIGHT (VLBW) INFANTS < 1500G WITH SUSPECTED LATE ONSET SEPSIS (LOS) A CLINICAL PRACTICE SURVEILLANCE FROM COMMUNITY BASED LEVEL III NEONATAL INTENSIVE CARE UNITS (NICU) AFFILIATED WITH A REGIONAL PERINATAL CENT

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Background: LOS occurring in neonates > 3 days is fairly common affecting up to 25% of Very Low Birth weight (VLBW) infants. The diagnostic approach (cultures obtained – Blood, urine and/or CSF), type and duration of antibiotic use (DOA) is reported to vary amongst neonatologists practicing in a RPC. Little is known about community hospital NICU based practices. OBJECTIVE: To determine current diagnostic screening and ABX prescribing practices for VLBW infants with suspected LOS amongst community based neonatologists.
Design/Methods: Prospective data surveillance initiated from five level III NICUs of a RPC (encrypted data from each NICU reported to a centralized data base) on all LOS evaluations done on VLBW infants < 1500g over one year. Data included: symptoms/lab screen abnormality category (CRP, I:T ratio) at the time of a sepsis evaluation (SE), DOL SE initiated, culture results with pathogen distribution (blood, urine and CSF), starting combination and DOA. Predefined clinical findings associated with SE (Table. 2), outcome variables grouped as diagnostic categories and DOA classified as <3 days, 4-8 days and >8 days analyzed (Table.1) and were compared between the diagnostic categories.
Results: 199 infants (BW 903±261 g and GA 27±2.5 weeks) including < 1000 g, n = 140; 1001-1500 g, n=59. Culture Positive sepsis (CPS) was noted in 47 (23%) infants with onset < 1000g 44± 41d; > 1001 29±23d ($p<0.01$). The commonest pathogens were CONS (51%), S.Aureus (12%), Gram Neg Org (25%) Candida (8%). Urine Culture was done in 49% of SE and was positive in 28% (Klebsiella isolated in 33%). CSF was obtained in 22%; all negative. A combination of Vancomycin/Gentamicin was the most common starting choice (45%). For CPS DOA was ≥ 8 days in 66% and with Culture Negative Sepsis (CNS) (n=90) DOA was ≤ 3 days in 66%.

Table 1. Diagnostic Category n (%)	Duration of ABX (DOA) n (%)		
	< 3 days	4-8 days	>8 days
LOS Culture Neg. 90 (45)	59 (66)	23 (26)	8 (8)
LOS Culture Pos. 47 (23)	1(2)	15 (32)	31 (66)
UTI (only) 20 (10)		9 (45)	11 (55)
Resp infection 18 (9)	3 (17)	7(39)	

Table 2. Symptoms/lab screen abnormality category at Sepsis Evaluation (SE)
Respiratory – ↑ apnea (50%)
WBC changes - ↑I:T ratio (38%)
Other – lethargy, ↑ CRP, thrombocytopenia (25%)
Suspect NEC (20%)
Glucose abnormality (7%)
Temperature instability (4%)

Conclusions: This is the first report to document practice surveillance related to LOS in a community hospital NICU setting and describes an incidence and distribution of pathogens consistent with published reports. DOA coverage in most cases (66%) was appropriate for both CPS and CNS cases. Urine culture was only performed in 50% cases however with a surprising high positive yield. These findings are important as a substrate for consensus building guidelines related to LOS evaluation, and targeted antibiotic strategies in the community setting.

EARLY-ONSET NEONATAL SEPSIS - DIAGNOSTIC ACCURACY OF LABORATORY DATA: C-REACTIVE PROTEIN VERSUS IMMATURE/TOTAL NEUTROPHIL RATIO

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Introduction: Accurate and timely diagnosis of early-onset neonatal sepsis (EONS) remains a challenge in Neonatology. In this era of multidrug resistance, it is mandatory to avoid unnecessary use of antibiotics. Rapid diagnostic tests that differentiate infected from non-infected newborns have a significant impact on neonatal care. Laboratory tests most often used for sepsis screening are C-Reactive Protein (CRP) and the ratio immature/total neutrophils (I/T). The aim of this study is to compare the diagnostic accuracy of two laboratory tests in the diagnosis of EONS: CRP and I/T.
Methods: It was performed a prospective study between July and December of 2012 in Braga`s Hospital in which were included newborns with gestational age of =37 weeks and with at least one of the following risk factors for infection: maternal peripartum fever, prolonged rupture of membranes (=18hours), colonization of group B Streptococcus (GBS) without adequate peripartum prophylaxis (according to the CDC-Guidelines 2010) and maternal chorioamnionitis. Septic screening was performed in the newborns with risk of infection with the assessment of the hemogram and CRP at 8-12hours and 24hours of life. The cut-off values used for CRP were <2,90 and =50mg/L; for the I/T ratio was <0,2 and =0,2. The newborns with suspected sepsis (positive septic screening or symptomatology) had microbiological cultures and were admitted to the Intensive Neonatal Unit to start antibiotic therapy. A descriptive statistical analysis and correlation tests between CRP and I/T values and EONS diagnosis were performed (SPSS version 18.0). This study was previously approved by the internal ethical commission.
Result: During the period of the study 1459 newborns were born: 127 (8,7%) had one or more risk factors, 58,2% were female, the average weight was 3294g (±416g), the average maternal age was 30,2years (±5,8), 47,2% had eutocic delivery and 52,8% had dystocic delivery (from these 47,8% were cesarean-section). None required resuscitation at birth. Concerning the risk of infection: 28,3% had peripartum fever, 66,1% had prolonged rupture of membranes, 14,2% had colonization with GBS without adequate prophylaxis and 0,8% had maternal chorioamnionitis. In 11,2%, =1 risk factors were identified. Thirteen newborns (10,2%) were admitted with suspected EONS and eleven were symptomatic. Sensitivity, specificity and negative predictive value for CPR (first and second assessments) was 30,8%/100%/92,2% and 46,2%/100%/94,2%; for I/T was 30%/98,9%/92,9% and 9,1%/100%/91,7%. An association was found between the diagnosis of sepsis and CPR (second collection) - Chi-Square test: p<0,001; and with I/T value (first and second collection) - Fischer test p<0,001 e p=0,004. No microbiologic agent was identified and all newborns completed antibiotic therapy without further complications.
Conclusions: The second collection of CPR had a higher sensibility therefore it is not an adequate early marker (which is according to the literature). The results of the analyzed individually parameters presented low sensitivity but the association of CRP and I/T values improved diagnostic accuracy. Specificity and negative predictive value were >90% for both parameters. Since the use of multiple markers can enhance diagnostic accuracy, the search for the ideal set of diagnostic markers of EONS should be pursued.

HIGHER CRP LEVELS IN VERY LOW BIRTH WEIGHT INFANTS WITH LATE-ONSET SEPSIS CAUSED BY COAGULASE NEGATIVE STAPHYLOCOCCI RESISTANT TO OXACILLIN

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Background and aims: Coagulase negative Staphylococci (CoNS) are most prevalent pathogens in late-onset sepsis (LOS) in very low birth weight (VLBW) infants. The aim of this study was to compare LOS caused by CoNS in terms of virulence and clinical relevance.
Methods: A retrospective observation analysis of all LOS caused by CoNS in VLBW infants admitted to our NICU during a 5-year period (2007 - 2011) was performed. Two groups of LOS were compared: the OXAS group caused by CoNS susceptible to oxacillin and the OXAR group caused by CoNS resistant to oxacillin, in terms of perinatal demographic data, related laboratory signs and clinical data.
Result: There were 68 VLBW infants with LOS caused by CoNS, 16 in the OXAS group (average BW ± SD 825 g ± 292 g; average GA ± SD 26 ± 3.44 wks) and 50 in the OXAR group (average BW ± SD: 725 g ± 232 g; average GA ± SD: 25.29 ± 2.24 wks). The OXAR group presented later day of onset (median ± 95%CL: 8.89 ± 2.08 days vs. 15.6 ± 3.63 days, p = 0,004), higher number of maximum CRP levels (median ± 95%CL: 27.24 ± 13.46 mg/l vs. 50 ± 13,18 mg/l, p = 0.026) as well as higher number of positive blood cultures (median ± 95%CL: 1.28 ± 0.21 vs. 1.84 ± 0.23, p = 0.001). No significantly differ morbidity was found between both groups.
Conclusions: Resistance to oxacillin in CoNS late-onset sepsis has a relevant influence on higher levels of CRP and number of positive blood cultures in VLBW infants.

SEPTIC ARTHRITIS IN NEONATAL INTENSIVE CARE UNIT: A RETROSPECTIVE STUDY

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Background: Septic arthritis is an uncommon, but serious disorder in newborns, especially preterm. It is not fearful of its mortality but because of the potentially late sequelae.We evaluated any cases of neonatal septic arthritis , so they were analysed for clinical, diagnostical, treatment and outcome.
Methods: Diagnosis of septic arthritis was made on the basis of the clinical criteria of Morrey et al. supported by raised CRP values, USG of the hip, and results of the bacterial culture of the aspirated joint fluid and ultrasound and radiological findings.
Result: The cases of septic arthritis reported in the retrospective study(1994-2008) were 10 (7 preterm-3 term infants).The infants shown fever, malaise, and prominent localizing signs at the affected joint.The joint most affected was the knee(7),followed by coxofemoral(3).The pathogen responsible was identified in 8 cases of 10, and in 6 cases(60%) was a gram-negative (67%E. Coli, 33%K. Pneumoniae) and in two cases a Gram positive (33.3%Staphylococcus aureus).These patients were successfully treated with intravenous antibiotics therapy (Cephalosporin, Penicillin, Vancomycin).No complication reported, including complete destruction of the articular cartilage and the underlying epiphysis, loss of the adjacent growth plate, and dislocation of the joint.
Conclusions: Septic arthritis of hip in neonates is a disease with severe long-term disability if not treated promptly.Prematurity and low birth weight predispose the child to frequent bacteraemia and hence septic arthritis. The epidemiology and natural history of neonatal septic arthritis are changing due to early recognition and intervention. The most important prognostic factor in predicting a favourable outcome is early diagnosis and therapy.

OUTCOMES OF VERY-LOW-BIRTH-WEIGHT INFANTS EXPOSED TO MATERNAL CLINICAL CHORIOAMNIONITIS: A MULTICETER STUDY.

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Background: Chorioamnionitis is a recognized risk factor of preterm delivery, however, controversy still persist concerning the relationship between maternal inflammation and neonatal morbidity and mortality.Objective: The purpose of this study was to determine the incidence of clinical chorioamnionitis in our units and its relationship to morbidity and mortality among very-low-birth-weight infants.
Patients and Methods: This was a prospective observational study of a cohort of very-low-birth-weight (VLBW) neonates admitted to 53 Neonatal Intensive Care Units collaborating in the Spanish SEN1500 network, representing about two thirds of all births in Spain, between January 2008 and December 2011. Clinical chorioamnionitis was defined by the presence of maternal fever ≥ 38º C in addition to at least 2 of the following criteria: uterine tenderness, leucocytosis (>15,000 cells/mm3), maternal tachycardia (>100 bpm), foetal tachycardia (> 160 bpm), or foul-smelling vaginal discharge. Demographic characteristics and outcomes were analysed, and a comparison between exposed and non-exposed infants was carried out with multivariate logistic regression analysis.

Outcomes	Adjusted Relative Risk	95% CI	p
RDS	0.716	0.622-0.823	<0.001
Patent ductus arteriosus (PDA).	0.768	0.674-0.876	<0.001
BPD	0.975	0.801-1.187	0.803
Early-onset sepsis	3.050	2.411-3.857	<0.001
Late-onset sepsis	0.841	0.740-0.957	0.009
Necrotizing enterocolitis (NEC)	1.214	0.997-1.478	0.054
Surgery for NEC	1.428	1.130-1.805	0.003
Severe IVH (grades 3 and 4)	0.918	0.757-1.112	0.381
Periventricular leukomalacia	1.073	0.859-1.341	0.535
Retinopathy of prematurity ≥ 3	0.751	0.538-1.049	0.093
Mortality	1.096	0.932-1.290	0.269
Survival without mayor morbidity*	1.006	0.888-1.166	0.937

*Mayor morbidity includes severe IVH, PVL, BPD, NEC or ROP.

Result: During the study period, 11464 VLBW infants were admitted to our units; 9535 (83.2%) had full data collected and were included. Of these, 1497 (15.6%) were exposed to maternal clinical chorioamnionitis. The incidence of exposure to clinical chorioamnionitis was higher at lower gestational ages: 34.2% at 22-26 weeks, 15.9% at 27-30 weeks, 4.4% at 31-34 weeks, and 1.6% at > 34 weeks (p < 0.001). The main results after adjusting for gestational age and birth weight are summarized in the table.Mortality was higher among infants exposed to maternal chorioamnionitis (22.4% v 12.5%; p<0.001), but this association disappeared after adjusting for GA and BW. Length of stay (days) until discharge home was higher in the chorioamnionitis group [mean (SD)]: 68.9 (32.4) v 53.9 (30.3); p<0.001, but this difference also disappeared after correcting for GA and BW. Time to death (days) was similar in both groups: 13.8 (24.7) v 14.8 (24.2); p=0.483.
Conclusions: The incidence of maternal clinical chorioamnionitis increases with decreasing GA, and is associated with a reduction in acute RDS and PDA in VLBW infants, but with a higher risk of early-onset neonatal sepsis, which are independent of GA and BW. After adjusting for GA and BW, there were no differences in survival or in survival without major morbidity.

CENTRAL CATHETER ASSOCIATED SEPSIS IN NEONATES: INCIDENCE AND ASSOCIATED FACTORS

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Introduction: The advent of the central catheters (CC) has played a significant role in modern medicine. The CC, are used in monitoring and therapy of critically ill patients. The catheter-related sepsis (CRS) is a common problem in health care, increased morbidity, mortality and costs, one reason for premature removal of the same and an explanation of the increase in the cost and use of hospital resources. It is estimated that in the United States of America (USA) was inserted about five million CC per year. The CC is responsible for approximately 250,000 cases per year of nosocomial bacteremia, although some estimate that can become 400,000 cases per year. The objectives of this study were to identify the cumulative incidence, incidence density and the factors associated with the SAC in a Neonatal Intensive Care Unit in Colombia, between 2005 and 2011.
Patients and Methods: prospective dynamic cohort study conducted in infants who were 743 inserted CC. We found the cumulative incidence and incidence density with confidence intervals of 95% (95%). With Stata ® 11.0 was identified by multivariate analysis using logistic regression, factors associated with catheter-related sepsis.
Result: During the assessment period occurred between 743 CRS 18 CC with a cumulative incidence of 2.4 per 100 CC (95% CI: 1.3-3.6 per 100 CC) and incidence density 4.3 CRS for 1000 days CC (95% CI: 2.5 to 6.8 CRS per 1000 days CC). Other complications included local infection (0.1%) and pneumothorax (0.1%). No differences were found between GA at birth, birth weight, age, income and gender (p> 0.05). The isolated bacteria were: Staphylococcus epidermidis seven (38.9%), Escherichia coli 4 (22.2%), Klebsiella pneumoniae 3 (16.7%), Staphylococcus hominis, other coagulase-negative Staphylococcus, Empedobacter brevis, Staphylococcus aureus with 1 (5.6%) each. The factors that best predict overall catheter-related sepsis were hospital stay prior to the insertion of CC = 3 days (aOR: 7.3, 95% CI: 2.2 to 24), Use of DC to administer parenteral nutrition (aOR: 4.1, 95% CI 95%: 1.2-13.8), more than three punctures to over CC (aOR: 3.9, 95% CI: 1:1-14) and permanence of percutaneous = 10 days or subclavian CC >15 days (aOR: 3 CI 95%: 1.1-9,3). The model has a sensitivity of 94.4% (95% CI: 81.1 to 100%), when only one variable is present, to a specificity of 99.4% (95% CI: 98.8 to 100%) when the four model variables are present. The area under ROC of the model is 0.863 (95% CI: 0.765 to 0.962), identifying the ideal cut for Model 2 or more variables present.
Conclusions: The cumulative incidence and incidence density of catheter-related sepsis in our series is similar to that found in the literature. Factors associated with the CRS are multiple and point to the need to review the indications for central catheter insertion, the techniques used for placement and maintenance.

PREDICTORS OF MORTALITY IN NEONATAL BACTERIAL INFECTION

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Introduction: Sepsis, a major cause of neonatal mortality, causes 41% of deaths in children under 5 years. Objective: To identify predictors of mortality in neonates with serious bacterial infections (SBI) in a Neonatal Intensive Care Unit (NICU).
Patients and Methods: Prospective cohort study with 120 infants with SBI, which killed 19. The analysis included descriptive statistics, bivariate analysis, multivariate logistic regression (LR) and methodology of classification and regression trees (CART).
Result: The model derived from the LR included: Leukopenia less than 5000/mm3 (aOR: 7.6, 95% CI: 1.8 to 32.5), birth weight less than 1500 g or gestational age less than 33 weeks (aOR: 5.5, 95% CI: 1.8 to 16.3), cardio-hemodynamic compromise with o without administration of inotropes (aOR: 4.9, 95% CI: 1,318,4), hyperglycemia greater than 126 mg / dL (aOR: 4.4, 95% CI: 1.3 to 15.7) and respiratory compromise with o without mechanical ventilation (aOR: 2, 95% CI: 1.2 to 10.6), with sensitivity of 80% (95% CI: 60-100%), specificity 82.2% (95% CI: 74.2 to 90%), positive predictive value 45.5% (95% CI: 27-64%), negative predictive value 95.4% (95% CI: 90.4 to 100%), with area under ROC of 0.806 (95% CI: 0.704-0.907). The CART model included: birth weight, intrauterine growth restriction, leukopenia, mechanical ventilation, inotropic, hyperglycemia and cerebrospinal fluid culture positive, with sensitivity of 84.2% (95% CI: 65.2 to 100%), specificity 98% (95% CI: 94.8 to 100%), positive predictive value 88.9% (95% CI: 71.6 to 100%), negative predictive value 97.1% (95% CI: 93.3 -100%), with area under ROC of 0.911 (95% CI: 0.826 to 0.997). The deaths were associated with pneumonia, meningitis, sepsis, necrotizing enterocolitis, sepsis and central catheter-associated urinary tract infections.
Conclusions: Associated infections in health care (23.4%) and not associated with health care (11%) are major causes of mortality. Prematurity and low birth weight are determinants of mortality, with the <1,500 g (47.4%) and = 32 weeks (57.9%), the most affected. LR model has excellent performance in predicting neonatal mortality in IBG. Using CART analysis excluded variables included in the RL, with equal predictive performance.

FGF10 OVEREXPRESSION AFTER HYPEROXIC INJURY TRIGGERS DE NOVO ALVEOGENESIS IN A MOUSE MODEL OF BRONCHOPULMONARY DYSPLASIA

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Background and aim: Bronchopulmonary dysplasia (BPD), the chronic lung disease of preterm infants, is characterized by impaired alveolar growth and pathologic vascularization. The specific molecular mechanisms associated with BPD are still not well known. Fibroblast growth factor 10 (FGF10) is known to play an important role in lung morphogenesis. We previously showed that Fgf10 overexpression elicits a protective effect on hyperoxic lung injury when overexpressed DURING the injury phase. Now we aimed to investigate the role of Fgf10 AFTER hyperoxic injury in a mouse model of BPD using loss-of-function and gain-of-function approaches. We also investigated the role of FGFR2b (main receptor for FGF10) signaling in normal alveogenesis and determined the consequences of long-term ubiquitous Fgf10 overexpression in mice.
Methods: 1) Rosa26rtTA/+;tet(O)solFgfr2b/+ (= loss-of-function) pups in normoxic conditions were fed or not with doxycycline food from P0 to P45 and the lungs were analyzed by measuring the mean linear intercept (MLI), alveolar airspace and septal wall thickness as well as histology. 2) Using Rosa26rtTA/+;tet(O)solFgfr2b/+ (= loss-of-function) and Rosa26rtTA/+;tet(O)Fgf10 (= gain-of-function) mice, we established a BPD model by exposing the pups to 85% oxygen from P0 to P8 (experimental group). Pups exposed to normoxia are considered as controls. From P9 through P45, the pups of each group were exposed to normoxia and fed either with normal food or doxycycline food to activate the transgene soluble Fgfr2b (encoding a dominant negative receptor for FGF10) or the transgene Fgf10. Morphometry analysis was carried out on the lungs at P15 and P45. 3) To study the tolerance of the mice to Fgf10 overexpression the Rosa26rtTA/+;tet(O)Fgf10/+ transgenic mouse line was exposed to doxycycline for 2 weeks. Then survival rate, histology, Ki67 and TUNEL staining were performed.
Result: 1) Blockade of FGFR2b ligands activity from P0 through P45 did not perturb normal alveogenesis. 2) Overexpression of soluble Fgfr2b has no impact on the 'repair process' after hyperoxic injury. 3) In contrast, the hyperoxia group with overexpression of Fgf10 significantly showed less alveoli simplification compared to the hyperoxia exposed pups without overexpression of Fgf10. The results from MLI, alveolar airspace and septal wall thickness showed significant differences. 4) Fgf10 overexpression after hyperoxic injury does not increase mortality. 5) Fgf10 overexpression for a two week period is well tolerated and effects (weight loss, mucosal proliferation) are completely reversible. 6) Fgf10 overexpression causes hypercellularity with no impact on apoptosis.
Conclusions: FGF10 triggers de novo alveogenesis after hyperoxic injury, is well tolerated when overexpressed ubiquitously and could therefore be used as a potential therapy for BPD. We are now focusing on determining the role of FGF10 signaling in de novo secondary septa formation. Our preliminary data indicate that FGF10 acts on specific mesenchymal cells relevant for BPD pathogenesis.

A DIFFERENT SECRETION PATTERN OF TRACHEAL ASPIRATE EXTRACELLULAR MATRIX COMPONENTS AND A POTENTIAL ROLE OF TENASCIN C IN THE DEVELOPMENT OF BRONCHOPULMONARY DYSPLASIA.

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Objectives: Injury and remodeling of the extracellular matrix (ECM) of an immature lung is a feature of bronchopulmonary dysplasia (BPD), in which inflammation and proteolytic degradation of lung tissue are increased by various elastases. Indeed, one of the representative ECM components, fibronectin, has been shown to be increased in preterm infants who develop BPD. The objective of this study was to simultaneously investigate time-dependent changes in the levels of several ECM components in tracheal aspirates, including fibronectin, hyaluronan and tenascin C, and their correlations with the level of TGF-beta1 to verify whether these molecules are still useful predictive biomarker for modern bronchopulmonary dysplasia (BPD).
Study Design: We conducted a prospective study of preterm infants with a gestational age < 28 weeks who received mechanical ventilation from the first day of life. Tracheal aspirate fluid was collected within 48 hours, and every week until four weeks of life, and the levels of hyaluronan, fibronectin, tenascin C and TGF-?1 were measured using ELISA assays. BPD was defined based on the oxygen requirement at a postmenstrual age of 36 weeks.
Results: A total of 79 infants were enrolled. Compared to the infants without BPD (n=50), those with BPD (n=29) exhibited higher median tenascin C levels at one and two weeks of life (710 vs. 282 ng/ml P=.008, and 995 vs. 302 ng/ml P=.009, respectively) and higher median fibronectin (7,024 vs 4,150 ng/ml P=.011) and hyaluonan (746 vs 515 ng/ml P=.039) levels only at two weeks of life. The receiver operator characteristic analysis indicated that the tenascin C levels at two weeks of life were the most predictive for the development of BPD (area under the curve: 0.75 sensitivity: 0.66 specificity: 0.79 P=.004). The levels of hyaruonan, but not tenascin C, correlated well with that of total TGF-beta1 from two to four weeks of life (TGF-beta1 vs. fibronectin: r=0.41 p =.004 at two weeks, r=0.65 P =.0002 at three weeks and r=0.91 P <.0001 at four weeks and TGF-beta1 vs. hyaluronan: r=0.38 p =.019 at two weeks, r=0.51 P =.007 at three weeks and r=0.89 P <.0001 at four weeks)
Conclusion: In this study, we presented data discussing the significance of tracheal aspirate ECM components in preterm infants and the associations of these components with the development of BPD. Finally, we found that an increased level of tenascin C, but not fibronectin and hyaluronan, in tracheal aspirate is closely associated with the development of BPD and is thus presumed to be a good early marker of lung injury in the pathogenesis of BPD. Furthermore, it is more likely that tenascin C, in addition to being a predictive biomarker for BPD, plays a crucial role in the pathogenesis of BPD. The findings of this study provide potential insights into the pathogenesis of BPD.

HISTONE MODIFICATIONS ARE ALTERED IN THE RENAL CORTEX OF FORMER CHRONICALLY VENTILATED PRETERM LAMBS

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Background: Preterm neonates who recover from neonatal chronic lung disease (CLD) frequently have long-term impairments. The molecular basis of long-term impairments is poorly understood. We recently showed that long-term impairments in the lung and brain are related to epigenetic alterations in histone covalent modifications. Histone covalent modifications influence regulation of gene expression. Changes in histone covalent modifications are triggered by abrupt changes in environment, such as preterm birth followed by prolonged mechanical ventilation (MV) with oxygen-rich gas. Whether changes in histone covalent modifications also occur long-term in the kidney of former preterm lambs that had been supported by MV and oxygen-rich gas is not known. We hypothesize that a course of mechanical ventilation followed by non-invasive ventilation in preterm lambs affects histone modification in kidneys beyond the neonatal period. Objective: We hypothesized that histone covalent modifications will be altered in the kidney after ~3 months or ~6 months of recovery from preterm birth and prolonged MV.
Design/Methods: Pregnant ewes were given dexamethasone before delivery of preterm lambs (~128d gestation [equivalent to ~28wk gestation in humans]). The preterm lambs were intubated, given surfactant, managed by MV for 3 days, weaned to high-frequency nasal ventilation (HFNV) (a variant of continous positive airway pressure CPAP) for 3 days, weaned from ventilation support, and lived for ~3 months or ~6 months more (preterm weaned; n=6). The recovered preterm lambs were equivalent to ~2 years or ~6 years postnatal age, respectively, in humans. Postnatal age-matched control lambs were born at term gestation (~3 weeks after the preterm lambs were delivered) and lived for 8 weeks (T+8wk control; n=5) or 17wk (T+17wk control; n=3). Lambs were fed ewe's colostrum and milk. Renal cortex was analyzed by immunoblot for trimethylated (me3) histone 3, lysine 4 (H3K4me3), H3K36me2, acetylated H3K9 (H3K9ac), H3K14ac, and H3K18ac. We chose these histone modifications because they are altered in the lung and brain of recovered former preterm lambs. Statistical significance was not tested because of small sample size per group.
Result: Former preterm lambs appeared to have less protein abundance of H3K4me3 at ~3mo (1.18±0.17 arbitrary normalized densitometry units; mean±SD) and ~6mo(0.91±0.04) compared to T+8wk controls (1.68±0.72) and T+17wk controls (3.23±2.26). H3K36me2 appeared to be less at ~3mo (1.10±0.53), but not at ~6mo (0.86±0.66) compared to T+8wk and T+17wk controls (1.41±0.43 and 0.85±0.29, respectively). H3K18ac and H3K9ac appeared to be less at ~3mo (1.01±0.45 and 0.01±0.01, respectively) compared controls 0.59±0.47 and 0.003±0.005, respectively). However, both H3K18ac and H3K9ac appeared to be more at ~6mo (4.87±3.58 and 0.02±0.01, respectively) compared to T+17wk controls (2.64±0.44 and 0.03±0.02, respectively). H3K14ac protein abundance appeared to be more at ~3mo (5.49±5.29) compared to T+8wk control (0.66±0.58), and less ~6mo (1.63±0.60) compared to T+17wk controls (0.80±0.15).
Conclusions: Histone covalent modifications appear to be altered in the kidney after ~3mo or ~6mo of recovery from preterm birth and prolonged MV. Our results are novel because they are among the first to identify epigenetic molecular responses in the kidney in former preterm neonates after a course of ventilation.

CIRCULATING ENDOTHELIAL PROGENITOR CELL WAS DECREASED IN INFANTS WITH BPD AND INHALED NITRIC OXIDE RAISED EPC NUMBER

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Introduction/Background: Recent evidence indicated that reduction of endothelial progenitor cells (EPCs) may participate in the development of bronchopulmonary dysplasia (BPD). Attentions have been given to the role of inhaled nitric oxide (iNO) in the prevention of BPD. However, the dynamic changes of EPC after birth and the mechanisms underlying the effects of iNO on BPD remain to be clarified.
Patients and Methods: Sixty-five infants with gestational age of less than 32 weeks or a birth weight less than 1500 g were included in this study. NO was administered to infants who receiving mechanical ventilation or CPAP at least 2 days between 7 and 21 days. EPC level was determined by flow cytometry at different time points (birth, 7, 21, 28 days of age and 36 weeks' PMA) and before and after the iNO treatment. Plasma concentrations of vascular endothelial growth factor (VEGF), stromal cell-derived factor-1 (SDF-1) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were determined by immunochemical assays.
Result: Twenty-five neonates developed BPD, thirty-five neonates survived without BPD and five infants died within 72 h after birth. The percentages of CD34+ cells, CD133+ cells were lower at 7 days than that at birth. The level of EPC was decreased at day 7 in infants who later developed BPD compared with no BPD infants (CD34+KDR+: 0.020[0.009-0.026] vs. 0.026[0.013-0.042]; KDR+CD133+: 0.004[0-0.015] vs. 0.008[0.004-0.013]; CD34+KDR+CD133+: 0.004[0.002-0.007] vs. 0.007[0.004-0.012], $P<0.05$). At day 21, the CD34+KDR+CD133+ cells were lower in infants with BPD than those without (0.002[0.001-0.005] vs. 0.004[0.003-0.010], $P<0.05$). Meanwhile, BPD infants had a persistent lower VEGF concentration compared with the no BPD infants from birth to day 21 of postnatal age. No difference was found in the plasma SDF-1 level between infants with BPD and without at any time points although there was a trend of decrease in BPD infants. No difference was found at day 28 or 36 weeks' PMA between the two groups. Moreover, the percentage of KDR+CD133+ and CD34+KDR+CD133+ cells was lower in severe BPD than in mild and moderate BPD infants ($P<0.01$). Importantly, we found the iNO treatment raised the circulating KDR+CD133+ and CD34+KDR+CD133+ EPC number (0.004[0.002-0.008] vs. 0.008[0.004-0.030], 0.004[0.002-0.007] vs. 0.007[0.005-0.024], respectively, $P<0.05$) along with the increase of plasma VEGF (289.7±101.2 vs. 554.5±259.7, $P<0.05$). No difference was found in the SDF-1 and GM-CSF level pre and post iNO treatment.
Conclusions: The level of EPC was decreased in infants with BPD compared with those without at day 7, and inhaled NO raised EPC level along with the increase of VEGF concentration. Further studies are needed to elucidate the mechanism of the decrease in EPC and VEGF in BPD infants and to investigate the role of iNO treatment in the prevention of BPD.

EPITHELIAL NOTCH ACTIVATION IS ESSENTIAL FOR ALVEOLAR MYOFIBROBLAST DEVELOPMENT AND ALVEOGENESIS

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Background: We have previously reported that Notch signaling regulates the balance secretory and ciliated cells in airways. However, the role of Notch signaling in postnatal lung development, including alveologenesis and airway epithelial homeostasis, is less clear.
Methods: We inactivated Notch signaling conditionally in the lung using mice carrying floxed alleles of the Pofut1 gene, which encodes an O-fucosyltransferase essential for Notch-ligand binding, and a Shh-Cre deleter mouse line, which targets the whole lung endoderm before bud formation. Immunohistochemistry, cell culture and transfection assays were used for analysis of the lung phenotype.
Result: Pofut1F/-;ShhCre/+ pups failed to thrive from postnatal day 3 and the mortality rate was around 80% within 2 weeks after birth. Clara cells did not form and the airways were lined by a thin metaplastic squamous epithelium. The distal differentiation, including formation of alveolar sacs and type I and type II cells, was not affected. However, poor alveologenesis resulted from less secondary crest and myofibroblast was found in postnatal mutant lungs. This phenotype was reminiscent of that seen in bronchopulmonary dysplasia (BPD) in preterm infants.
Conclusions: The data suggested that Notch signaling is required for normal alveologenesis and to maintain airway epithelial homeostasis during the postnatal period. The model shares some features with that of BPD models and may contribute to understand how abnormalities arise in the alveolar compartment of neonates.

TREATMENT OF PRETERM LAMBS WITH SEVERE SURFACTANT DEFICIENCY WITH A NEW SYNTHETIC SURFACTANT CONTAINING SP-B AND SP-C ANALOGUES

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Background: Synthetic surfactants (SF) are appealing; however, to date clinical responses to SF treatment indicate superiority of animal-derived surfactants. A new synthetic SF (CHF5633) containing SP-B and SP-C analogues has been developed and has been shown in a number of pre-clinical models to convey stability and a prolonged duration of action. The aim was to compare the short-term efficacy between CHF5633-treated and untreated preterm lambs with severe RDS.
Methods: 14 preterm lambs (80-90%GE) delivered by cesarean section were assigned to receive a CHF5633 bolus (200mg/kg, n=7), or only gas ventilation (control, n=7). Animals were managed for 6h on IMV. Cardiovascular parameters, PaCO2, PaO2, pH, Oxygenation Index (OI), Ventilation Efficacy Index (VEI), dynamic compliance (Cdyn), and tidal volume were measured.
Result: No significant differences were found between groups in any of the studied parameters, neither at fetal life nor at baseline. One animal in the control group died after 180 min of IMV. The treatment with CHF5633 significantly improved PaCO2, PaO2, pH, OI, VEI and lung mechanics in comparison to control animals ($P<0.0001$, Two-way ANOVA). 15 min after CHF5633 bolus treatment, PaO2/FiO2 ratio, PaCO2, pH, OI and VEI had already significantly improved in comparison to untreated control animals ($P<0.05$, One-way ANOVA). At baseline both groups showed very low Cdyn values (controls 0.08±0.04; CHF5633 0.06±0.04 ml/cmH2O/kg); CHF5633 treatment, however, significantly improved Cdyn in comparison to controls already at 30 minutes after surfactant therapy (controls 0.13±0.04; CHF5633 0.23±0.07 ml/cmH2O/kg, $P<0.05$, one-way ANOVA). In the period between 30 and 180 min, the heart rate was significantly higher in control animals (at 180 min: controls 196±33; CHF5633 141±48 bpm). MEAN±SD
Conclusions: In preterm lambs with severe surfactant deficiency, CHF5633 bolus treatment improves gas exchange and lung mechanics, and therefore, holds potential for the treatment of infants with RDS. The study was supported by CHIESI Farmaceutici S.p.A.

EFFECTIVENESS OF THREE TYPES OF EXOGENOUS SURFACTANT IN PRETERM INFANTS WITH HYALINE MEMBRANE DISEASE

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Introduction: hyaline membrane disease (HMD) is a complication that causes higher mortality in preterm infants, with exogenous surfactant administration standard therapy in this disease. Many studies establishing the benefits of this treatment in improving survival, bronchopulmonary dysplasia and reducing the incidence of pneumothorax. Several commercial surfactants, the most used the poractant alfa (Curosurf ®) and beractant (Survanta ®), and other less commonly used in our country as the bovactant (Alveofact ®). Most studies have been performed poractant alpha and beractant, which have been compared at different doses, while most bovactant jobs are observational and conducted in Europe. Objective: The objective of this study to compare the efficacy in terms of time of ventilation, oxygenation time, adverse events and complications in the administration of three types of surfactant poractant alpha, beractant and bovactant at currently recommended doses, and standardized the Neonatal Intensive Care Unit of Fundación Hospital San José de Buga, Colombia, between 2005 and 2012.
Patients and Methods: Retrospective cohort study with 93 preterm infants = 24 weeks and = 500 g birth weight for each surfactant 31. Exposition: 1st dose administration bovactant (Alveofact ®) 50 mg / kg, beractant (Survanta ®) 100 mg / kg initial and poractant alfa (Curosurf ®) 200 mg / kg. Outcomes: Mechanical ventilation time, duration of oxygen therapy, hospital stay, need for second dose of surfactant, adverse events surfactant administration and complications of prematurity. We assessed mortality, bronchopulmonary dysplasia (BPD) and mortality or BPD. Statistical analysis: Using Stata ® 11.0, using Chi2 or Fisher exact test for qualitative variables and ANOVA tests or Kruskal-Wallis test for quantitative and relative risk (RR) for associations, all with confidence interval of 95%.
Result: There were no differences for sex, weight and gestational age at birth. No statistically significant differences were found for duration of mechanical ventilation, duration of oxygen therapy, administration of a second dose of surfactant, hospital stay and complications. Adverse events occurred surfactant administration for poractant alpha and beractant. There were 30 (32.3%) deaths, 8 (25.8%) for bovactant, 10 (32.3%) beractant and 12 (38.7%) poractant alpha (p> 0.05). Mortality and / or DBP occurred in 10 (32.2%) neonates with bovactant, 10 (32.2%) with beractant and 14 (45.2%) with poractant alpha (p> 0.05).
Conclusions: Despite the differences in the composition and biophysical properties of the three surfactants doses, there were no statistically significant differences in the primary and secondary outcomes of infants between the three surfactants tested were very similar, taking into account the limitations of the work.

MOLECULAR AND ULTRASTRUCTURAL CORRELATES OF DIFFUSE LUNG DISEASE ASSOCIATED WITH SP-C MUTATIONS

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Background: Surfactant protein C mutations manifestations span from neonatal respiratory distress syndrome to adult familial pulmonary fibrosis. Besides transplant, early therapies may stabilize or improve symptoms but diagnosis is often delayed due to phenotypic and genotypic variability. The goal of this study was to identify surfactant-related genetic disorders in children 0-18 year-old with idiopathic diffuse lung diseases, and to determine the prevalence of SP-C mutations and their clinical and ultrastructural correlates.
Patients and Methods: Eligibility criteria were either unexplained, progressive neonatal-onset respiratory distress syndrome or chronic unexplained respiratory symptoms, plus diffuse lung disease on lung imaging. We sequenced SFTPC (the SP-C coding gene), SFTPB and ABCA3 in 87 patients, plus NKX2.1 (TTF-1) in a subset, over a 5-year period. We present here the correlations between genetic and clinical findings, plus lung tissue morphology, ultrastructure and surfactant proteins expression in the 5 patients who underwent lung biopsy. We compared these results with a cohort of 63 adults in whom we previously sequenced SFTPC.
Result: 8/87 children (9%) were SP-C mutation carriers, 7 of which mono-allelic (heterozygous) and 1 bi-allelic (double heterozygous). ABCA3 mutations were found in 14 (16%), TTF-1 deficiency in two (2%) and other genetic conditions in six (7%). No mutations were found among adults. Among SP-C mutants, median age at onset was 6 months, in occasion of a bronchiolitis episode in 4; 2 patients died, 3 were on oxygen and 2 on room air at a median follow-up of 25 months. 3 carried the I73T mutation and 1 E66K, both located in the non-BRICHOS sequence of the C-terminus propeptide. We identified 3 new mutations, A155P, P173H and V102M, all in the BRICHOS domain. Lung morphology consisted of desquamative interstitial pneumonia, but immunolabeling and transmission electron microscopy showed specific anomalies, consisting of abnormal intracellular surfactant, plus misfolded protein response in BRICHOS mutants, and aberrant proSP-C trafficking in non-BRICHOS.
Conclusions: In the Italian population SP-C mutations typically present in infancy, with variable clinical course and outcomes in part due to environmental factors. Electron microscopy studies showed specific type II cell anomalies that may be useful for early diagnosis if validated in future studies.

DEVELOPMENT OF A NEONATAL UPPER AIRWAY MODEL FOR IN VITRO AEROSOL DEPOSITION TESTING: CHARACTERIZATION OF AEROSOLIZED SURFACTANT FOR RESPIRATORY DISTRESS SYNDROME

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Background: Aerosolized surfactant is a promising technique to treat neonatal Respiratory Distress Syndrome (RDS). However, aerosol delivery to neonates is complex and few studies have addressed its feasibility in vitro.
Methods: A computer-design of an infant airway model was drawn in CAD, and 3D pieces were printed by means of rapid prototyping. Natural surfactant aerosols were produced by a pneumatically-driven intratracheal inhalation catheter (driving pressure range 4-6bar). Characterization of surfactant aerosols (particle size and distribution) was performed using Time of Flight technology. Further, deposition of surfactant aerosols within the thermoplastic model of the upper airways was measured.
Result: The printed neonatal tracheobronchial airway model successfully passed the quality control. Maximum surfactant aerosol production rate was achieved at 6bar (0.39±0.01ml/min; 31.54±0.52mg/min). Although a high percentage of deposition of the aerosolized mass (between 23.75±6.45% 4bar and 26.48±11.43% 6bar) was deposited within the printed model, the highest percentage of mass (between 64.95±7.40% 4bar and 66.43±11.46% 6bar) was measured beyond the exit of the model. The Mass Median Aerodynamic Diameter (MMAD) ranged between 8.52±0.16µm (6bar) and 9.36±0.35µm (4bar); higher MMAD values (13.26±3.41µm) where measured at the exit of the printed model.
Conclusions: Surfactant aerosolization seems to be feasible and holds potential as a treatment for RDS; however, further research is needed to adapt current technology to the requirements of the neonatal population.

A RETROSPECTIVE STUDY: DOES THE USE OF NASAL CPAP IN TERM INFANTS LEAD TO AN INCREASED INCIDENCE OF PNEUMOTHORACES?

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Introduction: Spontaneous pneumothoraces are a recognised cause of respiratory distress in neonates, the incidence of which is reported to be 1-2% in term infants. The risk is increased in neonates who require resuscitation at birth, CPAP or mechanical ventilation. In the Regional Neonatal unit in Belfast, Northern Ireland, Neonatologists had observed that the practice of using nasal CPAP in term infants with signs of respiratory distress had possibly increased. There was also anecdotal reporting that the rate of pneumothoraces had increased in this group of patients. Was the use of nasal CPAP in term infants with respiratory distress leading to an increased incidence of pneumothoraces? This study was designed to investigate this hypothesis. Objective The aim of the study was to examine whether the use of nasal CPAP in term infants for symptoms of respiratory distress may have led to an increase in the frequency of pneumothoraces.
Methods: Details of all patients between 1st January 2006 and 31st August 2012, who were admitted to the Regional Neonatal Unit, and coded with the diagnosis of pneumothorax, was requested from the coding department. This yielded 113 patients. Exclusion criteria then included gestation <37 completed weeks, congenital and pulmonary abnormalities including congenital diaphragmatic hernia and pulmonary hypoplasia. This produced a total study population of 36 patients. These 36 patient charts were then examined by the two authors and details recorded on a pre-agreed proforma. This included baseline information, mode of delivery, resuscitation, signs of respiratory distress, diagnoses, respiratory support prior to pneumothorax, intervention required and outcome measures.
Results: 47% of cases were delivered by elective c-section, 19% by emergency caesarean section and 17% by instrumental delivery. 75% did not require any resuscitation at birth and only 28% had symptoms of respiratory distress at delivery. . 50% of patients had a birth weight over 3.5kg. . 25% of patients had NCPAP prior to developing a pneumothorax. . 50% required an urgent needle thoracocentesis and further 39% went on to have a chest drain inserted. . We observed that from 2006-2011 only 1-2 patients per year who developed a pneumothorax had received nCPAP prior to diagnosis. However, in 2012 80% had received nCPAP prior to detection of an air leak. This may explain the anecdotal evidence that formed the hypothesis. .Incidence of Respiratory Distress Syndrome and Transient Tachypnoea of the Newborn were unchanged throughout the study. .In terms of outcome 78% were discharged home and 22% transferred to another neonatal unit for level 3 care.
Conclusions: We have demonstrated that the rate of pneumothoraces does not seem to be significantly increasing throughout the course of the study. However, the use of nCPAP in this group of patients was higher in 2012 than prior years and the 2012 incidence of pneumothorax was at the upper end of the range. It was interesting to note the high proportion of these infants (47%), with a diagnosis of pneumothorax, who had been born via an elective caesarean section. This may be explained by the increased risk of TTN with this mode of delivery.

AN AUDIT OF NEONATAL PNEUMOTHORAX CASES ON THE NEONATAL INTENSIVE CARE UNIT AT CHELSEA AND WESTMINSTER HOSPITAL

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Background: Chelsea and Westminster Hospital's neonatal intensive care unit (NICU) is a tertiary unit and a designated neonatal surgical unit in the UK. The prevalence of pneumothorax on the NICU has never been determined.
Aims: 1. To review cases of pneumothorax on NICU over a two-year period 2. To determine important associated factors in identified cases of pneumothorax
Patients And Methods: A retrospective audit from case note review of pneumothorax cases between 01/06/2009 and 31/05/2011 in the NICU at Chelsea and Westminster Hospital, UK. Data was collected using a data collection form.
Results: 39 cases of neonatal pneumothorax were identified, giving an overall prevalence of 3.2%. The prevalence in term neonates (at least 37 weeks gestation) was 4.0%. In preterm neonates (<37 weeks gestation) the average prevalence 2.5%, more specifically 9.1% in neonates delivered at <26 weeks gestation, 1.5% in neonates delivered at 26-30 weeks gestation and 1.8% in neonates delivered at 30-36 weeks gestation. Respiratory Distress Syndrome was the commonest cause of pneumothorax (59%). Low birth weight and delivery by Caesarean section were associated with pneumothorax and 70% of those with pneumothorax had a CRP >10, indicating sepsis. Over 50% of the neonates delivered by Emergency Caesarean section with pneumothorax had evidence of sepsis prior to developing pneumothorax.
Conclusions: Prevalence of neonatal pneumothorax on NICU was 3.2%, with the highest prevalence in term and very preterm neonates. Sepsis may have been an important contributory factor to the development of pneumothorax. It was not possible to compare prevalence in this NICU with other centres due to a lack of equivalent studies.

FIVE-YEAR TREND OF AIR LEAK SYNDROME (ALS) IN INFANTS ADMITTED TO A LEVEL III NICU - MAINLY A PROBLEM IN LATE PRETERM INFANTS?

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Background: Pneumothoraces or air leak syndrome (ALS) is a serious complication for newborn infants, especially in preterm and ventilated infants. Risk factors for ALS may include ventilation strategy/management, underlying pulmonary pathology or antenatal management such as antenatal steroids. The aim of this study was to investigate any change in the incidence of ALS in our Level III NICU over last 5 years. Method: This is a retrospective observational study. ALS was defined as any pulmonary air leak that required drainage (transient or continuous) as per the criteria established by the Australia and New Zealand Neonatal Network (ANZNN). Clinical and demographic details of infants with ALS, over 5-years (2006-2011, inclusive) were retrospectively accessed from the neonatal database.
Result: Over 5 years, there were 2254 admissions to Level III NICU care. 63 of these infants (2.8%) had ALS (viz. comparative ANZNN rate 4.9%). The incidence in VLBW infants had decreased from 4.3 %(16/370) in 2006 to 1.3%(5/383) in 2011; inversely related to gestational age. Among ventilated infants, 5.1%(63/1237) had ALS with a declining trend of 7.4% in 2006; as compared to 2.6% in 2011. The mean (±SD) gestation and birth weight in infants with ALS were 32.6(±5.3) weeks and 2066(±1008) grams, respectively. The majority of cases occured in infants >32 weeks gestation. 60% of infants with ALS (38/63) had a diagnosis of respiratory distress syndrome (RDS) recorded. Three-quarters (46/63) received surfactant, with the majority (44/63; 96%) administered before the airleak diagnosis was made. 92%(58/63) required ventilation with median duration of 41 hours (IQR: 5-157). 40%(25/63) required HFOV treatment, of which 50% died (13/25). The median time to air drainage was 22.5hrs (IQR: 4-48). Nearly a quarter died - with the greatest rate in infants at 28weeks (44%). The rates of intraventricular haemorrhage (IVH) were 22%(12/63) with grade =3 in 1/3 of them. The need for HFOV therapy was associated with an increased mortality risk with adjusted OR (95% CI) of 10 (1.8 - 59).
Conclusions: The incidence of ALS in our NICU shows a declining 5-year trend. ALS in our NICU is associated with significant mortality and morbidity in the most preterm. The majority of cases of ALS occurred in infants >32 weeks gestation.

IS WEIGHT TO HEIGHT RATIO A GOOD INDICATOR OF BODY FAT IN 3-7 YEAR CHILDREN ?

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Background & Aims: In adults, waist-to-height-ratio is found to be a better measure than BMI and waist circumference for the prediction of cardiometabolic risks factors. The aim is to assess whether waist-to-height-ratio is a better estimate of body fat percentage and cardiometabolic risk factors than BMI or waist circumference in children (3-7 years).
Methods: waist-to-height-ratio, waist circumference and BMI were determined by standardized procedures. 2H2O and 2H218O isotope dilutions were used to assess body fat percentage in 61 children (3-7 years) from the general population. In 75 overweight/obese children (3-5 years), bio-electrical impedance (Horlick equation) was used to assess body fat percentage and cardiometabolic risk factors, including diastolic and systolic blood pressure, HOMA2-IR, leptin, adiponectin, triglycerides, total cholesterol, HDL- and LDL-cholesterol, TNFa and IL-6 were determined.
Result: In 3 to 4-year-old children (N=30), waist-to-height-ratio and BMI were not related to body fat percentage, whereas waist circumference was moderately correlated (r=0.48). In 6 to 7-year-old children (N=31), both BMI (r=0.68) and waist circumference (r=0.56), but not waist-to-height-ratio, were associated with body fat percentage. In the overweight/obese children, waist-to-height-ratio, BMI and waist circumference were significantly related to body fat percentage (r=0.65, 0.81 and 0.81, respectively), systolic blood pressure (r=0.23, 0.30, 0.36, respectively), HOMA2-IR (r=0.53, 0.62, 0.63, respectively), leptin (r=0.70, 0.77, 0.78, respectively) and triglycerides (r=0.33, 0.36, 0.24, respectively), but not consistently with other parameters.
Conclusions: In young children, waist-to-height-ratio is not superior to waist circumference or BMI in estimating body fat percentage or cardio metabolic risk factors.

A QUALITATIVE STUDY IN AN IRISH GENERAL PRACTICE OF THE KNOWLEDGE AND ATTITUDES OF PREGNANT WOMEN REGARDING WEIGHT AND NUTRITION IN PREGNANCY.

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Excessive gestational weight gain and maternal obesity are strongly associated with both short and long term maternal and foetal complications. There is a lack of information on the beliefs and attitudes of pregnant women on weight and nutrition.
Our main objective was to identify the knowledge and attitudes among pregnant women regarding gestational nutrition and weight. 10 pregnant women in a training general practice with a patient population of 3000 took part in individual audio taped interviews.
The method of qualitative description was used in data analysis. Five main themes were identified: (i) Fear of postnatal weight retention, (ii) The legacy effect of the first pregnancy on weight (iii) Little awareness of link between gestational weight gain and infants' health risks (iv) Acceptance of doctor's advice and (v) Barriers to physical activity in pregnancy.
Women considered weight mainly in the context of their own health. There was a lack of awareness on the effect of excess gestational weight on their baby's in-utero, birth and future weight. In contrast, mothers to-be appeared to be concerned to protect their newborn's health through adequate pre-natal nutrition.

WEIGHT GAIN FROM BIRTH TO 1 YEAR, BREAST FEEDING DURATION AND STROKES HISTORY AS RISK FACTORS OF METABOLIC SYNDROME IN ADOLESCENTS

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Background and aim: Prevalence of metabolic syndrome (MS) in children grows up nowadays. Noticing of MS sings in obese children direct us to expect cardiovascular and metabolic disease development in adulthood. The study aim was to determine influence of weight gain from birth to 1 year, breast feeding duration and family history on MS rate in adolescents.
Material and Methods: 300 adolescents (4th and 5th Tanner stages) from children obesity study cohort were examined for MS features (body mass index (BMI) = 97th percentile, waist circumference (WC) =90th percentile for genders, levels of triglycerides (TR) = 1.7 mmol/l and HDL-cholesterol (HDL-C) = 40 mg/dl, systolic blood pressure (SBP) = 130 mm Hg and diastolic (DBP) = 85 mm Hg, blood glucose (BG) = 5.6 mmol/l). Insulin level was measured by immunoenzyme assay. Infancy data about weight gain from the birth to 1 year (WG1Y), breast feeding duration (BFD) and family history of type 2 diabetes mellitus (T2DM), obesity, heart attack and strokes in the 1st and 2nd degree relatives were collected from medical charts and parents' survey. Statistical analysis was performed by SPSS15.0 software (medians, percentile ranges, Mann-Uitny U-test, multiple liner regression).
Result: Study participants were divided according to sex: female (f) (n=167) in their median age 15.7 (14/0 - 16.9) yrs, BMI - 25.0 (21.6 - 30.8) kg/m2, WC - 83.4 (69.1 - 93.1) cm; and males - 15.9 (14.8 - 17.0), 29.5 (20.7 - 33.9), 99.3 (91.5 - 107.6); (p=0.06, 0.001, 0.0001 respectively). Gender differences were noticed in infantile history data: weight at birth (0.001) and 1 year (0.0001), WG1Y (0.002). SBP and DBP were increased in males compare to female (p=0.0001). The same differences were observed in TR (p=0.02) and HDL-C levels (p=0.04). Factor independently influenced increased on risk of MS development were excessive weight gain before the 1st year of life (ß=0.23, p=0.02) and BFD (ß=-0.22, p=0.05). MS z-score and prevalence were elevated in patients with positive family history of strokes (p=0.01 and 0.02 respectively).
Conclusions: Excessive weight gain during the 1st life year and short breast feeding period were the risk factors of MS development in adolescents. MS development was influenced by stroke occurrence in the 1st and 2nd degree relatives.

OVERWEIGHT AND OBESITY IN SCHOOL-AGE CHILDREN: CASE SERIES

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Introduction: Childhood obesity is a public health serious problem. The WHO considers it the new worldwide syndrome, the century's pandemic, since its prevalence is increasing at an alarming rate, especially in developed countries. In Portugal, about 32% of school-age children are overweight, with 14% of them obese. It is a chronic, multifactorial and multisystemic disease. Its early identification and prevention are essential to prevent morbidity and mortality associated.
Objectives: To study the prevalence of obesity (O) / overweight (Ow) and associated co-morbidities, in the population's students of the 1st year of primary education, of the S. António's School, in Lisbon, in the academic year 2012-2013.
Methods: Consulting the registers of the students's global heath exam from 5 to 6 years.
Variables: age, sex, weight, height and co-morbidities (according to ICD-10). Ow and O were defined according to BMI percentile (BMI percentile =85 and <95 - Ow; BMI percentile =95 - O). Comparative statistical analysis (SPSS v.19).
Result: We evaluated the records of 241 children (125 males and 116 females) with a mean age of 5.7 years (5 to 6.5 years). Of these, 6.2% were identified by their attending physician as a case of Ow/O. There was, however, a true prevalence of 31.1% (57.3% in females and 42.7% males), corresponding 17.8% to O and 13.3% to Ow. Of the 166 children without O/EP (Group 1 - G1), it was registered in 86 the presence of comorbidities (52%) vs in 39 children (52%) of 75 with O/Ow (group 2 - G2), emphasizing: ophthalmic pathology (18.1% G1 vs 18.7% G2); gastrointestinal disease, including caries (15.7% G1 vs 20% G2); mental/behavioral/language pathology (14.4% G1 vs 21.3% G2); respiratory disease (13.2% G1 vs 5.3 G2) and hearing disorders (5.4% G1 vs 8% G2).
Discussion: There was a high prevalence of Ow/O in the studied population (superior to the literature), underdiagnosed/undervalued by their physicians. There was also a predominance of Ow/O in females. Regarding the associated co-morbidities, the presence of caries, behavior/language disorders and ear's pathology, were associated more with Ow/O. It is extremely important to call the attention of physicians to this problem of childhood obesity, so as to achieve an early diagnosis to allow timely intervention, thereby reducing morbidity and mortality associated with it.

ASSOCIATION BETWEEN NEONATAL WEIGHT CHANGE AND BLOOD LIPID LEVELS AT 4 YEARS OLD

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Excessive or insufficient neonatal weight losses (NWL) have been associated with health problems in the neonatal period, but little is known about its medium and long term consequences. Our objective was to evaluate the effect of neonatal weight changes, namely excessive or insufficient NWL, on total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C) and triglycerides (TG) levels in 4 years old children. Generation XXI included 8647 newborns recruited between 2005/2006 at the public units providing obstetrical and neonatal care in Porto. Information was gathered by face to face interview and additional data abstracted from clinical records, including birth weight (BW). Neonatal anthropometrics were obtained by trained interviewers and the analysis was restricted to those weighed up to 96 hours of life. Neonatal weight change was estimated as (weight - BW) / BW × 100, adjusted for age in hours. We categorized as excessive NWL (bellow 10th percentile of the distribution of weight change: = -9.5%), normal NWL (between 10th and 90th percentiles: -9.4% to -4.2%) and insufficient NWL (above 90th percentile: = -4.1%). At age 4-5, children were reevaluated according to standard procedures, including a fasting blood sampling. TC, HDL-C and triglycerides levels were measured. LDL-C was estimated according to Friedewald formula (LDL-C = TC - HDL-C - 0.2 x TG). We present life course data for 516 normal term singletons with no congenital malformation. Adjusted regression coefficients and 95% confidence intervals [ß (95%CI)] were computed using generalized linear models. Compared with normal NWL children, children with insufficient NWL had higher levels of TC [1.564 (-6.573; 9.701)], HDL-C [0.795 (-2.273; 3.864)], LDL-C [0.525 (-6.370; 7.419)] and TG [1.220 (-6.827; 9.267)] and children with excessive NWL had higher levels of HDL-C [0.428 (-2.603; 3.460)] and lower levels of TC [-2.315 (-10.355; 5.724)], LDL-C [-2.627 (-9.438; 4.185)] and TG [-0.586 (-8.536; 7.364)], being the most favorable profile. This study provides evidence for medium term effect of weigh changes in the first few days of life on blood lipid levels, being the only study so far addressing this issue. We concluded that the neonatal weight changes do not affect TC, HDL-C, LDL-C and TG blood levels at 4 years old.

LIPID PROFILES IN FORMER PRETERM TYROLEAN PRESCHOOLERS - PRELIMINARY DATA

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Introduction/Background: Cardiovascular disease is the leading cause of death worldwide. An increasing body of evidence suggests that former preterm infants are prone to develop an unfavorable cardiovascular risk profile in adult life (Irving 2000) and at school age (McEniery 2011). Whether metabolic changes are present at an even earlier age is unknown to date. The aim of this study was to investigate whether overweight/obesity and lipid alterations, major modifiable cardiovascular risk factors, can be detected in former preterm infants at a preschool age.
Patients and Methods: 35 former preterm infants (male: n=22, female: n=13) born in Tyrol between September 2006 and September 2007 with a gestational age <32 weeks (median: 29+4, IQR: 27+5, 30+6) and a median weight of 1200 g (IQR 992.5, 1517.5) at birth were examined at a corrected age of 5 years (median 5 years and 4 months, minimum 5 years, maximum 5 years and 8 months). Current weight and height were measured with calibrated medical precision scales and a Harpenden stadiometer, BMI percentiles were determined by means of a BMI reference data set (Kromeyer-Hauschild 2001) and blood samples were drawn after a minimum overnight fasting period of 12 hours.
Result: The median BMI percentile in our collective was 14.0 (IQR 6.5, 34.5), one child was considered as overweight (BMI percentile >95), one as obese (BMI percentile >97). Blood samples could be obtained from 29 patients (male: n=16, female: n=13). The mean total cholesterol level in this cohort was 165 mg/dl (± 27 mg/dl SD), the mean LDL cholesterol level 101 mg/dl (± 20 mg/dl SD) and the mean HDL cholesterol level 59 mg/dl (± 11 mg/dl SD). 15 patients (51.7%) fulfilled the age-specific pediatric hypercholesterolemia criteria (total cholesterol >150 mg/dl and LDL >100 mg/dl). The mean triglyceride level was 57 mg/dl (± 22 mg/dl SD), with one value lying above the age-specific reference range of >110 mg/dl. All laboratory parameters were independent of gestational age, size for gestational age (presence or absence of smallness for gestational age) and current BMI percentile. No gender-specific differences were detected.
Conclusions: To best of our knowledge, we are the first to show that hypercholesterolemia might be a relevant complication in former very and extremely preterm infants even at a preschool age. Whether these laboratory findings are associated with an unfavorable cardiovascular outcome later in life has to be addressed by future studies.

DIET: CAUSE OR SOLUTION ON CHILDHOOD OBESITY? THE ROLE OF FIBER.

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Introduction: Childhood obesity is a worldwide epidemic with well known adverse effects, that justify the continuous needing for new effective treatments. Dietary fiber and its mechanism of action, particularly in the prevention of obesity, have been the subject of extensive research. The literature still leaves many questions unanswered, but some studies show that the intake of dietary fiber is inversely related to weight gain, but there isn´t consensus on recommendations for the daily intake of fiber. OBJECTIVE: To determine the daily intake of dietary fiber in children / adolescents with primary obesity before a dietary intervention.
Methods: We evaluated through the application of dietary questionnaire to 24 hours earlier, the average consumption of dietary fiber of children / adolescents seen for the 1st time in consultation Pediatrics / Nutrition CHEDV. This information was provided by the patient. We used the "Manual of food Quantification " (FCNAUP, 1996), with photos for comparative assessment of the quantity of food intake. Quantification of fiber consumption and energy was made through the program Microdiet version 28.8. There is not a consistent and globally accepted recommendations for the daily intake of fiber, the American Heart Association recommends consuming 25-30g/dia fibers in the adult. The National Academy of Sciences (USA) recommends 14g / 1000 kcal, from 1 year of age, and stratified the ideal fiber intake by age and sex (1-3 years 19g/dia; 4-8 years: 25g / day, 9-13 years: 31g to 26g for males and females, 14-18 years: 38g for men and 26g for women). The American Academy of Pediatrics recommends a total fiber-based rule, valid above 2 years of age, total fiber / day = age + 5 (minimum) to 10.
Results: We evaluated 42 children / adolescents with primary obesity (46% male) with a mean age of 12 years (minimum 8maximum 17). The average daily intake of fiber was 10.8 g / day (min 0.36, max 24.42). Ten cases (23%) had a total fiber than 14g/dia, and these correspond to those patients who ingested greater daily calories and the relationship fiber/ kcal demonstrated to be diminished 10 to 12g/1000Kcal in 3 cases, other <10g fiber / 1000 Kcal. The average consumed Kcal per day (not accounted drinks) was 1696.9 kcal, which should correspond to a minimum value of 23.75 g of fiber. DISCUSSION: In this obese population, there was a very low rate of ingestion of fibers. The subgroup with a fiber intake exceeding 14g/dia had still a low value demonstrated in a reduced relationship fiber / calorie. Dietary fibers give an early satiety, contributing to the prevention of obesity. Not surprisingly, this group of children present a low rate of fiber intake. This finding reinforces the enormous challenge of treating this disease, given the profound changes that are necessary to establish in dietary habits. The fibers can thus influence future therapeutic strategies.

CARDIOVASCULAR RISK FACTORS IMPACT IN CHILDHOOD

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Introduction: In the last decades, diseases such obesity, diabetes mellitus, dyslipidemia, and essential hypertension, became frequent in childhood pathology. The rising prevalence of them and the presence of cardiovascular risk factors even in children around ten years old are argumentes strong enough to reconsider the cardiovascular degenerative pathology. The key of these may be atherosclerosis. Objectives: The aim of this study is to determine the presence of cardiovascular risk factors in children and their effect on the artery, in fact, the modification of the intima-media thickness on carotid artery. **Methods:** The study had included 80 children aged between 10 and 18 years old, all of them with obesity. The protocol included the measurement of blood pressure (BP), body mass index (BMI), laboratory tests (blood levels of glucosis, total cholesterol, tryglicerides, low density lipoproteins and high density lipoproteins, , uric acid, and oral test of glucosis tolerance), echocardiography for calculation the mass of the left ventricle and Doppler of main carotid artery and calculation of the intima-media thickness (IMTc). **Result:** We had found a strong positive correlation between IMTc and BMI, the level of systolic blood pressure, of total cholesterol, tryglicerides and low density lipoproteins and a negative correlation with high density lipoproteins levels. All the subjects had impairment on oral test for tolerance at glucosis. **Conclusions:** The measurement of IMTc with Doppler technique is accesible and easy to apply in children. It is usefull for identification of early structural changes in the artery due to atherosclerosis and has a very good correlation with the presence and clustering of cardiovascular risk factors in children.

HOME TRANSCUTANEOUS ELECTRICAL STIMULATION THERAPY TO TREAT CHILDREN WITH ANORECTAL RETENTION - A PILOT STUDY

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Background: Anorectal retention (AR) contributed to 70% of childhood chronic constipation. Laxative has not been effective with poor outcomes. We aimed to test the effectiveness of transcutaneous electrical stimulation (TES) to treat children with AR in a pilot study. We hypothesized that TES would overcome symptoms of chronic constipation in children with AR.
Methods: A pilot study (2009-2011) with ethics approval (Ethics30029A) in 10 AR children. Parents/children were trained to administer home-based TES, 1-hour daily for 3 months, using a battery-powered interferential stimulator. Quadripolar interferential stimulation (4kHz carrier frequency, 80-160Hz beat frequency, 30mA) with 4 sticky electrodes (4cm x 4cm) were placed, 2 on the suprapubic area and 2 on the back at presacral area. Daily continence diary, PedsQL4.0 questionnaires and NTS were compared before and after TES. Statistical analyses performed with STATA 12, with $p< 0.05$ considered significant.
Result: Ten children (4 female, ages: 5-10yrs, mean: 8yrs) administered home-based TES successfully. Symptoms improved significantly in 70-90% of children with AR with improved defecation frequency (0.9 to 3.0 BA/wk, $p< 0.01$), reduced soiling (5.8 to 1.4 days of soiling/wk, $p< 0.01$) and abdominal pain (2.0 to 0.4 days of pain/wk, $p< 0.002$). Stronger urge to defecate developed in 9/10 children and laxative use was reduced/stopped in 6 children with 1 child remained on same laxative dose ($p< 0.01$, chi square). PedsQL scores improved in both the childand parent-reported assessments ($p< 0,00$). Though gastrointestinal transit did not improve after TES, the median index improved from 13.5 to 15.3 post TES.
Conclusions: Home-based TES is a promising and useful adjunctive treatment to overcome constipation in children with AR. This has expanded the use of TES as a treatment option for the more common form of constipation and may well be an option in adults with chronic constipation.

TRANSCUTANEOUS ELECTRICAL STIMULATION AND INTRACTABLE CHRONIC CONSTIPATION IN CHILDREN

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Background: Intractable chronic constipation in the form of slow-transit constipation (STC) often resistant to medical treatment. Some children required appendicostomy for antegrade enemas to improve symptoms. Transcutaneous electrical stimulation (TES) was used by physiotherapists to overcome STC in children successfully. This study aimed to examine the effectiveness of home-based TES when STC children were trained by a naïve clinician. We hypothesized TES would improve symptoms with reduce laxative use.
Methods: A prospective study (2009-2011) whereby a surgeon was trained to deliver TES method to STC children/parents, who then self-administered TES at home (1 hr/day x 6 months) using a battery-powered interferential stimulator. Daily continence diary (including laxative use) was recorded before and throughout TES; PedsQL4.0 questionnaires and gastrointestinal nuclear transit scintigraphy (NTS) were completed before and after TES. Appendicostomy for antegrade enemas was offered if TES failed to improve symptoms. Statistical analyses performed with paired t-test & chi-square test; $p < 0.05$ considered significant.
Result: Sixty-two children (34 female, ages: 2-16yrs, mean: 7yrs) completed home-based TES successfully. Symptoms improved significantly in 56/62 (90%) STC children with gastrointestinal transit index improved after TES. The 2 children who stopped laxative prior to TES had symptom improvement without further laxative use. Only 6 children (10%) required appendicostomy for antegrade enemas.
Conclusions: Home-based TES is non-invasive. It is a promising treatment for STC children with avoidance of surgery and reduced laxative use with improved symptoms in most children. Success required clinician training and close patient contact.

CHILDHOOD CHRONIC CONSTIPATION AND GASTROINTESTINAL TRANSIT PATTERNS

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Background: Constipation may be a part of a generalized gastrointestinal (GI) tract disorder. Nuclear transit scintigraphy (NTS) provides transit through the stomach, small bowel, colon and anorectum. This study aimed to determine different colonic and rectal transit patterns in children with chronic constipation (CC) and their association with upper GI tract disorders.
Methods: A retrospective analysis of NTS (1999-2011) performed in children with intractable CC. The 48-hour NTS protocol involved Gallium-67 citrate milk drink with images acquired at 0-2 hrs (gastric emptying study) and at 6, 24, 30 and 48 hrs (small bowel & colonic transit studies). The geometric centre calculation was based on % of radioactivity in each region of interest (ROI). Six ROIs were employed (1=pre-colonic, 2=ascending colon, 3=transverse colon, 4=descending colon, 5=recto-sigmoid colon and 6=toilet).
Result: A total of 955 NTS was performed (1999-2011; 288 repeat & 667 new studies). In the 603 children (284 female, 2-23yrs, mean 8.5±4.1yrs) included for this study, 19% had normal colonic transit (NT), 52% slow colonic transit (ST) and 29% rapid proximal colonic transit (RT). Only 1/3 of children had AR. About 20% of children had delayed gastric emptying & delayed small bowel transit.
Conclusions: There are 3 distinct colonic transit patterns in children with CC: normal, slow & rapid. About 1/3 of children with CC had AR at 48 hrs & was associated with NT, ST and RT. In addition, 21-24% children with CC had upper GI tract transit disorders.This may have important implications in the treatment of childhood chronic constipation as it helps to determine its severity and in selecting the best treatment option available.

GROWTH AND DEVELOPMENTAL OUTCOMES OF INFANTS WITH HIRSCHPRUNG DISEASE PRESENTING IN THE NEONATAL PERIOD: A RETROSPECTIVE STUDY.

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Background: Limited information is available on the growth and neurodevelopmental outcomes of neonates with Hirschprung disease. We aimed to describe the outcomes of Hirschprung disease presenting in the neonatal period.
Method: All cases of neonatal Hirschprung disease are admitted to the sole tertiary children's hospital of Western Australia. Cases were identified by interrogating the histopathology and neonatal databases. Retrospective chart review.
Result: 54 cases were identified (2000-2010). The median gestational age was 39 weeks; median birth weight: 3430 grams: 21 were females (39%). The recto sigmoid was involved in 40 (74%) and long segment or total colonic aganglionosis in 14. Seven had chromosomal anomalies. The majority (87%) of the infants with short segment disease and 36% of infants with long segment disease underwent primary pull through procedure. Median duration of first hospital stay was 17 days (range 8, 163). Seventeen (31%) infants developed anal stenosis requiring multiple dilatations for 3-12 months. Hirschsprung assosciated enterocolitis occurred in 14 (26%) infants at anytime within first year of life. There was 1 death not related to Hirschprung disease. One-year neurodevelopmental information was available on 42/46 non-syndromic survivors: 34/42 had Griffiths' assessments with a median score of 94 (IQR: 87,100; range 49, 110); however, 9/42 (21%) non-syndromic, survivors either had a Griffith score of <87 or failed paediatric developmental assessments. No infant was blind or deaf. One infant with a chromosome anomaly had cerebral palsy.
Conclusions: Hirschprung disease appears to carry ongoing gastrointestinal and neurodevelopmental morbidities. Larger, long-term follow up studies are necessary.

REVIEW OF OESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA IN BRAGA HOSPITAL

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Background: Oesophageal atresia and tracheoesophageal fistula is one of the congenital anomalies seen worldwide, occurring with an incidence of 1 in 2500 births. Prenatal detection rate increased from 26% to 36.5% over the last two decades. Survival in infants with isolated oesophageal atresia born at term is high.
Material and Method: We did a retrospective review of newborns admitted at Braga Hospital, pediatric surgery department to Minho Region, from 1st January 2012 to 31st January 2013, analyzing newborns with oesophageal atresia and tracheoesophageal fistula.
Result: We admitted 7 patients, all caucasians. 6/7 were term newborns and 1/7 preterm baby 35 weeks gestational age. 6 females and 1 male. 5/7 newborns were born at Braga Hospital, 1/7 at Famalicão Hospital and 1/7 at Guimarães Hospital. 6/7 newborns had distal tracheoesophageal fistula and 1/7 had proximal and distal fistula. None of them had prenatal diagnosis. The birth weight of these newborns ranged from 2115 g to 3995 g. The diagnosis was made in the first three hours of life, by the presence of copious secretions in the mouth, food vomiting and the inability to advance the orogastric tube. All the babies were operated after 24 hours of sings presentation (> 48h to 96 hours of life). 6/7 underwent thoracoscopy and 1/7 underwent thoracotomy. None of the newborns had surgical complications. The mortality rate was 0%. 3/7 were born with other congenital malformations. 5/6 newborns, who underwent thoracoscopy, were discharged between 12th and 21th days of life. The newborn who underwent thoracotomy was discharged in the 50th day of life. 1/6 baby who underwent thoracoscopy was discharged in the 93th day of life, because she had a severe laryngomalacia. Currently one baby, 6 months old, has severe esophageal stenosis, without fistula, and is doing esophageal dilation as outpatient.
Conclusions: In our review none of the newborns had prenatal diagnosis. 6/7 babies underwent thoracoscopy cirurgy to esophageal repair and correction of tracheoesophageal fistula, which allows shorter hospital stay. One of these patients had longer hospital stay because she had a severe laryngomalacia. The baby that was submited to thoracotomy was discharged only at 50th day of life. Strictures, leaks and reflux are the most common complication of esophageal atresia repair, and a carefully follow-up is important for early detection of complications, as we saw in a one baby.

ASSOCIATION BETWEEN CELIAC DISEASE AND ENDOCRINE AUTOIMMUNE PATHOLOGIES

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Background: Celiac disease (CD) is a gluten-associated pathology, that occurs in genetically predisposed individuals. As we know, CD is often associated with autoimmune pathologies, such as insulin-dependent diabetes mellitus (IDDM) and autoimmune thyroiditis (AIT). OBJECTIVES AND STUDY Evaluate: . Prevalence of IDDM and AIT in celiac patients; . Temporal relationship between CD and IDDM, and CD and AIT; . Thyroid function and ultrasound pattern in patients who have both AIT and CD.
Patients And Methods: In our survey, we recruited 97 celiac patients, 65F and 32M, followed-up in our Department of Pediatrics from 2009 to 2013; all of them were screened for AIT and IDDM. We grouped our patients into 2 parts: age at diagnosis under and over 12 years old. We also divided patients affected from IDDM+CD into 3 groups: . IDDM onset before CD; . CD onset before IDDM; . Simultaneous onset.
Results: Among our 97 celiac patients, 28 (16F, 12M) were affected by IDDM too (F/M 1,33:1), and 10 (7F, 3M) werer concomitantly affected by AIT (F/M 2,33:1). Patients affected from CD+AIT were mostly under 12 years old (60%, 6/10), divided into 4F and 2M (F/M=2:1); the over 12 years old ones had a prevalence of 40% (4/10), divided into 3F and 1M (F/M = 3:1). Among patients affected from CD+IDDM, diabetes was diagnosed before in 67,86%, after in 17,85%, simultaneously in the remaining percentage of patients. In patients with CD+AIT, CD was diagnosed before in 80% of cases, while in 20% AIT diagnosis came before CD one. Among our 10 patients affected from AIT, 4 (3M, 1F) had a good thyroid function, 6 had, instead, a low thyroid function. Ultrasound patterns were also different: 8 patients had a grade 2, while 2 patients had a grade 1(Sostres S, Reyes MM, J Endocrinol Invest 1991; 14: 115-21).
Conclusions And Discussion: Prevalence of IDDM (28.86%) that we noted in our sample results from a bias due to the fact that we recruited our patients in a center of diabethology. Prevalence of AIT (10,3%) observed in our population is comparable with the one we find in scientific literature, with a F/M ratio 2,33:1 in patients under 12, becoming 3:1 in subjects diagnosed after 12 years old. We can speculate about onset of IDDM before CD: it could be due to a misunderstood, and consequently not treated, CD. In fact, gluten could be an immunological trigger for IDDM. As of association CD-AIT, we noted a significant difference in onset age of CD and of AIT, and that CD is usually diagnosed before AIT in 80% of patients, while just in 20% AIT was diagnosed before CD.

CUTANEOUS MANIFESTATIONS IN PEDIATRIC COELIAC DISEASE

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Background: Involvement of the skin is considered amongst atypical extraintestinal way of disease presentation.
Objectives And Study: To Evaluate type and frequency of skin and mucocutaneous involvement in pediatric patients affected by Celiac Disease (CD). To Establish a relationship between skin involvement and years of disease or between skin involvement and Gluten Free Diet (GFD).
Methods: Sixtysix patients (45 F e 21 M) affected by CD, aged between 18 months and 20 years, diagnosed according to ESPGHAN Revised Criteria, were investigated for concomitant associated diseases and for dermatological manifestations. All diagnosed patients were strongly recommended to start a GFD regimen. Patients were divided in to three groups on basis of duration of disease: . Group 1 with CD since less than 2 years; . Group 2 with CD lasting more than 2 and less than 10 years; . Group 3 with CD lasting more than 10 years.
Results: In our survey, dermatological manifestations were present in 13 (20%) patients. In most cases (70%) they were females. In four patients dermatological manifestations were associated with atypical way of CD presentation. Mucocutaneous manifestations (oral aftosis, psoriasic dermatitis, urticaria, Duhring dermatitis) and onychodystrophy were the most common. Most patients with skin involvement were affected by CD since less than two years (Group 1). Onychodystrophy was more frequent at CD onset and often disappeared in patients on GFD gaving proof of being related to the underlying malabsorption. No relationship was established amongst other forms of skin involvement and GFD.
Conclusion: The awareness of cutaneous way of presentation of CD may be helpful in diagnosis of atypical forms in childhood as in adults. Urticaria may be due to concomitant gluten sensitivity affecting a subset of subjects with CD.

LACTOBACILLUS REUTERI DSM 17938 PREVENTS SHORT- AND LONG-TERM VISCERAL HYPERSENSITIVITY INDUCED BY ANTIBIOTIC ADMINISTRATION TO SUCKLING RATS

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Background: Infantile colic and excessive crying affect a large proportion of young, otherwise healthy infants. Colic etiology is not well understood, but has been associated with fecal microbiota alterations. Three clinical studies have shown that Lactobacillus reuteri DSM 17938 (Lr) efficiently reduces crying time in colicky infants, but its mechanism of action is not known. We aimed to investigate the hypotheses that 1) dysregulation in early microbiota colonization may trigger colic by inducing visceral hypersensitivity and 2) Lr can prevent these alterations.
Materials & Methods: Rat pups were exposed to daily intragastric administration of amoxicillin (ATB) or water (Water) from postnatal day 7 (PND7) to PND21. ATB pups received an additional gavage of either vehicle (ATB-PBS), Lr (ATB-Lr) or another probiotic with anti-inflammatory properties (Bifidiobacterium breve NCC2750, ATB-Bb). Water pups received vehicle (Water-PBS). Visceral sensitivity to colorectal distension (CRD) was assessed in basal conditions at PND30 (weanling) and PND70 (adult) and after 5 day water avoidance stress (WAS) only at PND70. In vivo gut permeability was monitored at PND28. At PND30, colonic tissue was analyzed for levels of the tight junction proteins occludin and JAM-A, inflammation microscopic scores, mucosal PGP9.5 positive nerve fiber areas and expression of 84 genes involved in Innate and Adaptive Immune Responses. Mesenteric lymph nodes were analyzed for protein levels of 23 cytokines and chemokines.
Results: At PND30 basal visceral sensitivity was higher in ATB-PBS than in Water-PBS rats for all volumes of CRD tested. ATB-Lr, but not ATB-Bb, displayed lower sensitivity than ATB-PBS in the largest volumes. ATB-PBS showed higher permeability and lower occludin levels than Water-PBS. Neither probiotic significantly restored permeability to Water-PBS levels. Conversely, ATB-Bb displayed higher permeability than ATB-PBS. Increased positive PGP9.5 nerve fiber density was detected in the colonic mucosa of ATB-PBS. A trend to restoration was observed with both probiotics. None of the other outcomes assessed at PND30 differed significantly across the groups. At PND70 no differences in visceral sensitivity were observed in basal conditions among the groups. However, visceral hypersensitivity observed in Water-PBS in response to WAS was exacerbated in ATB-PBS. Interestingly, Lr prevented this exacerbated response.
Conclusion: In our model early treatment with amoxicillin, an antibiotic largely used in pediatric practices, induced visceral hypersensitivity, which was prevented by L. reuteri DSM 17938, a probiotic shown to efficiently reduce crying time in colicky infants. Our results suggest that early alterations in microbiota colonization may trigger colic by inducing visceral hypersensitivity and point out to a potential mechanism of the probiotic. They also suggest that microbiota dysregulation during infancy may increase the risk of functional visceral pain later in life by exacerbating the gut sensitivity response to stress. Interestingly administration of L. reuteri may prevent this negative imprinting.

AUDITORY EVENT-RELATED POTENTIALS AND OUTCOME AT PRESCHOOL AGE AFTER VERY PRETERM BIRTH.

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Background and aims: Auditory event-related potentials (aERP) are neurophysiological correlates of sound discrimination and processing. Pathological aERP have been associated with various cognitive dysfunctions and behavioural problems. In children born at term, changes in obligatory aERP components such as decreased P1 amplitudes have been found in ADHD, autism spectrum disorders and dyslexia, all common in children born very preterm. In low-birth-weight infants at preschool age, small P1 amplitudes correlated with cognitive test results. Previous study groups have been small with few very immature infants. Thus, our aim was to study in a large cohort of very preterm infants if obligatory aERP components (such as P1 and N2) correlate with cognitive and behavioural outcome at preschool age. We have previously shown that very preterm children at preschool age had lower mean P1 amplitudes than children born at term or late preterm.
Methods: The children were recruited at birth (gestational age mean±SD 27.4±1.9 weeks, birth weight 996±288 g) and examined (N=70) at 4.3-5.3 years of age. EEG was recorded while they listened to a repeated standard tone, randomly replaced by one of three deviants (different in frequency, perceived sound location, or duration). Latencies and mean amplitudes for the main obligatory responses P1 and N2 were measured. On the same day, the children were tested using Wechsler Preschool and Primary Scale of intelligence - revised (WPPSI-R) and A Developmental Neuropsychological Assessment (NEPSY - subtests Visual attention, Phonological processing, Narrative memory, and Sentence repetition). Their parents filled in the Strength and Difficulties Questionnaire (SDQ). Children scoring below 85 in any of the WPSSI-R subscales, on the 25th percentile or below on a NEPSY subtest, or higher than 6 on the Hyperactivity subscore of the SDQ (Hyperactivity) were considered abnormal for this subtest or subscore. As the age at examination correlates with P1 and N2 (submitted), all results were corrected for age at examination.
Result: We found a significant positive correlation between the P1 amplitude and Performance IQ (PIQ) (ß=0.217; p=0.032), and between the P1 latency and both PIQ (ß=0.228, p=0.044), Processing speed IQ (ß=0.227; p=0.038), and Narrative memory (ß=0.213; p=0.046). Another 4 subtests/subscores showed a trend to significant correlation to the P1 latency (Verbal IQ p=0.060; Full-scale IQ p=0.052, Hyperactivity p=0.060, Visual attention p=0.070). The N2 amplitude correlated negatively with Hyperactivity (ß=-0.214; p=0.042) and Phonological processing (ß=-0.224; p=0.030). Children with abnormal Hyperactivity score had shorter P1 latencies (p=0.023), lower N2 amplitudes p=0.014) and trend to shorter N2 latencies (p=0.068) than normal children. Children showing abnormally long Visual attention execution times had longer P1 latencies than normal children (p=0.048).
Conclusions: Very preterm born children at preschool age show obligatory ERP responses that are different from full-term children and correlate with cognitive outcome and hyperactivity. Abnormal primary auditory processing and sound discrimination may play a role in the development of cognitive and behavioural problems in very preterm children. Prematurity may have a similar impact on auditory and cognitive development as genetic (e.g. dyslexia) and environmental influences leading to these dysfunctions.

REGIONAL CHANGES OF CORTICAL THICKNESS IN CHILDREN BORN PREMATURELY AND CHILDREN BORN WITH INTRAUTERINE GROWTH RESTRICTION AT SCHOOL AGE

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During the prenatal and early postnatal development human cerebral cortex undergoes significant changes. Prenatal patterning of the cerebral cortex is highly driven by genetic influence and can be seen as temporal and regional changes of cortical thickness. Nevertheless, the postnatal changes of cortical thickness fallowing the premature birth are still unexplored. Thus, we performed quantitative analysis of school age children born prematurely in order to test to which extent the early exposure to sensory information (premature birth), alteration in nutrition (intrauterine growth restriction, IUGR) as well as the environment in which they have been raised (socio-economic status of parents) affect the maturational trajectories of the cortical areas upon reaching the school age. MR images of the 40 prematurely born children (Gestational age (GA) = 28.80±3.05 gestational weeks (GW)) scanned at school age (6.62±0.48 years) were acquired using the MPRAGE 3D protocol of the 3T Siemens TrioTim System. We have calculated the sex-, gestational-age specific z scores (-0.47±1.3) of the birth weight (1105.25±440 g) for all the subjects included in our study. Subjects were divided in two groups: IUGR (N=13) and premature subjects with adequate growth (N=27). IUGR was defined as GW below 10th-percentile for GA and gender, and based on criteria of placental insufficiency according to intra-uterine growth assessment, prenatal ultrasound and Doppler measurement within the umbilical artery. Socio-economic status (SES) was estimated by means of six-point scale (LARGO scale) for both paternal occupation and maternal education; the lowest SES score was 2 (highest education), the highest 12. High-resolution T1 weighted images (1x1x1mm3) were processed using the CIVET, a fully automated pipeline developed at the Montreal Neurological Institute, ACE Lab. The effect of the gestational age at birth, LARGO scale, age at scan, gender and the z-scores on the cortical thickness was tested using the general linear model, T statistics, and the SurfStat toolbox. Our results showed that the age at scan is negatively associated with the mean cortical thickness (p=0.059). Socio-economic status of parents (LARGO scale) has a global effect on cortical thickness. Lower education of the parents (higer LARGO score) is associated with the thinner mean cortical thickness, p=0.05 and explains the 25.19% variability of the cortical thickness, p=0.028. GA at birth affects the cortical thickness regionally and explains the 6.97% variability of the cortical thickness, p=0.042. Lower GA is associated with the thinner cerebral cortex in precuneus (bilaterally) and right middle temporal gyrus (posterior part), p=0.001. Lower birth weight, z-score, is associated with the thiner cerebral cortex in the right frontal operculum and posterior junction of the left fusiform and parahippocampal gyrus (p=0.015). In conclusion, both effects expressed by the socio-economic scale as well as the events of the prematurity affect the cortical maturation globally and regionally.

ASSESSMENT OF SPONTANEOUS MOTOR REPERTOIRE AT 14 WEEKS POST TERM AGE IN EXTREMELY LOW BIRTH WEIGHT (ELBW) CHILDREN IS ASSOCIATED WITH BRAIN VOLUMES AND CLINICAL FUNCTION AT 10 YEARS OF AGE

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Background: ELBW children have increased vulnerability to perinatal brain injury with consequences for neurological functioning. Prechtl's method of general movement assessment (GMA) is known to be a reliable method to predict motor disorders and especially cerebral palsy (CP) in later childhood. An additional detailed assessment of motor repertoire (AMR) performed at 3-5 months of age has been suggested to be of prognostic value for motor and cognitive development in children that do not develop CP. Our aim was to investigate whether ELBW children without CP and with present fidgety movements but abnormal assessment of motor repertoire would differ in brain volumes, IQ, motor skills and ADHD scores at age 10-11 compared to ELBW children with normal motor repertoire. Patients and
Methods: In this prospective follow up study of ELBW children born at the St. Olav University Hospital, Trondheim in 1999-2001, 31 ELBW children with mean birth weight 773g(SD146), and mean gestational age 26.1weeks(SD1.9) were included. At 14 weeks post term age the ELBW children were assessed with GMA and AMR. According to GMA, fidgety movements was classified as present(F+) or absent(F-). The quality of motor repertoire according to the AMR was classified as 'normal concurrent' if it was smooth, variable and fluent, and as 'abnormal concurrent' if it was jerky, monotonous or stiff. At age 10-11, cerebral MRI (1,5TSiemens Symphony) was performed in 26 of the ELBW children. For the image analyses we used FreeSurfer software package 5.1 and values for brain volumes were processed. The Wechsler-Intelligence-Scale-for-Children-III (WISC-III) was performed to assess full IQ. The Movement-Assessment-Battery for Children second edition (MABC-2) was used to assess general motor skills. The ADHD rating scale-IV was completed by one parent for assessment of hyperactivity and inattention. For the statistical analyses a general linear model with socio-economic-status (SES), age at testing and gender as cofactors was used to compare group differences.
Results: Eight ELBW children (26%) developed CP. Of the non-CP children that also had MRI (n=18), eight was assessed as F+ with normal concurrent motor repertoire, while ten children had F+ but abnormal concurrent motor repertoire. The children with abnormal concurrent motor repertoire had smaller total intracranial (1417.7vs1548.9cm3, p=.02), total white matter (413.1vs478.5 cm3, p=.005), total grey matter (701.7vs772.4 cm3, p=.02) and putamen (10.8 vs12.1 cm3, p=.01) volumes than children with normal concurrent motor repertoire. On the WISC-III the children with abnormal concurrent motor repertoire had lower verbal IQ scores as well as lower total scores on the MABC compared to those with normal motor repertoire. On the ADHD rating scale there was a higher inattention score (9.4vs2.7, p=.02) and total score (16.0 vs5.1, p=.03) among the children with abnormal concurrent motor repertoire.
Conclusion: When looking at spontaneous motor repertoire at 14 weeks post term age in a group of ELBW survivors, those with abnormal concurrent motor repertoire had smaller brain volumes and a combination of lower verbal IQ, lower motor skills as well reduced attention at age 10-11 than those with normal concurrent motor repertoire at week 14 post term.

WHITE MATTER VOLUME AND BIRTH WEIGHT ARE ASSOCIATED WITH CORTICAL THICKNESS IN PRETERM ADOLESCENTS

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Introduction/Background: Preterm birth affects cortical thickness (CTh) at adolescence. Previously, it has been described both a thicker and thinner cortex in preterm adolescents compared to their term peers. However, little is known about the variables associated with these brain abnormalities. We aimed to investigate the variables related to CTh abnormalities in a preterm sample during adolescence.
Patients and Methods: The sample comprised 46 very preterm (VPT) adolescents without major neurological complications at birth and 46 term peers. All participants underwent an MRI study and were cognitively assessed by means of the Wechsler Intelligence scales. The full intelligence quotients (FIQ), as well as the performance and verbal sub-indexes were obtained. FreeSurfer software was used to obtain volume-based values and surface-based brain measurements.
Result: In regard to the CTh maps, we observed regional thicker cortex encompassing medial orbitofrontal area bilaterally, left lateral occipital and right precentral region in preterm adolescents compared in comparison with their controls (statistically significant results; $p<0.05$). In addition, using atlas-based parcellations, VPT adolescents showed thinner right transverse temporal area. Cortical thickness correlation maps in the preterm sample showed increased CTh associated with WM volume decrements and lower weight at birth. Concerning cognitive performance FIQ and performance IQ correlated with WM regional decrements in preterm adolescents whereas we found a negative correlation between FIQ and CTh in term-born adolescents.
Conclusions: VPT adolescents evidenced long-term CTh abnormalities. Specifically, these abnormalities were related with white matter volume and weight at birth. White matter impairment but not changes in CTh explained cognitive performance in preterm adolescents who did not suffer brain injury at birth.

DEFICITS IN EPISODIC MEMORY RELATE TO REDUCED HIPPOCAMPAL VOLUMES IN VERY-LOW-BIRTH-WEIGHT (VLBW) YOUNG ADULTS.

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Background and aims: Hippocampus is regarded as a core structure for learning and memory functions. Cognitive deficits are common in VLBW (bw = 1500 grams) children and adolescents, including academic problems that may imply learning and memory deficits. However, reports on the relationship between episodic memory and hippocampal volume in VLBW adults do not exist. Reduced bilateral hippocampal volume has been reported in preterm born children and adolescents, however, only weak correlations between volume and memory functions have been described (Isaacs et al. 2003; Omizzolo, 2013). No study has examined the structural-functional relationship between hippocampal volume and memory profile in adults born with VLBW. Aim of study:To perform a comprehensive memory assessment in VLBW young adults and investigate the relationship between hippocampal volume and episodic memory in the VLBW subjects compared to age-matched term born controls.
Methods: In this hospital-based, longitudinal follow-up 42 non-disabled VLBW and 61 controls were examined at age 19-20 with WAIS-III, Wechsler Memory Scale-III and cerebral MRI. An automated MRI technique (FreeSurfer ver. 5.1) at 1.5 T for morphometric analysis of hippocampal volumes was applied. This method uses whole brain segmentation and automated labeling of neuroanatomical structures. Relative volumes were calculated based on the total intracranial volume and absolute volumes from each subject. The relationship between absolute and relative hippocampal volume and memory functions in the VLBW group was explored by partial correlations, controlled for gender and age at MRI. Results from memory tests that were significantly reduced in the VLBW group were included in the correlation analyses.
Result: All participants had IQ within normal range (VLBW: 72-110; Controls: 80-127), and there was no difference in socio-economic status between groups. The VLBW young adults scored significantly lower than controls on tasks assessing visual immediate and delayed memory and working memory, while the reductions were not significant on verbal memory tasks. The VLBW group had significantly smaller absolute left (mean 3683.3 (SE 55.3) mm3, $p<0.001$) and right (mean: 3676.8 (SE 61.6) mm3, $p<0.001$) hippocampal volumes than controls (left 3948.6 (SE 46.2) mm3; right 4012.1 (SE 50.2) mm3). Looking at relative volumes, the VLBW group had similar left (mean 0.244 (SE 0.003) mm3, $p=0.242$), but smaller right (mean: 0.243 (SE 0.004) mm3, $p=0.027$) hippocampal volumes vs controls (left 0.249 (SE 0.003) mm3; right 0.253 (SE 0.003) mm3). Significant correlations were found between left ($r=0.344$, $p=0.030$) and right ($r=0.038$, $p=0.016$) relative hippocampal volumes and visual immediate memory in the VLBW group. Total relative hippocampal volume was related to visual delayed memory ($r=0.350$, $p=0.034$), and right hippocampal volume correlated with working memory ($r=0.392$, $p=0.015$). No significant correlations were found in the control group between hippocampal volume and memory tests.
Conclusions: Being born preterm with VLBW has long-term negative consequences regarding memory functions, persisting into young adulthood. The absolute and relative hippocampal volumes were reduced in VLBW young adults compared to term born controls, indicating perinatal brain injury and/or abnormal brain development. Positive correlations were found between hippocampal volume and immediate visual and working memory function in the VLBW group.

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Background: Bayleys III is supposed to overestimate developmental performance of premature infants at 24 mo corrected age compared to older edition II. However, there are no cohort studies using the Bayleys III to assess the temporal evolution of the developmental performance and the impact of gestational age. The aim of the study was to compare the developmental profile in a cohort of premature infants at three serial time points, in order to assess the stability of the results in the context of the Bayley-III standardization in Greece.
Patients and Methods: Bayley-III scales (cognitive, language, motor, social-emotional, and adaptive behavior) were applied in 120 preterm infants (≤ 32 weeks) at a mean corrected age of 12, 24 and 36 months. Preterm infants were divided in 2 groups according to their GA: A (n=59, 24-28 wks), B (n=61, 29-32 wks). All developmental assessments (n=350) were performed by one researcher. A group of 30 full-term infants evaluated at same time points served as controls.
Results: Mean (SD) Bayley-III composite scores (CSs) and overall neurodevelopmental impairment (NDI %) for the 2 groups are shown in the table. Both groups of preterm infants had lower CSs than controls almost in all domains/time points. Overall scores in all domains were lower and stable in ELBW compared to VLBW, who showed a significant increase in all domains ($p<0.01$) over time. NDI (score<85) were higher in ELBW compared to VLBW but differences were significant only for the cognitive domain.
Conclusions: ELBW and VLBW infants have lower scores in all Bayleys' III domains as compared to full-term controls. ELBW infants have lower developmental performance with no improvement over time and significant higher cognitive NDI at the age of 3 years. We speculate that the similar performance observed in the first evaluation between ELBW and VLBW infants is due to the earlier intervention.

		cognitive	language	motor	Social emotion	adaptive
Group A GA:26.4(1.1) BW:978(194)	12mo CSs	94(18)	92(16)	87(17)	100(15)	102(34)
	NDI %	23	29	37	19	25
	24mo CSs	90 (20)	90 (19)	85 (14)	107 (20)	90 (19)
	NDI %	34	36	43	10	36
	36mo CSs	94 (19)	94 (18)	91(21)	108 (20)	89 (23)
	NDI %	23	30	41	7	39
Group B GA:30.6(1.2) BW:1370(350)	12mo CSs	92 (21)	91 (17)	89 (17)	104 (17)	96 (21)
	NDI %	27	36	32	13	27
	24mo CSs	94 (24)	88 (23)	92 (28)	109 (19)	92 (21)
	NDI %	31	36	35	11	31
	36mo CSs	102 (21)	97(19)	97 (22)	112 (16)	96 (20)
	NDI %	11	26	30	3.5	31
Control Fullterm GA:39.6(1.2)	12mo CSs	100 (9)	95 (9)	97 (11)	115 (20)	119 (9)
	24mo CSs	107 (11)	107 (14)	101 (14)	115 (16)	111 (6)
	36mo CSs	99 (7)	110 (12)	115 (21)	110 (19)	111 (10)

ANXIETY NETWORKS AND BRAIN MORPHOMETRY IN VERY LOW BIRTH WEIGHT ADOLESCENTS

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Introduction/Background: Anxiety and its symptoms are related to abnormal neuroimaging findings in the right ventral attention network, part of the anxiety cognitive network, and hippocampus and thalamus, part of the anxiety fear-response network. These areas have been previously reported to be affected in the preterm population. Aim: To assess whether anxiety is associated with changes in cortical thickness and volumes of the right ventral attention network areas, and volumes of hippocampus and thalamus in very low birth weight (VLBW) adolescents.
Patients and Methods: Fifty VLBW (birth weight =1500g) and 57 term control adolescents were assessed at 14-15 years of age. Anxiety diagnosis, sub-clinical diagnosis and symptoms were assessed with diagnostic interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children) and Achenbach System of Empirically Based Assessment (ASEBA) with Youth Self Report (Anxious/Depressed, Somatic Complaints, Withdrawn/ Depressed Syndrome Scales, and the compounding Internalizing Problems Score). Cortical thickness, total brain volume and volumes of subcortical and cerebellar grey and white matter were obtained using an automated MRI segmentation technique (Freesurfer). Associations were analyzed by linear regression and ordinal logistic regression. We adjusted for age, gender and total intracranial volume.
Result: More VLBW adolescents had anxiety diagnoses and symptoms than controls. On MRI, they had thinner cortex in the right ventral attention network areas, including the right ventrolateral prefrontal cortex (rVLPFC), right medial temporal lobe (rMTL), and part of the right temporoparietal junction (rTPJ) compared to controls. They also had smaller thalamus than controls. In the VLBW group anxiety diagnoses and symptoms were associated with smaller right thalamic volumes OR= 3.98 (1.09 to 14.51), p=.036 per cm3 decrease. Higher Somatic Complaint scores group were associated with smaller hippocampal volumes (B=-.753 (-1.424 to -.081), p=.029). Decreased thalamic volumes were also associated with higher scores on Withdrawn/Depressed (B=-.800 (-1.464 to -.136), p=.019), Somatic Complaints (B=-.379 (-.735 to -.023), p=.038), Anxious/Depressed (B=-.631 (-1.254 to -.007), p=.048), and Internalizing Problems (B=-1.299 (-2.283 to -.315), p=.011). Higher Withdrawn/Depressed scores were related to thinning of the rMTL (B=-.237 (-.445 to -.028), p=.027) and part of rTPJ (B=-271. (-.485 to -.153), p=.014).These associations were not found in the control group.
Conclusions: Anxiety diagnoses and symptoms seem to be associated with changes in both the anxiety fear-response network areas and the right ventral attention network areas in VLBW adolescents.

GROWTH AND DEVELOPMENT IN SYMMETRICAL AND ASYMMETRICAL GROWTH RESTRICTED PRETERM-BORN CHILDREN

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Objective: To determine how symmetrical (proportionate) and asymmetrical (disproportionate) growth restriction influence growth and development in preterms from birth to four years.
Design/Methods: Community-based cohort study of 810 children consisting of 86 symmetrical growth restricted (SGR), 61 asymmetrical growth restricted (AGR), and 663 non-growth restricted (NGR) preterms, born during 2002 and 2003. Symmetrical growth restriction was defined as a birth weight (BW) below the 16th percentile (-1 SD) in comparison to fullterms and a head circumference (HC) z score not exceeding the infant's BW z score by > 1 SD. Asymmetrical growth restriction was defined as a HC z score exceeding that for BW by > 1 SD as a proxy of brain-sparing. Developmental delay was assessed by the Ages-and-Stages-Questionnaire at four.
Result: Longitudinal gains in weight and height were similar for SGRs and AGRs and less in comparison to NGRs. At four, z scores for weight were -1.1 for SGRs and -0.7 for AGRs versus 0.3 for NGRs. Z scores for height were -0.9 and -0.6 versus -0.2. Gains in HC were 2 cm more in SGRs, but at one year they were -0.2 versus 0.2 (AGRs) and 0.1 (NGRs). Developmental delay increased with odds ratios of 2.5 (95% confidence intervals, 1.1-6.0) for SGRs and 2.1 (95% confidence intervals, 0.7-5.9) for AGRs.
Conclusions: Weight and height gains were similar for AGRs and SGRs but poorer compared to NGRs. SGRs caught up on HC. Developmental delay was more likely in growth restricted preterms and independent of HC at birth.

CLINICAL ALERT: HIGH RISK OF CEREBRAL SINOVENOUS THROMBOSIS IN PRETERM INFANTS

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Background and purpose: The reported incidence of neonatal cerebral sinovenous thrombosis (CSVT) ranges from 1 to 12 per 100.000 live born infants. Only neonates with clinical symptoms suggestive of CVST are screened. We report the prevalence of CSVT established with serial cranial ultrasound in a prospective cohort of preterm infants.
Methods: Preterm infants below 29 weeks of gestation admitted on our neonatal intensive care unit were studied with cranial ultrasound (CUS). The scan protocol included visualization with color Doppler imaging of the transverse and superior sagittal sinus through the anterior fontanel (8.5 MHz probe) and through the mastoid fontanel (13 MHz probe). When feasible, magnetic resonance imaging was performed to confirm CUS-diagnosed CSVT.
Result: CUS documented CSVT in 11 of 249 preterm infants. Transverse sinuses were most frequently affected. All infants with CSVT were asymptomatic. Postnatal age at diagnosis ranged from 5 to 34 days. The mean gestational age was significantly lower in infants with CSVT. Of the risk factors studied only duration on mechanical ventilation was associated with CSVT; it was significantly longer in the CSVT group.
Conclusions: Systematical serial CUS of infants below 29 weeks of gestational age showed a remarkably high incidence of CSVT of 4.4%. Extensive color Doppler imaging including scans through the mastoid fontanel can detect CSVT at an early stage. Management of this possibly significant condition needs attention.

CAN QUALITY OF INFANT MOTOR BEHAVIOR AT 3 MONTHS POST-TERM AGE PREDICT LATER MOTOR AND COGNITIVE OUTCOME AT 10 YEARS OF AGE IN HIGH-RISK CHILDREN?

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Introduction/background: 'Neurologically high-risk infants' are usually subjects for follow-up, whether they are born with very low birth weight (VLBW: <1500g) and/or neonatal encephalopathy. An infant's typical spontaneous movements around three months of age are called fidgety movements, and lack of such movements have been shown to predict major handicaps, such as cerebral palsy (CP). However, even when fidgety movements are present, high-risk infants may be at risk for later impaired outcome. A detailed assessment of the quality of infant motor repertoire can possibly identify later motor as well as cognitive problems in children with presence of fidgety movements. The aim was to determine whether analysis of quality of infant motor repertoire has predictive value for motor and cognitive outcome at age 10 in children at risk for later neurological impairment. Patients and methods Video-recordings of 40 'neurologically high-risk' infants, comprising 31 VLBW children and nine high-risk children with birth weight =1500g, were analysed according to the Prechtl's General Movements Assessment at 14 weeks post-term age. Fidgety movements were classified as present or absent. Quality of the concurrent motor repertoire was classified as normal if smooth and fluent, and abnormal if jerky, monotonous or stiff. Poor motor outcome was defined as a score =5th centile on the Movement Assessment Battery for Children-2, while poor cognitive outcome was defined as total IQ <85 on Wechsler-Intelligence-Scale for Children-III. Pathological outcome was defined as poor motor and/or cognitive outcome.
Results: At 14 weeks post-term age, nine (23%) children had absence of fidgety movements, including six (19%) VLBW children. All these children were later diagnosed with CP. Of the remaining 31 children with presence of fidgety movements, including 25 VLBW children, 11 high-risk children (eight VLBW) had poor motor outcome and ten children (seven VLBW) had poor cognitive outcome, whereof nine children (five VLBW) had both poor motor and cognitive outcome. Altogether, 14 children (10 VLBW) had pathological outcome. Among the high-risk children with presence of fidgety movements, pathological outcome at 10 years was identified by abnormal motor repertoire at 14 weeks post-term age in 86% (95% CI: 0.60-0.96) of the children. On the other hand, 71% (95%CI: 0.47-0.87) of those with normal clinical outcome was identified by presence of fidgety movements and a normal motor repertoire. Among VLBW children with presence of fidgety, sensitivity of abnormal motor repertoire was 0.90 (95%CI: 0.60-0.98) for pathological outcome and specificity of normal motor repertoire was 0.73 (95%CI: 0.48-0.89) for normal clinical outcome.
Conclusions: This study is the first to combine motor and cognitive outcome in a long-term follow-up study. Results show that assessment of infant motor repertoire, as part of the General Movements Assessment, may discriminate between infants in need of follow-up due to risk of impaired motor and/or cognitive outcome and those who do not need such follow-up, both among high-risk infants in general, and VLBW children in particular. This will help clinicians to prioritise their resources, and in the latter case to reassure parents at an early age.

FIVE-YEARS-OLD CHILDREN WITH CEREBRAL PALSY BORN LATE AND MODERATE PRETERM IN 2001-2005 FROM A EUROPEAN NATIONAL SURVEILLANCE REGISTRY

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Background: Concern about children born moderate or late preterm (32-34 and 35-36 weeks gestational age) has been growing recently. We aimed to assess the contribution of this subgroup for the pool of children with cerebral palsy (CP) and to explore their clinical and functional characteristics.
Patients and Methods: The Portuguese Surveillance of Cerebral Palsy at 5 years of age, a national, population survey, is affiliated to the Surveillance of Cerebral Palsy in Europe, sharing its definitions, classifications and tools. From the whole registry, survivors at five years age from the birth-cohorts 2001-2005, born and living in Portugal were selected. Prevalence rates (95%CI) were estimated. Clinical types of CP and functional outcomes were compared between children born moderate or late preterm (MLPT) and those born extreme preterm (EPT <28 weeks), very preterm (VPT <32 weeks) and at term (=37 weeks)..
Results: From 816 children with CP from the index birth-cohorts, 623 were selected (13.5% missing values for gestational age among 720 eligible children). Children born MLPT (99) account for 15.9% of cases (95%CI 13.18-18.92; annual min. 11.1; max. 20.0), while children born EPT account for 11.9% and those born VPT to 17.7%. The proportion of children with spastic CP was 86.9% in those born MLPT, closer to children born EPT or VPT (90%) than to those born at term (75%) (p<0.001), similarly the proportion of children with dyskinetic CP (7.1%) was closer to children born VPT (7.3%) than at term (17.6%) (p=0.001). Children with spastic CP born MLPT were bilaterally affected in 65.1%, closer to those born at term (61.2%) than to those born EPT (73.1%) or VPT (82.8%) (p=0.001). The prevalence of epilepsy in children born MLPT (40%) was similar to those born at term (45.5%) and higher than among EPT (28.8%) or VPT (29.1%) (p=0.006). No clear difference on the pattern of distribution through GMFCS levels was found, though children with CP born at term were more frequently rated at grade 5 (33.4%) than MLPT (16.8%), VPT (18.5%) and EPT (19.1%) children. The pattern of distribution through BFMF levels was significantly better among MLPT children (62.4% at grades 1-2) than in those born at term (49.2%) and similar to VPT (60%) and EPT (63.6%) (p=0.039). Similar significant differences in patterns of distribution were seen for verbal expression, feeding ability and drooling control. No significant differences on the prevalence of cognitive impairment (IQ <70) were registered (59.1% in MLPT) but the prevalence of severe cognitive impairment (IQ <50) was similar between MLPT (41.9%) and children born at term (47.8%) and higher than VPT (27.1%) and EPT (37.9%) (p=0.002).
Conclusions: Children with CP born moderate or late preterm share clinical features and functional outcomes both with more preterm children and children born at term. Whether differences and similarities depend on the nature of the lesion and insult requires further research.

LONG-TERM OUTCOMES OF EXTREME PRETERMS IN A DISTRICT GENERAL HOSPITAL

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Introduction/Background: In Northern Ireland, most district general hospitals (DGHs) have neonatal units (NNUs) of varying size and capacity, and premature babies are often cared for locally with only some being transferred to the tertiary centre. 3500 babies were delivered in one of these district general hospitals in 2011, and 303 babies were admitted to the local NNU. The 1995 and 2006 EPICure studies showed increasing numbers of preterm survivors, quoting 39% and 52% survival to discharge respectively. 17% had serious cranial USS changes, 14% had treatment for ROP, and 51% CLD. With no recent local data available and no formal network for comparing local and tertiary outcomes, the aim of this study was to collate information for bench-marking on outcomes at 2 years of extreme preterms recently born or treated in this DGH.
Patients and Methods: We collected information on babies with birthweight < 800 grams who were born or treated in this local hospital from January 2006 to December 2009. We used NICORE (Neonatal Intensive Care Outcomes Research and Evaluation) and VON (Vermont Oxford Network) databases, admission diaries, notes and letters to extract clinical data, summarising the neonatal course and current medical / developmental issues. For babies transferred for care closer to home during the neonatal period, we contacted the receiving hospitals for information.
Results: 31 babies with birthweight < 800 grams were treated primarily in the DGH during this time, 23 in-born and 21 ventilated. Mean birthweight was 691 grams and gestation 25 weeks. 58% of these preterms survived to discharge. Of the 13/31 babies who died, leading diagnoses were chromosomal abnormality and lung disease. CLD, ROP and PDA complicated progress of > 60% of survivors. At 2 years, 7 of the 18 survivors have major complications, including cerebral palsy, epilepsy, hydrocephalus and blindness.
Conclusions: At 2 years, 39% of survivors have major difficulties, while many more have 'minor' developmental issues. The preterm outcomes for 2006 to 2009 tally with national statistics for survival (58% vs 52% EPICure) and outcomes. We plan to repeat this retrospective study in 2014, following the progress of babies born from January 2009 to December 2012.

A RISE IN IGF-I LEVELS AT A MEAN POSTNATAL AGE OF 31 TO 33.5 WEEKS IS AN INDEPENDENT PREDICTOR FOR HEIGHT AT 3 AND 5 YEARS OF AGE IN VERY PRETERM CHILDREN

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Background: Growth promoting mechanisms in preterm infants is partly unknown and important to evaluate. Aim: We aimed to study longitudinally growth in infants born very preterm and investigate the influence of early postnatal IGF-I levels on height (H) standard deviation scores (SDS) in children born preterm at older ages.
Design/Methods: 50 children born very preterm (gestational age (GA)<32 weeks) were studied from birth to five years of age and Weight SDS and HSDS were recorded continuously. In all children early postnatal levels of insulin growth factor (IGF)-I and anthropometrical data were studied. The children were divided into four groups according to different GA (23-25 (early), 26-28 (mid) and 29-31 (late)) weeks and subjects born with birth weight SDS below -2 SDS (SGA), independently of GA.
Result: In all subjects, the lowest WSDS during early postnatal weeks occurred at (mean±SD) week 30.0 (±1.0) for all children with GA<27 weeks and at week 31.1 (±1.1) for GA>27 weeks ($p<0.001$). At 40 weeks early GA had lower WSDS compared to late GA group ($p<0.05$), and lower HSDS compared to both mid ($p<0.05$) and late ($p<0.01$) groups. From 5 months of age these differences disappeared. WSDS in SGAs, was lower compared to mid and late GA groups: at 40 weeks ($p<0.001$ and $p<0.0001$), at older ages only to late GA: 5 months ($p=0.01$), 10 months ($p<0.05$), 1.5 years (y) ($p<0.05$), 2y ($p=0.05$), but not at 3y ($p=0.17$) or 5y. HSDS also differed between these two groups at 40 w ($p<0.0001$), 5 months ($p<0.01$), at 1.5y ($p<0.05$) but not at 3 y ($p=0.28$) or 5 y ($p=0.83$). The IGF-I increment (IGF-diff) between week 31 (range 30-32.5) and 33.5 (range 32.6-34.6) correlated to HSDS at 5 years ($r=0.46$, $p=0.002$) in all subjects. In forward stepwise multiple analyses with HSDS as dependent variable, corrected for WSDS and target height SDS (THSDS), the IGF-diff was a predictor for HSDS. At 3 years the values were for WSDS (ß=0.69, $p<0.0001$) and IGF-diff (ß=0.21,$p<0.038$), (adjusted $r2=51\%$, $p<0.0001$) THSDS and BW SDS did not add anything further to the analysis. At 5 y with WSDS (ß=0.68, $p<0.0001$) and IGF-diff (ß=0.35,$p<0.001$), corrected age (ß=0.20,$p=0.022$) and THSDS (ß=0.13,$p=0.16$), (adjusted $r2=72\%$,$p<0.0001$).
Conclusions: From 5 months of age subjects born with GA 23-25w did not differ in WSDS and HSDS compared to preterms born with GA 26-31w. At 3 years of age subjects born SGA had caught up in HSDS and WSDS. A more profound individual rise in IGF-I levels at PMA 33.5 weeks compared to PMA 31 weeks was reflected in increased height at 3 and 5 years of age in very preterm infants. The period (30 to 34.6 weeks) is the time for the lowest weight SDS, the so-called nadir. Efforts during that critical time to optimize nutrition intake might have long-term effects on growth.

THE EFFECT OF NUTRITIONAL FACTORS ON GROWTH IN INFANTS BORN EXTREMELY PRETERM. A POPULATION BASED RETROSPECTIVE OBSERVATIONAL STUDY

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Introduction: Extremely preterm infants are prone to suffer from under nutrition and growth restriction. Improving nutritional regimen could have a crucial impact on growth and neurodevelopment. In this study we wanted to evaluate the effect of early start of parenteral nutrition including aminoacids and lipids from day one in extremely preterm infants on growth velocity (weight and head-circumference).
Patients/Methods: Population based retrospective observational study of two cohorts of extremely preterm infants, with gestational age between 22+0 - and 26+6 weeks. Subjects in the first cohort had a slow introduction of parenteral nutrition (2004-2007). The nutritional regime in the second cohort includes an early start of parenteral nutrition including aminoacids and lipids from day one (2008-2011). To test for differences between cohorts with regards to z-score in weight and z-score in head circumference, ANCOVA was used with cohort as a fixed factor and baseline levels of z-score in weight and head circumference respectively as a covariate in the statistical analysis. All tests were two-sided, p-value below 0.05 was regarded as statistical significant. Analyses were done using the SPSS (IBM Statistics), IBM Inc, US, version 17 or higher.
Result: Cohort 1: 136 infants were born alive and 119 survived to 28 days, cohort 2: 203 infants were born alive and 182 survived to 28 days. Mean GA was 25+2 (range: 22+6 - 26+6). Mean for birth weight, length and head circumference were 782g (range: 347-1189g), 32.7cm (range: 27-40cm) and 23,3cm (range: 19-27cm) respectively. There was no significant difference, when comparing mean and standard deviation for gestational age and birth weight between the two cohorts. When mean is corrected for baseline there were a difference in z-score for weight at 28 days ($P<0.001$), but not for head circumference ($P=0,24$).
Conclusions: The statistically significant difference in mean z-score for weight at day 28 clearly strengthens our hypothesis that changes made in nutritional administration have improved the growth velocity in preterm infants admitted to the NICU. Monitoring and interpreting the growth of preterm infants should be a major area of focus in the neonatal ward.

AUDIT OF NEONATAL PARENTERAL NUTRITION IN NORTHERN IRELAND 2012

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Introduction: Extreme Prematurity is a nutritional emergency as babies enter a catabolic state within hours of birth. Nutrition is therefore considered a vital aspect of care which should be optimised. Parenteral nutrition (PN) is the administration of nutrition intravenously and is an essential component of neonatal care whilst enteral nutrition (EN) is established and the immature gut matures. PN is a complex process, requiring placement of an appropriate feeding catheter, catheter care, accurate calculation and administration of calorific requirements, monitoring of electrolytes and blood chemistry. There are many potentially serious complications. The aim of the project was to assess the practices and support for delivery of Neonatal Parenteral Nutrition in the five Trusts in Northern Ireland against standards derived from the ESPGHAN nutrition guidelines, NCEPOD Report on Parenteral Nutrition and the NICE Quality Standards for Specialist Neonatal Care. It was anticipated that the results will inform neonatal nutrition practice in Northern Ireland and support the development of regional guidelines for neonatal parenteral nutrition. Method The sample size was 200 infants, representing > 10% of annual neonatal admissions in Northern Ireland. The first 40 babies admitted to each of the 5 main neonatal units in Northern Ireland commencing 1st April 2012 were selected for inclusion. Identification of cases was done prospectively and data collection completed prior to discharge. For each infant, the following data was collected: .Availability of local policy/guideline for PN .Time of initiation of PN + availability of standard PN .Appropriate PN Prescribing .Biochemical monitoring .Documentation of Central Catheter Care .Complications of PN .Access to Nutritional Expertise
Results: The range of gestation on admission was 24-41 weeks; median 34. Weight ranged from 0.6Kg-4.97Kg, median 2.24Kg. .The median time of commencement of PN was 9 hours; range 1- 96 hours. The individual unit medians of PN commencement ranged from 2 - 24hrs. .Overall use of Standard PN was 48%. This varied significantly between neonatal units with a range of 15-95% .The access used for PN administration was; 67% peripheral, 17% UVC, 11% no access, 5% long line. 2% had complications with central access. .There was excellent documentation of catheter care; 100% had doctor's name and grade, date, time and catheter type and 84% documented catheter tip position. .The duration of PN ranged between 0-89 days, median 3 days. EN commencement ranged between 0-74 days, median day 1 and full EN was reached between 0-21 days, median day 4. .Patient outcomes: 75% were discharged home, 19% were transferred to another NICU, 4% were transferred to a postnatal ward and 2% died (none related to PN).
Conclusions: There is significant variation in practice for PN administration across the region, particularly the timing of initiation and type of PN used. There may be overuse of PN in some infants. Each unit has excellent aspects of care and areas for potential improvement. A unified approach to PN prescription as a regional guideline may assist with ensuring each infant receives care determined by regional consensus ‘best practice.'

GROWTH FROM HOSPITAL DISCHARGE UNTIL 3 YEARS OF AGE AMONG CHILDREN BORN VERY PRETERM

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Background/introduction Improvement in nutrition of very preterm infants (VPI) has been investigated and improved for the last 2 decades. There is though still a need for improvement and studies involving nutrition and long term follow up on growth after hospital discharge is very relevant. This study compares growth until 3 years of age among children born very preterm (2004-2008) and fed 3 types of nutrition from hospital discharge until 4 months corrected age (CA): Group A received breast milk without fortification, group B received breast milk with fortification, and group C received a preterm formula.
Patients/method: The study was a randomized controlled study on nutrition after hospitalization. Within a 4-year period VPI from 4 different neonatal care units in Denmark were enrolled in the study. Inclusion criteria were gestational age (GA) = 32. Exclusion criteria were diseases possibly influencing eating ability at discharge (e.g. malformations or surgery due to necrotising enterocolitis). Prior to hospital discharge the infants were randomized to breastfeeding with or without fortification, and infants not breastfed received a preterm formula. Weight, length and head circumference was prospectively registered from hospital discharge until 3 years of age, Change in weight, length or head circumference (HC) from time of randomization (prior to hospital discharge) until 3 years of age was calculated into delta Z-scores according to a reference.
Results: At 36 months of age the number of VPI within each group was A 61, B 65, and C 65 VPI respectively. No significant differences were found on weight and HC delta Z-scores at 2 and 3 years of age. Group C improved (delta Z-score) more on length growth compared to both A and B during the entire study period. Comparing group C versus A there was a significant difference on length delta z-score at term, 2, 4, 6 and 12 months CA ($p<0.05$). Comparing group C versus B there was a significant difference at 2, 4, 6 and 24 months CA. It also shows that the growth in all 3 groups have a higher delta z-score at 3 years of age compared to the delta z-score at term (A: term = -0,49, 3 y= -0,13) (B: term=-0,41, 3 y= -0,26) (C: term= -0,70, 3 y= 0,16).
Conclusions: Length growth among children born very preterm seems to improve more in a group fed a preterm formula compared to breast milk. All groups achieved some catch-up growth throughout the period of 3 years.

TIME TO MOVE UNRESTRICTED IS RELATED TO WEIGHT GAIN IN THE FIRST YEAR OF LIFE

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Background: Movement by an infant during the first year of life might influence its activity level and thereby influence growth in early childhood. Aim: To examine whether the time that an infant is able to move unrestrictedly and time spent in baby seats are related to weight and waist circumference at age 9 months and growth from 9 to 24 months.
Methods: In the GECKO Drenthe birth cohort, weight and height were measured in Well Baby Clinics at the ages of 9 and 24 months. Time spent moving unrestrictedly and time spent in baby seats were reported on a questionnaire at age 9 months. Children born <37 weeks or with a low birthweight (<2500 g) were excluded. Outcomes were defined as the Z-scores for weight-for-height, weight-for-age, and waist circumference-for-age at the ages of 9 and 24 months, and changes in Z-scores as between 9 and 24 months of age.
Result: The time an infant is able to move unrestrictedly at age 9 months was inversely related to Z-score waist circumference at 9 months, and the change in Z-scores weight-for-height and weight-for-age between the ages 9 and 24 months. For time spent in baby seats, 'never users' showed a decline in Z-score weight-for-height as compared to those who used baby seats. On the contrary, Z-score waist circumference-for-age declined in children sitting for 1 hour or more in baby seats.
Conclusions: More time spent moving unrestrictedly in infancy may contribute to a healthy growth pattern.

PARENTERAL NUTRITION FOR NICU PATIENTS: COMPARISON OF CURRENT PRACTICES ACROSS EUROPE

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Background: Growth rates in a neonatal intensive care unit (NICU) rarely achieve results comparable to intrauterine growth rates. Level of adherence to guidelines for parenteral nutrition (PN) in preterm infants remains unclear. Objective To assess variation among PN protocols and to evaluate guideline compliance across NICUs of four European countries (the United Kingdom, Germany, Italy and France).
Methods: Survey conducted in a double blinded manner. Senior physicians completed a questionnaire addressing routine PN protocols, awareness and implementation of guidelines.
Results: Seventy-four percent of the units of the 4 countries were surveyed (70% of NICUs in the UK; 71% in Germany; 83% in Italy and 74% in France). Of the 199 received, 161 surveys were included in the analysis. 63% of the respondents initiate amino acid (AA) infusion on D0 with a starting dose of =1.0 g/kg/d reported by 60%. Most NICUs (91%) aim for a target dose for AA of 3 or 4 g/kg/d. Lipid administration is initiated on D0 by 20% and an additional 48% on D1. An initial lipid dose of 0.5 or 1.0 g/kg/d was reported by 98% of respondents, with a target dose of 3 or 4 g/kg/d for 76% of them. Significant variations in PN protocols were observed among countries but the type of hospital or the number of admissions per year had only a marginal impact on the PN protocols. Eighty percent of the respondents stated that they were aware of some PN clinical practice guidelines.
Conclusions: PN practice varies greatly among NICUs and countries. Clinicians initiate PN earlier than in the past but the initiation of PN is still frequently not compliant with current guidelines. There is an urgent need to improve translation and distribution of international or European guidelines in NICUs in order to improve preterm infant outcome.

LONGITUDINAL INSULIN LIKE GROWTH FACTORS (IGF)S IN RELATION TO GESTATIONAL AGE (GA) OR TARGET HEIGHT STANDARD DEVIATION SCORE (THSDS) IN VERY PRETERM INFANTS DURING EARLY POSTNATAL WEEKS

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Background: Levels of various growth factors in blood in very preterm infants may reflect growth and contribute to better understanding of early development. Aim: We aimed to investigate early postnatal levels of insulin-like growth factors in infants born very preterm and relate to early growth development.
Design/ Methods: 72 children born very preterm (GA<32 weeks) (mean age±SD) 28.1±2.1 weeks were studied with weekly blood samples in which IGF-I, IGF-II, IGF binding protein (BP)-1, IGFBP-3 and acid-label subunit (ALS) were analyzed. The infants were divided into four groups according to their GA or birth weight (BW) SDS 1) GA 23-25 weeks (early)(n=16), 2) 26-28 weeks (mid)(n=18), 3) 29-31 week (late)(n=21) or 4) SGA (BW <-2 SDS)(n=17). Infants were also categorized into 3 groups according to target height (THSDS) 1) THSDS <-1 (low), 2) THSDS =-1 or =1 SDS (mean) or 3) THSDS >1 (high). ANOVA and post-hoc Fichers test were used.
Result: BWSDS did not differ between the GA groups (p=0.82). All GA groups had higher BWSDS compared to the SGAs (p<0.0001). WSDS during early postnatal weeks were similar between the three GA groups with an initial fall followed by a continuous rise to PMA 36.5 weeks. The SGAs had the lowest WSDS at both nadir and at PMA 40 weeks compared to all GA groups. A lower THSDS was found in the SGAs compared to mid GA (p<0.05). WSDS, adjusted for GA and BWSDS, was lower in the low THSDS gr at nadir and at 40 w compared to mean THSDS (p<0.01), whereas adjusted levels of IGF-I or Height SDS did not differ. Levels of IGF-I, IGFBP-3 and ALS rose in all GA groups from week 31(range 30-32.5) to week 36 (range 34.7-37.3), although IGF-I in late GA decreased from week 33.5 (range 32.6-34.6) to week 36. At week 36 the SGAs still had lower IGFBP-3 compared to late GA (p<0.05) and ALS to early GA (p<0.01) and early GA had higher IGF-I compared to all other groups (p<0.05). Levels of IGF-II were higher in the low GA at week 29 (range 27.5-29.9) (p<0.01), and higher in late GA week 33.5 (p<0.05). The SGAs had a very high IGFBP-1 value after birth (mean 502 ug/L) that remained elevated at week 31. Mean IGFBP-1 generally decreased from week 31 to 36, a reduction more pronounced in the SGAs (p<0.01 vs mid/late GA), not observed in late GA. The IGFBP-1 was highest in the SGAs at week 31 with concomitant mean WSDS -4.6 and lowest in the late GA (p<0.0001).
Conclusions: WSDS decreased initially in all groups postnatally followed by a rise. IGF-I, IGFBP-3 and ALS increased from week 31 following similar patterns. The similarity of these curves makes patterns reliable although the stimulator remains unknown, as growth hormone is expected to induce this action later on. The high IGFBP-1 in the SGA group at week 31 might reflect malnutrition or anoxia. Low THSDS seems to have an influence on WSDS during early postnatal weeks not reflected in IGF-I levels, possibly reflecting genetic predictors.

IMPROVED NUTRIENT PROVISION WITH NASO-JEJUNAL FEEDS IN EXTREMELY LOW BIRTH WEIGHT INFANTS.

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Introduction/Background: Achieving adequate growth with enteral feeds in ELBW infants remains challenging. Those with significant respiratory morbidity are often nutritionally compromised. Lower oesophageal sphincter immaturity and aspiration of milk feeds may result in reduced enteral and thus caloric intake. Parenteral nutrition administration with its associated complications may be prolonged in this group. We describe our practice of aiming to achieve adequate enteral caloric intake and growth by introducing naso-jejunal (NJ) feeding in this high risk group of patients.
Patients And Methods: 9 ELBW infants received total or partial NJ feeding between January 2011 - March 2013. Median gestation was 24(24 -28) weeks. Median birth weight was 705(570 - 896)g. Median Birth Z score was 0.49(-1.74 - 0.62). All infants had significant respiratory disease and remained ventilated at the time of commencement of NJ feeding. Retrospective case note analysis was performed analysing the initiation and establishment of naso-gastric (NG) feeds, volume and caloric intake achieved before and after introduction of NJ feeds. Weight gain before, during and after the introduction of NJ feeds was assessed. Infant's oral feeding outcome at discharge was reviewed.
Results: All infants were fed maternal expressed breast milk (MEBM). This was commenced at a median of 5(1-9) days. Full nasogastric feeds were established at a median of 20(13-33) days. Median NG volume achieved was 150(135-180)ml/kg/day. Median NG caloric intake was 104(93-140)kcal/kg/d. Median NG protein intake was 2.3(2 - 4.1)g/kg. In one infant breast milk fortifier (BMF) was introduced. NJ feeds were commenced at a median of 40(19-97) days. Median weight at this point was 1.19 (0.75-1.49)kg; Z-score; -1.89 (-3.57- -0.54). Documented reasons for commencement of NJ feeds were gastro-oesophageal reflux in 7 and recurrent aspiration in 2 infants. All infants had radiological evidence of broncho-pulmonary dysplasia at the time of commencement of NJ feeds. Median NJ volume achieved was 180(160-180)ml/kg/d. Median NJ caloric intake was 135(110-144)kcal/kg/d and protein intake was 3.6(2.4-4.2)g/kg. Three additional infants had BMF introduced and tolerated, one infant had peptijunior (50%) introduced and the remainder were fed MEBM. No infant received supplementary parenteral nutrition during NJ feeding period. The median number of days on NJ feeds was 33(10-58) days. Minimal NG feeds were continued in all infants during NJ feeding. No complications of NJ feeding were noted. All infants gradually re-established oral and NG feeding. Feeding assessments performed suggested safe swallow in 8 infants, but 2 remained NG feed dependent at the time of discharge due to disorganised and inefficient suck pattern. Overall, growth remained challenging with a median discharge z score of -2.1(-3.5 - -1.1) but improved growth velocity was seen during NJ feeding.
Conclusion: The introduction of NJ feeds in this high risk population facilitated an improved calorie and protein intake and avoided the reintroduction on parenteral nutrition. ESPGHAN guidelines (2010) on nutritional requirements in premature infants suggest an intake of 110-135 kcal/kg/d and 3.5-4.5 g protein/kg/d which was achieved on NJ but not on NG feeds in our group.

GROWTH AND NUTRITION OF MODERATE AND LATE PRETERM INFANTS

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Background: Relationships between nutrition, growth and later morbidities have been extensively studied in extremely preterm infants, with poor growth linked to adverse developmental outcomes. Recent epidemiological studies show that moderate and late preterm infants are also at increased risk of adverse outcomes (1,2). but little is known about nutrient intakes and growth in these infants and whether enhanced nutritional care might improve outcomes. This study aimed to characterise nutrition and growth patterns of a cohort of moderate and late preterm babies and assess nutritional adequacy as judged by postnatal growth and adherence to published recommendations (3).
Methods: Perinatal and neonatal diagnoses, and growth measurements at birth and during initial hospital stay were extracted from notes of all infants with gestational age 32+0 to 36+6 weeks born in our tertiary maternity unit between 1st January and 30th June 2012. Daily intakes of all intravenous and enteral fluids, and nutritional supplements were entered onto a purpose-designed nutritional database, enabling daily intake of 33 nutrients to be calculated. Data were analysed using Microsoft Excel. Patients 176 eligible infants were born during the study period. Infants were excluded if not admitted to the neonatal unit, had major congenital abnormality or died during their stay. Eighty-six infants had characteristics analysed. Forty-eight infants 32+0 to 34+6 weeks had detailed nutritional evaluation.
Results: Perinatal complications were common: 28% maternal hypertension, 46% delivery by caesarean section, 63% diagnosed with RDS and 22% with neonatal hypoglycaemia. Average Z score for birth weight was -0.56 (SD 0.92), with 17% defined as IUGR (BW <10th centile). Average change in Z-score between birth and discharge was -0.8 to -1.0. Nutrient intakes were generally low in the first three weeks: with protein, calcium and phosphate less than 80% recommended across all gestations. Use of parenteral nutrition was higher in the least mature; 46% at 32 weeks, 11% at 33 weeks and 6% at 34 weeks. Nutrient intakes were generally higher in 32 and 33 week populations across all macro and micronutrients analysed. Vitamin intakes were low in the first 2 weeks with a notable increase in week 3, likely due to commencing multivitamin supplements at 14 days. Breast milk feeding was higher in the 32 week cohort, both at reaching full feeds (54%) and at discharge (62%). 77% of the 32 week population received some preterm formula.
Conclusions: Moderate and late preterm infants are a population with a high incidence of pathology. Both intrauterine and extrauterine growth restriction are common and nutrient intakes in the first 3 weeks of life are generally below recommended. Our findings suggest that the more preterm babies (32-33 weeks) receive greater nutritional support but still have poor neonatal growth. The development of nutritional guidelines targeting this specific population may allow health outcomes to be improved.
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DOES HYPERGLYCEMIA IN HYPERNATREMIC PRETERM INFANTS RESULT IN INTRAVENTRICULAR HEMORRHAGE?

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Background: Hypernatremia and hyperglycemia are highly prevalent in extremely low birth weight preterm infants during the first week of life, and both can lead to hyperosmolarity and osmotic shifts. We hypothesize that hyperglycemia in hypernatremic preterm infants will increase the risk of intraventricular hemorrhage (IVH). Objective: To determine if hyperglycemia during first week of life increases the risk of IVH in hypernatremic preterm infants. Design/
Methods: Single center retrospective review of 216 preterm infants with a GA =28 weeks (admitted over a 9 year period) who had serum sodium, and blood sugar monitored at least every 12-24 hours and more frequently if indicated during the first week of life. Hyperglycemia was defined as blood sugar exceeding 200 mg /dL requiring insulin infusion. Logistic regression analysis identified which of the commonly cited risk factors of IVH, including hyperglycemia could predict the outcome of IVH in hypernatremic (serum sodium=150 mmol/L) preterm infants.
Result: Seventy-six (35%), and 126 (58%) of 216 infants studied developed hyperglycemia and hypernatraemia, respectively. Maximum median serum sodium was 153 mmol/l (range 150-181, IQR 151-156), occurring on median postnatal age of 4 days (range 1-11, IQR 3-5). Median postnatal age at detection of IVH on cranial ultrasound was 5 days (IQR, 3-8). IVH was more frequent in infants with hypernatremia (p=0.012, OR 2.0, 95% CI 1.2- 3.5) or hyperglycemia (p=0.006, OR 2.3, 95% CI 1.3- 4.1) alone, and in infants with both (hypernatremic plus hyperglycemic group 40 of 53, 75% versus non-hypernatremic non-hyperglycemic group 80 of 163, 49%; p=0.001, OR 3.2, 95% CI 1.6- 6.4). Univariate analysis identified male gender, multiple gestation, patent ductus arteriosus, histopathological chorioamnionitis, early onset culture-proven sepsis, and hypotension requiring inotropes to be associated with IVH, in addition to hypernatremia, hyperglycemia, or hypernatremia plus hyperglycemia. Multivariate regression analysis confirmed independent association of IVH with hypernatremia plus hyperglycemia (p=0.015, OR 2.6, 95% CI 1.2- 5.5), but not with hypernatremia or hyperglycemia alone.
Conclusions: Hyperglycemia during the first week of life increases the risk of intraventricular hemorrhage in hypernatremic preterm infants.

EARLY ENTERAL NUTRITION AND POSTNATAL GROWTH OF PRETERM VERY LOW BIRTH WEIGHT INFANTS

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Introduction/Background: The importance of adequate growth in very preterm infants is receiving increased attention due to its relationship to long-term neurodevelopment as well as overall health outcomes. Many researchers are now determining the most effective nutritional strategies, evaluating which of these strategies, as well as their optimal use, lead to the most effective outcomes in terms of body growth, body composition, and neurodevelopmental outcomes.
Patients and Methods: In a prospective cohort study the dependence of postnatal growth of very preterm infants until hospital discharge on their nutrition during the neonatal period was evaluated. Forty consecutively admitted infants with birth weight of < 1250 g, gestational age of < 30 wks. and normal intrauterine growth were enrolled into the study. Exclusion criteria were major congenital anomalies or death. Information about perinatal events that are known to affect postnatal growth was prospectively collected. Type of enteral feeding product, its daily volume, total parenteral and enteral energy and nutrient consumption as well as growth parameters (weight, height and head circumference) were recorded each week starting from the corrected age of 28 wks. till hospital discharge. A standard feeding protocol was followed for all babies but intravenous lipids were not used because of lack of them. Adequacy of postnatal growth was evaluated with the Fenton growth curves (2003).
Results: Postnatal growth retardation (< 10% for the corrected age) at the moment of hospital discharge was found in 31 infants (77,5 %) and in 16 infants (40 %) the retardation was severe (< 3% for the corrected age). Mean (SD) birth weight and gestational age of growth retarded babies were 1004,84 (172,06) g and 28,065 (1,82) wks. accordingly as compared to 1013,33 (146,63) g and 27,11±1,76 wks. in infants with appropriate growth parameters (p>0,05). Prevalence of main perinatal risk factors and morbidity were similar in the groups of infants with and without postnatal growth retardation. In majority of patients enteral feeding was started on the first day of life (1 [1-3] days for growth retarded infants vs. 1 [1-2] days for babies without postnatal growth retardation; p>0,05). During the first 14 days of life all infants were fed with special preterm formula. By the end of neonatal period 18 growth retarded babies (58 %) and 7 infants without growth retardation (78 %) were fed with breast milk (p>0,05). No fortification was used. Based on the results of logistic regression analysis lower daily enteral nutrition volume by the 7-9th days of life and lower level of energy provision with the same level of total protein consumption were significant and independent cause of postnatal growth retardation (OR=0,94; 95 % CI: 0,89-0,99) at the moment of hospital discharge.
Conclusions: Our data provide additional evidence that quality of early nutrition of very preterm newborns may affect long-term growth and health outcomes. Early enteral nutrition is extremely important in settings were resources are limited. Perfecting of clinical feeding practice with optimal feeding product use remains an important reserve for improvement of clinical outcomes in very preterm newborns.

THE INFLUENCE OF PROBIOTICS ON THE PH OF STOOL IN PRETERM INFANTS LJILJANA STANKOVIC, GYNECOLOGY AND OBSTETRICAL CLINIC "NARODNI FRONT", BELGRADE

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Introduction: Colonization of bowels in premature baby with lactic bacteria happens later than in term children. It has been shown, that the stool of children who where fed with breast milk had lower pH, than the stool of the children who were fed with formula milk. The aim: of our study was to investigate whether over time, with longer use of probiotic lactic bacteria, these bacteria colonize the intestine and decreases the pH of the stool?
Material and Methods: Primary groups (20 males and 17 female) include infants fed with formula milk for premature babies with probiotic Lactobacillus rhamnosus Liobif x 2 ½ ampoule per day, gestational age 32.99 ± 1.33, body mass of 1642.43 ± 219.61 grams, Apgar score in the first minute of 7.32 ± 1.0 and in fifth 8.03 ± 0.83. The study included 8.27 ± 1.79 at day of life. In the study, which lasted 28 days, the testing of pH stool was scheduled 9 times for each child. Out of planned 333 stool samples we analyzed 306. We determined pH of each stool sample. By method of nonparametric correlation characteristics of the PH stools & Day of the studies the following linear correlation was obtained: r = -0.421, df = 306, t = 8439, the probability of the null hypothesis p (H0) <0.001.
Result: The values of pH stool decrease during the study.
Conclusions: Longer use of probiotics is associated with improved bowel colonization of lactic bacteria and lower pH stool.

THE MANAGEMENT OF ENTERAL NUTRITION AT A LOT OF PREMATURE NEWBORNS WITH EXTREMELY LOW BIRTH WEIGHT

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Introduction: Morpho-functional multiple organ immaturity of newborns with a birth weight under 1000 grams leads to particular diseases, through frequency and gravity, therefore nutrition is introduced only gradually over the first weeks of life. The introduction of early enteral feeds at these newborns is often delayed due to concern that early introduction may not be tolerated and may increase the risk of necrotising enterocolitis. It involves early initiation of low volume hypocaloric feeds in preterm neonates in order to stimulate the development of the immature gastrointestinal tract of the preterm infant, enhance digestive tolerance and decrease time to reach full enteral feeding independently of parenteral nutrition.
Aims: Authors aim to determine the effect of early trophic feeding on digestive tolerance improvement, and the incidence of necrotizing enterocolitis in extremely low birth weight newborn and to determine the effect of formula milk compared with human breast milk on growth and development in preterm infants.
Material and method: The study was carried out in the Premature and Neonatology Department during three years on a group of 50 premature newborns with birth weight under 1000 grams (800 - 1000 grams) without severe asphyxia.
Result: All the newborns received early trophic feeding (formula milk - group I, human breast milk with breast milk fortifier- group II) associated with parenteral nutritional. Once minimal enteral feeding started, the newborns in both groups have received the same type of milk (breast milk or formula), mode of feeding (bolus gavage or continuous) and rate of feed volume advancement. The newborns were monitored for any evidence of digestive intolerance (gastric residuals or clinical signs of necrotizing enterocolitis), the growth curves and sepsis signs were followed . Body weight was measured at the same time each day .
Conclusions: Minimal enteral feeding with human breast milk compared with minimal enteral feeding with formula milk improves weight gain. Feeding with formula milk rather than breast milk slightly increases the incidence of morbidity (necrotizing enterocolitis, invasive infection) in ELBW infants. Neonatal intensive care should promote natural feeding as the best neonatal metabolic support, its protective effects being correlated with the nutritional characteristics and multiple functions of non nutritive components.

EXTREME MATERNAL ACIDOSIS LEADING TO FETAL DISTRESS AND EMERGENCY CESAREAN SECTION AT 32 GESTATIONAL WEEKS

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Ketoacidosis during the pregnancy is a medical emergency for both the mother and the fetus, In this case a non-diabetic woman (G2P1) presents an extremely severe ketoacidosis. The aetiology was an unusually short wasting period associated with vomiting. The infant presented a severe metabolic and lactic acidosis at birth. The maternal medical history consists of a consanguinity, an Ullrich-type congenital muscular dystrophy (collagen VI-related myopathy without genetic mutation in COL6A1-A3) and a familial glycosuria (mutation found in the genes coding for the Na+-glucose co-transporter SGLT2) The pregnancy was uneventful until 32 weeks. Suffering from malleolar fracture a few days before admission and being on paracetamol treatment she was admitted for vomiting and severe polypnea. The blood gases showed : pH 7.06, pC02 9 mmol/L, HCO3 2 mmol/L, lactate 0.9 mmol/L; anion gap highly increased (28 mmol/L), serum glucose normal, creatinine normal and acetone-ketonuria (4+). The fetal monitoring was normal. She got one dose of betamethasone 6 mg, and after her transfer a dextrose 10%infusion and Sodium bicarbonate 400 mmol . The control blood test showed : pH 7.52, pC02 12 mmHg, HCO3 10 mmol/L, and 3-hydroxybutyric acid 8020 mmol/L with a massive urine secretion, a negative toxicology screening. The fetal monitoring showed a very weak variability and complicated decelerations. A baby girl weighing 1890 g was born at 32 GA by an emergency cesarean section, Apgar 1/6/7. The blood gas control of the cord blood (veinous) showed : pH 7.01, p02 10.1 mm Hg, pC02 34 mm Hg, HCO3 8 mmol/L, lactate 7.5 mmol/L. The resuscitation consisted of intubation for tracheal aspiration (meconial fluid), ventilation with T-piece, perfusion with dextrose 10% and fluid therapy, and nasal CPAP ventilation. The spontaneous breathing appeared after 2 minutes of life. The blood gas control at H1 showed : pH 7.05, p02 50 mm Hg, pC02 22 mm Hg, HCO3 8 mmol/L, lactate 12 mmol/L. Despite a moderate respiratory distress she had very good respiratory drive, and radiologically an image of hyaline membrane disease stage III. She was intubated, received one dose of surfactant and was ventilated on high frequency oscillator D0-D2. Concomitantly she received a total of 2.4 meq/kg of sodium bicarbonate, a fluid resuscitation of 48 ml/kg , an inotropic medication on D0. The blood gas control at H5 showed : pH 7.15, HCO3 15 mmol/L, lactate 5.5. mmol/L. The blood gases normalised by 12 hours of age. She showed transitory signs of coagulopathy, rahbdomyolysis and liver enzyme elevation. A hereditary metabolic disease was excluded. The additional treatment included : conventional ventilation D2-D5, insulin infusion D1-D2, calcium supplementation, fresh plasma, fentanyl-infusion and phototherapy. The neurological tests were normal except a bilateral non complicated intraventricular haemorrhage (Papile II) with transitory periventricular hyperechogenicity until D21. Maternal diagnosis was confirmed a severe starvation ketoacidosis and may have been aggravated by underlying maternal conditions (reduced glucose availability and limitation of gluconeogenesis). The severe acidosis can affect fetus by reducing the uterine blood flow, causing a fetal acidosis, reduce the Pa02 and increase the lactate. The baby could be discharged on D42 with a normal clinical and neurological examination.

LEPTIN UMBILICAL CORD IN NEWBORN INFANTS DELIVERED BY PREECLAMPTIC MOTHERS: ARE THERE DIFFERENCES IN TERM AND PRETERM INFANTS?

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Background: Controversy exists regarding preterm and term newborns leptin cord blood levels and their relationship with size at birth. Association between preeclampsia and leptin cord blood levels has not been thoroughly understood yet. Our hypothesis is that leptin cord blood level, rather than be preterm or term, it depends on the cause of premature birth. Objective To compare the leptin cord blood levels in preterm infants delivered by preeclamptic and non preeclamptic mothers and healthy term newborns.
Methods:A cross sectional study included very low birth weight (VLBW) preterm infants with GA < 32 weeks and BW < 1500 grams, and healthy term newborns with GA = 37 weeks, born in our Hospital from January 2010 to May 2011. Exclusion criteria were congenital malformations or chromosomal anomalies, STORCH infections or HIV+ mother, perinatal asphyxia, and maternal diabetes. Comparison of maternal and neonatal data, and of leptin cord blood levels between preterm delivered by preeclamptic mothers, preterm delivered by non-preeclamptic mothers and a control group of healthy term newborns without maternal preeclampsia were performed by Kruskall-Wallis, Tukey and Chi- square tests. Cord blood was stored in EDTA-containing tubes and immediately centrifugated and the plasma was frozen at - 80°C. ELISA - R&D Systems (Human Leptin Quantikine SixPak, R & D Systems Inc. MN, USA) was used. The study was approved by the institutional review boards and hospital's ethics committee.
Results: We included 121 newborns, 61 male (50.4%), 45 (37.2%) c-section, 35 (28.9%) SGA. Of 55 preterm infants, 24 were delivered by preeclamptic and 31 non-preeclamptic mothers, and 66 healthy term newborns. Maternal Body Mass Index (BMI) was significantly higher in preterm delivered by preeclamptic than non preeclamptic mothers and term newborns (31.7 ± 6 x 26.8± 6 x 30.1±6; p=0.009).The median leptin cord blood levels of preeclamptic preterm, non-preeclamptic preterm and healthy term newborns were 87.9 (32-266), 11.2 (1.3-31.8), and 42.3 (8.6-84.5) respectively. There were significant differences between preeclamptic and non preeclamptic preterm newborns (p=0.0001), and between preeclamptic preterm and term newborns (p= 0.032).
Conclusions: We suggest that leptin levels in preterm newborns depend on the etiology of prematurity, and preeclampsia is associated with high leptin cord levels in very low birth weight newborns.

THE DEVELOPMENT AND IMPLEMENTATION OF A RISK ASSESSMENT TOOL (LABOUR) FOR ATTENDING DELIVERIES ON LABOUR WARD

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Background: Attendance at neonatal deliveries is an essential role in paediatrics. A recent survey of junior doctors revealed high levels of anxiety when attending deliveries due to the limited information provided by midwifery staff when requesting the attendance of a paediatrician at deliveries. As a result, a risk stratification tool, LABOUR, was developed to improve communication between midwifery staff and paediatricians, to ensure the attendance of paediatric staff at deliveries with the necessary experience and skills to optimise neonatal outcome. This audit aimed to identify limitations in the information provided by midwives regarding the progression of labour and the potential for neonatal compromise at delivery.
Methods: A prospective audit was conducted recording the information volunteered by midwifery staff when requesting the attendance of a Paediatric SHO at deliveries. The audit criteria included: Location Age (gestational) Birth type Ongoing concerns (e.g. CTG abnormalities) Urgency Risk factors (e.g. Group B Streptococcus, meconium, maternal pyrexia/tachycardia). These were deemed important in conducting a risk assessment prior to attending a delivery to determine whether senior assistance would be required.
Results: The information from a total of 50 calls was documented. Of these, 98% provided the location, 82% the birth type and 48% the urgency. Detailed information regarding gestation, CTG traces and risk factors for neonatal compromise were 16%, 18% and 24% respectively. Following the initial audit, the LABOUR risk-stratification tool was implemented on the delivery suite. The acronym was placed above phones and attached to patient notes. One month after implementation a re-audit of calls to the Paediatric SHO was conducted. The information provided from 50 calls included: location 94%, gestation 60%, birth type 86%, ongoing concerns 57%, urgency 71%, risk factors 60%.
Conclusion: The LABOUR tool has improved communication of essential information from midwives to junior paediatricians enabling them to determine the potential risk for neonatal compromise at delivery and to ask in advance for senior assistance. The initial study also suggests a reduction in the number of admissions of term babies to SCBU from the delivery suite.

INVESTIGATION OF NEONATAL ENCEPHALOPATHY: THE LOST PLACENTAL 'BLACK BOX'

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Background: After an aeroplane crash, recovery of the 'black box' is a high priority for investigators; analysis of recorded parameters frequently identifies cause or contributing factors. The placenta may likewise provide an invaluable record of the pre-'crash' period in hypoxic ischaemic encephalopathy (HIE); its examination often identifies significant factors such as inflammation or vasculopathy. Our aim was to determine the frequency of histopathologic placental examination and chorioamnionitis in a high-risk population of encephalopathic newborns.
Methods: We studied neonates =36 weeks' gestation admitted with suspected HIE to four tertiary-level UK centres between 01/07/06 and 30/06/11. We assessed if placental histopathological examination was carried out and if so whether there was evidence of chorioamnionitis and/or funisitis.
Result: 361 infants were admitted with HIE in the 5-year study period. Placental data were unavailable for 141 outborn infants. Only 54/220 (25%) inborn babies had placentas submitted to pathology. Histopathological examination confirmed chorioamnionitis and/or funisitis in 17/54 (31%) cases.
Conclusions: Placental examination serves several vital roles in babies born with suspected HIE: it defines pathophysiology, provides important prognostic information regarding future neurodevelopmental outcome, and shows mitigating factors of medico-legal relevance to causation of brain injury. Intrapartum infection and chorioamnionitis are associated with poor neonatal outcomes including cerebral palsy. Only 25% placentas from HIE babies born in our centres were submitted for examination, yet those examinations showed a high incidence of chorioamnionitis. The low rate of placentas being submitted for examination in neonates born depressed, coupled with the high incidence of proven chorioamnionitis in those examined, is itself depressing.

CAN A CHANGE IN INSTITUTIONAL PRACTICE BY AVOIDING ELECTIVE C-SECTION BEFORE 39-WEEKS GESTATION DECREASE NICU ADMISSIONS AND HOSPITAL COSTS?

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Introduction: Several reports associate elective C-sections before 39 weeks gestation (EC-S<39W) with increased Neonatal Intensive Care Unit (NICU) admissions. ACOG recommends against EC-S<39W gestation. In 2010 we began strongly discouraging elective C-section deliveries before 39 weeks (soft stop) and stopped allowing them in 2011 (hard stop). There are no reports of decreasing NICU admissions and hospital costs by avoiding EC-S<39W.
Objective: To determine if an institutional practice change will decrease NICU admissions and hospital cost for infants born by elective C-section before 39 weeks.
Design/Methods: We reviewed the data from electronic records of all deliveries at Joe Di Maggio Children's Hospital performed from January 2009 to August 2012. We compared the number and mode of all deliveries as well the rate of admissions to the NICU of infants born by EC-S<39W. Hospital costs of EC-S<39W infants admitted to the NICU were estimated. Appropriate statistical tests were used. RESULTS: The data is summarized in Table1. A total of 14,644 deliveries were performed during the study period, 40.9% of which were by C-section. There were no significant differences in the yearly variation of total deliveries or the percentage of C-sections. There was a significant decline in the number of EC-S<39W (from 303 to 0 $p < 0.01$), with an initial decrease during the 'soft stop' period and a further decrease in the 'hard period'. The number of infants admitted to the NICU born by EC-S<39W also decreased significantly from 62 to 0 ($p < 0.01$); the correlation between these variables was 0.7. The estimated NICU cost for this population was substantially reduced.
Conclusion: Delaying EC-S<39W resulted in a significant reduction in admissions to the NICU of late preterm or early term infants. This practice was cost effective. While physician education and encouragement resulted in some decline in elective deliveries before 39 weeks, a 'hard stop' was necessary for a major change in practice.

NATIONAL SURVEY ON MANAGEMENT OF NEONATES BORN TO MOTHERS WITH POLYHYDRAMNIOS TO EXCLUDE OESOPHAGEAL ATRESIA IN THE UNITED KINGDOM

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Background and aims: It is common practice in many neonatal units across the United Kingdom(UK) to insert a nasogastric tube(NG) at birth to exclude oesophageal atresia in babies born to mothers with polyhydramnios. There is limited evidence to support this practice. We performed a national survey to find out practices across neonatal units in the UK.
Methods: A structured questionnaire was sent to all the British Association of Perinatal Medicine members working in the UK from November 2012 to January 2013. . The same questionnaire was conducted via telephone for any remaining UK neonatal units not covered by this initial process. All the responses were analysed.
Result: We received 50 responses from Neonatal units across the UK. 40% were level 3 units and 60% were level 2 units. 24%(12) have written unit guidelines. 52%(26) of the units routinely check for oesophageal atresia in all babies born to mothers with polyhydramnios, while 16%(8) use a risk-based approach. 54%(27) pass NG or orogastric tubes, 50%(25) aspirate the tube and check the acidity. 44%(22) check the NG tube position radiographically if the aspirate is not acidic.
Conclusions: The practice of passing an NG tube in neonates born to mothers with polyhydramnios varies from hospital to hospital across the UK due a to lack of evidence. Larger studies looking into the incidence of oesophageal atresia in neonates born to mothers with polyhydramnios are required to standardise this practice and to also ascertain if a risk-based approach would be more appropriate.

IS ANALYTICAL CONTROL NEEDED FOR THE INFANTS BORN TO MOTHERS WITH AUTOIMMUNE HYPOTHYROIDISM? PROTOCOL REVISION TO IMPROVE CLINICAL CARE

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Introduction: The most common cause of hypothyroidism is the autoimmune disorder known as Hashimoto´s thyroiditis. The estimated risk of developing transient congenital hypothyroidism (TCH), caused by maternal TSH receptor blocking antibodies in Hashimoto disease is one in 180,000 newborns. However, a recent review of neonatal thyroid disorders recommended that infants of mothers with hypothyroidism should be screened for TCH at two weeks of postnatal age.
Materials and method: The aim of our study was to improve the quality of neonatal care by reviewing the results after the application of a follow up protocol for the infants born to mothers with autoimmune hypothyroidism. A retrospective study was conducted at the Puerta de Hierro Majadahonda Hospital, with a third level neonatal intensive care unit. The study took place during 16 months (january2012 to april 2013). On december 2011, the accepted protocol of infants born to mothers with autoimmune hypothyroidism in our hospital was as follows: -to perform universal screening with thyroid stimulating hormone (TSH) at 48 hours of life by blood blotter. - analytical control in our laboratory with TSH and free thyroxine levels (FT4) at one month of age. These results were centralized in a specific neonatal register. -If the result was altered, we repeated it with TSH, FT4 and T3 every two weeks until normal levels were obtained and a thyroid ultrasound was made. If the second test was abnormal, the pacients were followed up by a pediatric endocrinologist We reviewed the medical records of the infants born to mothers with autoimmune hypothyroidism and perform the descriptive statistics with the values obtained.
Results: There were 4403 deliveries in this period (16 months). One hundred and forty to newborns were reviewed as infants born to mothers with hypothyroidism. The incidence of maternal autoimmune hypothyroidism was 3.2% in our series. There were 10 patients lost (7%), the test was applied to all of them and these results were considered in the analysis of the results. A single test was necessary in 119 patients/142 (83.8%) with normal values. Two or more test were performed in13 patients/142 (9.1%); [9 : 2 test, 2 : 4 test and 2 :5 test]. 13 patients were diagnosed with transient mild hyperthyrotropinemia (normal peripheral hormones and eventually normalizing TSH values in the trace). Only four of them needed a thyroid ultrasound, which showed no abnormalitis. TSH values at one month of age : Mean: 3.22 mIU / ml. SD 1.39, coefficient of variation of 0.43.Median:3 mIU / ml. Regarding maternal treatment with L-thyroxine: 142 mothers: 126 required treatment during pregnancy and 10 not. The data is unknown in 6 cases.
Conclusion: We found no congenital hypothyroidism caused by maternal TSH receptor blocking antibodies in Hashimoto disease. Routine postnatal screening in all infants born of mothers with autoimmune hypothyroidism, other than universal screening program after birth, is unjustified. After the review of our protocol we propose not to make any additional analytical control in order to avoid unnecesary test, improving clinical care.

THYROID FUNCTION TESTS IN NEONATES BORN TO MOTHERS WITH THYROID DISEASE: AN ANALYSIS OF PRACTICE AND OUTCOME

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Background: Trans-placental transfer of anti-thyroid medication or, rarely, thyroid receptor blocking antibodies in mothers with autoimmune thyroid disease, can cause neonatal hypothyroidism. Hyperthyroidism may result from trans-placental transfer of thyroid receptor stimulating antibodies (TR-Ab) from mothers with Graves' disease, or, rarely, in Hashimoto thyroiditis. Previous studies have suggested we are undertaking too many thyroid function tests (TFT) in neonates, particularly in those born to mothers with hypothyroidism, due to the rarity of thyroid blocking antibodies. Further implications identified include the extra stress of hospital visits, blood tests and cost implications. AIM: There is no national guidance on how to manage or investigate neonates born to women with thyroid disease. This survey aims to identify the burden of thyroid function testing in these newborns and whether the results impact on our management.
Patients And Methods: Babies born to women with thyroid disease have TFT at 7-14 days at a weekly blood clinic and were identified from the appointment diary. Data collected included maternal thyroid status, maternal diagnosis and treatment, baby's TFT results and whether treatment, admission or referrals were required.
Results: 5109 women delivered live births during 2012, of which 82 (1.6%) mothers had thyroid disease, including 8 (0.2%) with Graves' disease or hyperthyroidism. 81 babies had TFT in blood clinic due to maternal thyroid disease over 62 weeks (January 2012 to March 2013); totalling 114 appointments and 98 TFT. 3 TFT were haemolysed or insufficient. 13 (11%) appointments 'did not attend' (DNA). The first clinic appointment was at mean 13 days (range 12 to 31). 21 (26%) babies had follow-up. The mean number of follow-up appointments was 0.4 (range 0 to 3). Maternal diagnoses were: hypothyroidism (63, 78%), hyperthyroidism (3, 4%), Graves' disease (7, 9%), unknown (7, 9%). Maternal current medications: thyroxine (62, 77%), carbimazole (1, 1%), propylthiouracil (3, 4%), unknown (12, 15%). 41 mothers (51%) had thyroid antibodies tested (TR-Ab and thyroid peroxidise antibodies), of which 40% were abnormal. No babies born to mothers with Graves' diseases or hyperthyroidism had raised TSH. 8 babies had raised TSH in clinic, of which 3 mothers were thyroid antibody negative, 4 had raised thyroid peroxidise antibodies (anti-TPO) and 1 had both TR-Ab and anti-TPO. All babies with raised TSH in clinic subsequently, on follow-up, had a normal TSH and did not require treatment, admission or referral.
Conclusions: Our data supports that unquestioned thyroid function testing in babies of mothers with thyroid disease seems neither sensitive nor specific in identifying babies at risk. These tests have health economic implications. The theoretical charge per appointment (including processing the bloods) is £133. If babies born to mothers with hypothyroidism were not tested a theoretical saving of £8,395 per year could be made. Costs are also psychological; parental anxiety attending clinic, observing blood tests and waiting for results could be avoided. Based on our conclusions, together with evidence from other studies and guidelines, we will propose a new local protocol for managing babies born to mothers with thyroid disease.

IMPROVING THE ADMISSION TEMPERATURE IN PRETERM INFANTS - A TERTIARY NEONATAL EXPERIENCE

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Introduction: The way we manage our babies in the first hour of life has influence over the rest of the neonatal course. Temperature on admission to neonatal unit in preterm infants relate directly to the outcome. Hypothermia on admission to neonatal unit is associated with increased neonatal mortality. Unfortunately >46% of babies born at <29 weeks gestation in UK are still noted to be hypothermic on admission (<36.5 C). A review of our own practice revealed a need for improvement of our delivery of early neonatal care particularly the early temperature control in preterm infants. The aim of this project was to improve the admission temperature for all preterm infants born in house at <29 weeks gestation. The standard of care being all babies born at <29 weeks gestation should have a temperature >36.5 C on admission.
Methods: During this project we reviewed our practice and identified areas for improvement, prospectively educated our staffs, encouraged staff to self-audit and instigate their own goals for improvement. We learnt lessons as we progressed and acted on them promptly. We prospectively collected data looking at initial stabilisation, temperature support received at birth and temperature on admission over a period of 4 months (May to August 2012). For planned stabilization and subsequent admission to neonatal unit from obstetric theatres, we use a stabilization room attached to the theatre on one side and the neonatal room on the other side. Other babies get admitted to the neonatal from different rooms in delivery suite located on the same floor.
Results: Data was collected from 25 preterm infants during this period. 19 infants were admitted from stabilization room, 5 infants from labour suite and 1 from main theatre. 12 infants (63%) admitted from stabilization room had temperature >36 C. 5 infants (26%) had temperature <36 C (35.2-35.8 C) - transwarmer wasn't used in 3 cases and no plastic bag was used in one case. 2 infants admitted from the stabilization room had temperature >37.5 C - both infants had sepsis. 3 out of 5 infants (60%) admitted from the labour suite had admission temperature >36 C. 2 had temperature <36 C (one was born before the arrival of neonatal team, transwarmer wasn't properly activated in the other). The infant admitted from main theatre had temperature >36 C. A significant improvement was noted in admission temperature during this period compared to a 3 months period earlier in the year (Admission temperature <36.5 C in 36% infants during study period compared to 60% earlier in the year. Similarly admission temperature <36 C dropped from 23% to 19%.).
Conclusions: An improvement in the structure of the stabilization room (re-design of airflow), early use of transwarmer, plastic bag and hat, installing a heating cabinet for towels - all were important steps for this improvement. Recognition of important issues, regular update with reminder of issues among nursing and medical colleagues and improved teamwork were the key points for success. There is still a large room for improvement and a continuous teaching programme would now help to sustain this improvement.

USE OF AND COMPLICATIONS OF FEMORAL VASCUALR CATHETERISATION IN THE NEONATAL INTENSIVE CARE UNIT

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Background: Cannulation of the femoral vessels to establish central venous access and invasive arterial access is widely used in paediatric intensive care but less so in neonatal care. Barriers to the use of technique include technical difficulties in insertion and concern about vascular and infections complications. We use femoral vessel cannulation in babies when other forms of access are not available. We have performed a retrospective analysis of 5 years experience with this technique to describe the complication rates.
Methods: The electronic patient records of all babies admitted to our unit from 1/1/2008 to 31/12/2012were searched to identify all femoral arterial or venous cannulations. Data was abstracted included demographics, details of line insertion and reported complications. Data on positive blood cultures were obtained from our laboratory database. All positive blood cultures were reviewed to establish whether this could be classified as a Catheter Associated Blood Stream infection (CABSI).
Result: 135 lines were placed in 94 babies. 26 had a single arterial line only. 40 had a single venous line only. 7 had both a single arterial line and a single venous line. The remainder had multiple insertions. 51 arterial lines were sited for a median (range) of 4.2 days (30 mins to 31 days). 82 venous lines were sited for a median (range) of 5 days (3 hours to 43 days). Altogether there were 701.25 days of care given with either one or two femoral lines. Median (range) gestation and birth weight was 27 (23 to 41) weeks and 950 (520 to 4390) grams for babies with arterial lines and 27 (23 to 42) weeks and 905 (510 to 4610) grams for babies with venous lines. 6 arterial and 3 venous lines were removed because of ischaemia in the leg. No baby experienced a permanent ischaemic injury. The line was kept in until no longer clinically needed for 14 arterial lines and 13 venous lines. Some babies were transferred to another centre with the line still in place (5 arterial, 7 venous). Some died of their illness whilst the line was still in place (11 arterial, 26 venous). Other reasons for removal were; occlusion (8 arterial, 11 venous), fell out (1 arterial, 6 venous), concern about potential infection (6 arterial, 16 venous). 23 episodes of CABSI were identified. This gives an infection rate of 17% and a CABSI rate of 33 per 1000 catheter days.
Discussion: Catheterisation of the femoral vessels is possible in even the smallest neonatal patients, half of the babies in our study were below 27 weeks gestation and 950g. These catheters allowed us to administer parenteral feeds and vasoactive drug infusions to a babies in whom we could not establish other forms of access. Although some babies experienced compromise to the distal circulation, we saw no permanent ischaemic injuries. The associated infection rate is higher than that reported in most neonatal populations, although this may be a function of the nature of the illnesses that these babies were experiencing.

AUDIT OF NEONATAL ENTERAL NUTRITION IN NORTHERN IRELAND 2012

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Introduction: Parenteral nutrition (PN) is the administration of nutrition intravenously and is an essential component of neonatal care whilst enteral nutrition (EN) is established and the immature gut matures. However, the aim is to establish full enteral feeds sufficient for growth. Maternal human milk is the ideal enteral feed but due to preterm delivery, stress and maternal ill health, there can be a delay and difficulty in obtaining maternal expressed breast milk. If unavailable, alternative options include donor breast milk and preterm formula. NICE quality care standards for breastfeeding state there should be 'evidence of a written local policy on breastfeeding and expressing milk for babies receiving specialist neonatal care.' 'Mothers of babies receiving specialist neonatal care can expect to be offered support to start and continue to breastfeed, including support to express milk.' (NICE Quality Standard for Specialist Neonatal Care). The aim of the project was to assess the practices and support for delivery of Neonatal Enteral Nutrition in the five Trusts in Northern Ireland against standards derived from the NICE Quality Standards for Specialist Neonatal Care. It was anticipated that the results will inform neonatal nutrition practice in Northern Ireland and support the development of regional guidelines for neonatal enteral nutrition.
Method: The sample size was 200 infants, representing > 10% of annual neonatal admissions in Northern Ireland. The first 40 babies admitted to each of the 5 main neonatal units in Northern Ireland commencing 1st April 2012 were selected for inclusion. Identification of cases was done prospectively and data collection completed prior to discharge. For each infant the following was collected: .Availability of local policy/guideline for EN/Breastfeeding/maternal milk expression/Donor milk .EN practices; timing of initiation/milk used/duration to full enteral feeds .Access to Nutritional Expertise
Results: The range of gestation on admission was 24-41 weeks; median 34. Weight ranged from 0.6Kg-4.97Kg, median 2.24Kg. .The median time of commencement of EN was day 1; range 0-74 days. Full EN was reached between 0-21 days, median day 4. .Initial milk used was; 48% EBM, 35% formula, 14% DEBM and 3% never received EN. .63% received some EBM; 27% received DEBM. .Milk at full EN was; 36% formula, 30% EBM, 14% EBM + formula, 9% DEBM, 7% none. .On discharge 55% were on formula, 28% EBM. .Range of corrected gestation at discharge: 28-44 weeks, median 37. Weight range 0.81 Kg-4.97Kg, median 2.47Kg. .Patient outcomes; 75% were discharged home, 19% were transferred to another NICU, 4% were transferred to a postnatal ward, 2% died (none related to EN).
Conclusions: Whilst there is an increasing emphasis on the use of maternal breast milk in preterm infants, rates of EBM use fell from 48% on initiation of enteral feeds to 28% at discharge. Only 63% of neonatal admissions in Northern Ireland ever received EBM. On discharge, 55% of babies were receiving exclusively formula milk. Each unit has aspects of care that are excellent and aspects which could be improved. A unified approach to enteral nutrition as a regional guideline may assist with ensuring that each infant receives care which has been determined 'best practice.'

IS NEONATAL GONAD RADIATION EXPOSURE A SIGNIFICANT PROBLEM IN PREMATURE INFANTS?

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Background: Preterm infants have multiple radiographs during their admission to neonatal units. We do not know the cumulative effects of this radiation on developing tissues, especially the gonads. There are no national guidelines regarding exposure or specific landmarks to exclude in radiographs for neonates.
Aims: We aim to determine number of radiographs and incidental inclusion of gonads and overall radiation exposure.
Methods: Retrospective review of male babies admitted to tertiary neonatal unit during 2012 (12 months) who were gestation less than 32 weeks or birth weight under 1500 grams and had radiographs performed during their stay. We exclusion radiographs performed at other units and lateral views. RESULTS: 78 babies were included and 587 radiographs were reviewed. The gestational age was from median 27 weeks (IQR 26-30 weeks), and 1.06kg (IQR 0.84-1.28kg). The mean number of radiographs per patient was 7.5 (SD 7.2). 124 long line position radiographs were excluded, as these require visualisation of the whole line tract. 25/46 (54%) abdominal radiographs and 86/162 (53%) chest/abdominal radiographs included below the pubic symphysis,. 111/208 (53%) radiographs included mean 13.5mm (SD 9.3) below the pubic symphysis; with 57.5% just below the pubic symphysis, 38% imaged below the buttock crease and 4.5% included the knees. There was no significant difference in exposure rates depending on indication for radiograph. There were no radiographs repeated for inadequate views in this series.
Conclusion: We are currently exposing the male gonadal area in over 50% of abdominal view radiographs. Potential effects on neonatal tissues are increased due to rapid growth and a high mitotic state. Currently, there are no studies assessing long term outcomes due to radiation exposure. We should aim to minimise radiation exposure to these areas, especially as this is not required to alter clinical decision making. Gonad shields are commercially available, and could be used to limit radiation to this area. These are becoming less used in paediatric/adult radiology due to obscuring images leading to repeat exposure. The higher incidence of cryptochidism in premature babies limits the utility of landmarks of gonad position. Despite limited evidence, we should minimise potential harm; imaging when clinically indicated and limiting radiograph windows to include only necessary areas.

HOW SAFE IS INSULIN USE IN PRETERM INFANTS?: A UK TERTIARY NEONATAL INTENSIVE CARE UNIT EXPERIENCE

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Background: Hyperglycaemia is associated with increased complications of prematurity and is common in the first two weeks of life in very preterm infants (VPI). Insulin treatment for neonatal hyperglycaemia is standard practice in many neonatal services (67% in a UK survey). Insulin treatment usually peaks on days 4-10.The existing evidence base demonstrates insulin improves blood glucose control but does little to quantify risks (hypoglycaemia). Hypoglycaemia risks brain injury. Randomised controlled trial (RCT) evidence indicates the risk of hypoglycaemia increases with more aggressive blood glucose (BG) control from birth although this is not how insulin is used in clinical practice. Recently, the American Society of Parenteral and Enteral Nutrition guidelines recommended caution in the use of insulin treatment in preterm infants because of the risk of hypoglycaemia. Aim: To audit compliance with the local insulin-treated hyperglycaemia protocol (2 successive BG measurements >12mmol/l) with a specific focus on the incidence, duration and timing of hypoglycaemia in relation to insulin treatment.
Methods: Infants (<1200g; <29 weeks) were identified from a previous RCT: the SCAMP nutrition study. In this study, infants were restratified into insulin-treated and non-insulin-treated groups (ie not original randomisation). Because insulin-treatment is strongly gestation dependent the non-insulin-treated group provides a contemporaneous comparator (ensuring identical clinical guidelines were applied) in VPI but not a gestation/birthweight matched control. The clinical data set included mean daily BG (MDBG) (estimated from intermittent BG monitoring), number/duration/timing of hypoglycaemic episodes (divided into severe: <2.7mmol/l and moderate: 2.7-4.0mmol/l) and insulin use. Hypoglycaemia in first 24 hours was measured but excluded from analysis (as this is substrate/endocrine related and not due to insulin-treatment).
Results: All 150 infants from the SCAMP study database (October 2009 - May 2012) provided data. 72 (48%) infants received insulin during the first 15 days. The mean (sd) birthweight/gestation was significantly lower in the insulin-treated group (800 g versus 976 g and 26.1 weeks versus 27.1; $p<0.01$ for both comparisons). There were no clinically important violations of the hyperglycaemia clinical guidelines with regards to initiation of insulin-treatment. However, there was evidence of pragmatic delays in stopping insulin-treatment based on BG monitoring. In general, these delays were to avoid rebound hyperglycaemia. The MDBG was consistently higher in the insulin-treated group, peaked on day 6 in both groups (10.9 versus 7.2mmol/l; $p<0.001$) with the largest difference occurring on day 4 (3.8mmol/l). In the insulin-treated group there were 358 insulin-days with a peak in insulin-treatment on day 7. No infants received insulin on day 15. The number of severe hypoglycaemic episodes (<2.7mmol/l) was 53 versus 46 in the insulin and non-insulin-treated groups respectively ($p=0.39$). Only 4 episodes occurred while on the insulin infusion (involving 3 patients). In total there were 34 (16.3%) episodes of moderate hypoglycaemia (2.7-4.0mmol/l) associated with insulin treatment. The average number of BG measurements per infant was significantly higher in the insulin-treated group (87 versus 54 ; $p<0.01$).
Conclusion: Using an insulin-treatment threshold for hyperglycaemia of >12mmol/l has a low risk for hypoglycaemia but results in MDBG levels up 3.8 mmol/l higher than a reasonable comparator population.

BETTER NICU MANAGEMENT USING EFQM SYSTEM

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The management of the department of neonatology in Hillel Yaffe Medical Center considers the collaboration of the well baby nursery (WBN) and the neonatal intensive care unit (NICU) of the utmost importance, creating common language for both units, facilitating the transfer of infants from one unit to the other most effectively, creating a professional handling of the infant and its family, resulting in an improved service The department management sought an additional method of management, and the organization consultant together with the quality unit introduced the EFQM model. The targets of the intervention were: A. Improving customer service - humane attitude and inpatient quality aspects; B. Creating better integration in the department between NICU and WBN through a successful joint management experience; C. Improving customer service - from the professional (medical) standpoint. The challenge is complex due to the different nature of the units, the management method that is uncommon in medical departments of health systems in Israel, and the department's administrative structure built of complex matrix-based authority systems. As we did not collect numerical data before introducing the EFQM model to the department, the improvement is not analytically measureable. Yet, all employees feel the change, and are much satisfied. And we introduce a patients' satisfaction questionnaire, and started collecting data. We are at the beginning, but the achievements are already evident: . Strengthening communication within the department between units; . Building tools as a basis for introducing changes and service promoting such as satisfaction surveys; . Establishment of joint working teams to improve processes and outcomes. This application format in a medical department is unique, and emphasizes the basic assumptions, i.e. the involvement of the majority of employees in the process; sustained activity over time.

'SAFE TAXI': QUALITY IMPROVEMENT PROGRAM FOR NEWBORN'S FIRST VEHICLE RIDE HOME

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Introduction/Background: Car seats prevent injury and death in children during motor vehicle accidents. However, not all parents of newborns follow this recommendation sometimes due to cultural reasons of being unexposed to regular communication means used to deliver safety education. Therefore, we developed and evaluated an educational intervention to enhance parents' use of car seats for their newborn's first ride home from the hospital.
Patients and Methods: Parents of newborns who did not bring car seats prior to discharge were identified. Parents were offered a loaner car seat to use in a 'safe taxi' service. Car seats were donated and all taxi drivers were trained to install the car seats safely. The program was evaluated using pre-program questionnaires and follow-up phone calls 4-8 weeks post discharge using open-ended questions which were evaluated using framework analysis methodology.
Result: Twelve parents participated in the program during the study period and all agreed to participate in the evaluation process. Eleven parents were Jewish and one was Muslim; all reported being religious. Most (75%) reported that they had not previously used car seats routinely, and the reason was not financial. Following the 'safe taxi' program 83% reported the use of car seats when traveling. Upon follow-up, all participants reported that the program increased their awareness and use of car seats.
Conclusions: The program answered the needs of a population that is mostly not exposed to the mainstream modes of safety education due to cultural factors. The intervention was well received by the parents; it increased awareness, changed practices, and assured that more newborns traveled home safely fastened in a car seat.

ADVERSE DRUG REACTIONS IN CHILDREN - HOW SAFE ARE MEDICINES WE PRESCRIBE IN HOSPITAL?

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Background: Assessment of the harms of medicines is as important as assessment of their benefits. Most medicines currently used in children were developed before the introduction of the European paediatric medicines regulation in 2007. Underreporting of adverse drug reactions (ADRs) is common and current study data on adverse drug reactions (ADRs) in children is incomplete due to methodological differences between studies. Only half of all studies provide drug data and very few studies provide data on causality, severity and risk factors of paediatric ADRs. In order to investigate the safety of paediatric medicines currently used in hospitalised children we wanted to assess the incidence of ADRs, to characterise these ADRs in terms of type, drug aetiology, causality and severity and to identify risk factors. Patients
Methods: We undertook a year-long, prospective observational cohort study of admissions to a single UK paediatric medical and surgical secondary and tertiary referral centre (Alder Hey). Children aged between 0 and 16 years 11 months and admitted for more than 48 hours were included. Observed outcomes were occurrence of ADR and time to first ADR for the risk factor analysis.
Result: 5881 children (6601 admissions) were included, 17.7% of which experienced at least one ADR. Opiate analgesics and drugs used in general anaesthesia (GA) accounted for more than 50% of all drugs implicated in ADRs. 0.9% of ADRs caused permanent harm or required admission to a higher level of care. The five most common reactions were nausea and/or vomiting, pruritus, constipation, diarrhoea and somnolence, together accounting for 64% of all observed ADRs. Children who underwent a GA were at more than six times the risk of developing an ADR than children without GA (HR 6.40; 95% CI 5.30-7.70). Other factors increasing the risk of an ADR were increasing age (HR 1.06 for each year; 95% CI 1.04-1.07), increasing number of drugs (HR 1.25 for each additional drug; 95%CI 1.22-1.28) and oncological treatment (HR 1.90; 95%CI1.40-2.60).
Conclusions: This is the largest study of ADRs among paediatric in-patients. ADRs are common in hospitalised children. Children who had undergone a GA had more than 6 times the risk of developing an ADR. GA agents and opiate analgesics are a significant cause of ADRs and have been underrepresented in previous studies. This is a concern in view of the increasing number of paediatric short-stay surgeries since ADRs may be occurring in the community. The small number of severe ADRs is reassuring, however, more work needs to be undertaken to minimize the effect of commonly occurring reactions which are potentially avoidable such as opiate induced vomiting or constipation. Most ADRs are medically well recognised and clinically not severe. However, ADRs can cause significant distress to children and their parents.

CRANIAL DEFORMATIONS, DIMENSIONS AND CERVICAL RANGE OF MOTION IN HEALTHY NEONATES

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Background: Deformational plagiocephaly (DP) is a relatively common occurrence in otherwise normal infants. The prevalence peaks at around 7 weeks of age, being 22.1%. Torticollis is often proposed as a predisposing factor for DP and co-occurrence rates up to 97% have been reported in later infancy. However, little is known of the prevalence and relationship of these conditions just after birth and the association between neonatal and subsequent nonsynostotic cranial deformations remains controversial. Objectives were to determine the prevalences and characteristics of DP and torticollis in healthy neonates and to examine the relationship between cervical range of motion (ROM), head molding and head size. We also sought out to provide normative values for anthropometric measurements describing cranial height.
Patients and Methods: This was a prospective, cross-sectional study. 129 healthy infants born in the University Hospital of Oulu were examined at the mean age of 46 hours. A digital photographic technique combined with computer-based cephalometric analyses was used to determine DP and to measure the Cephalic Index. Digital goniometry was used to measure the cervical ROM. The distances from ear to ear and from glabella to opisthocranion were measured along the scalp and a novel index representing cranial height was derived.
Result: 7.8% of the newborns had DP and 4.7% had torticollis. Significant risk factors for DP included gestational diabetes ($p = 0.011$), vacuum assisted delivery ($p = 0.006$) and prolonged second stage of labor ($p = 0.048$). DP was not associated with torticollis. However, the range in lateral flexion was linearly reduced by cranial asymmetry ($r = -.216$, $p = 0.014$) when assessed as a continuous variable. CI correlated strongly with cervical ROM in all directions (CI and range for head rotation $r = -.346$, $p < 0.001$; CI and range for lateral flexion $r = -.288$, $p < 0.001$; CI and forward flexion $r = -.275$, $p = 0.002$), meaning that brachycephalic infants (i.e. infants with shorter, wider heads) have more restricted cervical movements than their counterparts. Those with a higher CI also have relatively higher craniums ($r = .446$, $p < 0.001$) but smaller head circumference ($r = .229$, $p = 0.009$), indicating that in brachycephalic infants a larger part of the cranial volume is shifted into head height and there is in fact less variation in total cranial volume than what head circumference alone would suggest.
Conclusions: Newborns with DP had no torticollis, which suggests that torticollis presenting with plagiocephaly in later infancy often develops postnatally. Brachycephalic newborns have a more limited cervical ROM which could be prone to developing further cervical imbalance and/or positional preference and finally DP.

POPULATION STUDY OF THE BONE TISSUE STRUCTURAL-FUNCTIONAL STATE IN CHILDREN AND TEEN-AGES IN THE EAST OF UKRAINE.

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Introduction: The problem of osteopenia and osteoporosis in children turned from a rare pediatric problem to a frequent pathology which is difficult to diagnose. This problem is especially urgent for the present-day in Ukraine because the level and quality of therapeutic and diagnostic care as well as nutrition quality are influenced by the transformation of the society. More updated (X-ray absorptiometry, Computed tomography, magnetic resonance imaging, ultrasonography, ultrasound and X-ray densitometry) methods allow early revealing of impairments in the bone tissue formation. Each of these methods has its advantages and disadvantages. At present main disadvantage is a high cost of the equipment and its absence in Ukrainian hospitals as well as absence of densitometric standards for separate population groups in a definite region. We prefer ultrasound densitometry as it is accurate, noninvasive, nonionizing; the equipment is portable; the findings can be received instantly, which allows to use it in the system of population monitoring of healthy children and for clinical monitoring of children with chronic somatic pathology.
Patients and methods: The purpose of our study was standardization and unification of evaluation of the bone tissue structural-functional state in children and teen-agers residing in the East of Ukraine. Using ultrasound densitometry of calcaneal bone we performed population study of the functional-structural state in representative stratified groups of children residing in the Easte of Ukraine (total 1126 children and teen-agers aged 9-17).
Results: According to the findings of population study we worked out special nomograms for evaluation of structural-functional state of the bone tissue in children population in Ukraine for the use by medical practitioners. Special nomograms of density index of the bone tissue and absolute values for speed of sound waves, broad-band ultrasound attenuation were calculated using the findings of the study. The nomograms considered the age and gender differences in the rate of the bone tissue accumulation. The reference values of the densitometry indices were expressed in a standard way, as mean (M) and mean standard deviation (d=SD) of the value in each standard population group of children and teen-agers. The nomograms simplify the assessment of densitometry indices taking into account the age, sex, influence of ecological and alimentary factors.
Conclusion: The necessity of implementation of nomograms for evaluation of the bone tissue structural-functional state in children and teen-agers in regions with different ecological and medical and social characteristics was proved.

DELIVERY ROOM PRACTICES IN PREMATURE INFANTS IN FRANCE IN 2011: PRELIMINARY RESULTS FROM THE NATIONAL FRENCH COHORT STUDY EPIPAGE 2

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Background: Premature birth occurs in around 7% of deliveries in France and is responsible for a large proportion of perinatal mortality and childhood morbidity. The Epipage 2 study was conducted in France in 2011 and nationally collected obstetrical and neonatal data on all births occurring between 22 and 34 weeks of gestational age (GA) during pre-specified time periods. The objective of this study is to compare delivery room (DR) practices, collected as part of Epipage 2 study, according to GA categories and to geographical areas.
Methods: In 2011, data were collected in the 25 French regions during 7 months for premature births occurring between 22 and 26 weeks GA, during 5 months for premature birth occurring between 27 and 31 weeks GA and during 1 month for premature birth occurring between 32 and 34 weeks GA. The present study only included live births after 24 weeks GA. Data were collected from obstetrical and neonatal charts by dedicated local investigators. Perinatal data were collected including existence, nature and motivation of resuscitation manoeuvres, umbilical cord blood pH, and 1, 5 and 10 minutes Apgar scores. A standardised questionnaire was completed focusing on specific DR practices.
Result: The population consisted in 909 infants born between 24 and 26 weeks GA (group 1), 855 infants born between 27 and 28 weeks GA (group 2), 2053 infants born between 29 and 31 weeks GA (group 3) and 1207 infants born between 32 and 34 weeks GA (group 4). DR resuscitation manoeuvres decreased in frequency as GA increased concerning respectively 88%, 89%, 72% and 34% of infants in groups 1, 2, 3 and 4. When no resuscitation was provided in the DR, the reason was 'palliative care based on antenatal decision' for 54% of cases in group 1, vs 5% in group 2, vs 1% in groups 3 and 4. Umbilical cord pH was similar between groups (mean 7.3). The proportion of 10 minutes Apgar score = 6 at 10 minutes was 23%, 10%, 4% and 2% respectively for groups 1, 2, 3 and 4 although the rate of missing data was high in groups 1 and 2. Concerning DR practices the following results are expressed for groups 1, 2, 3 and 4 respectively: - Delayed cord clamping: 3% vs 4% vs 5% vs 1% - Oxygen delivery: 80% vs 81% vs 70% vs 39% - Positive pressure delivery: 75% vs 82% vs 70% vs 33% - Intubation: 87% vs 76% vs 40% vs 9% - Premedication prior to intubation: 3% vs 5% vs 10% vs 11% - Surfactant administration: 70% vs 54% vs 37% vs 20% - Chest compression: 11% vs 6% vs 4% vs 2% - Epinephrine administration: 6% vs 4% vs 2% vs <1% - Transfer alive to a neonatal unit: 87% vs 98% vs 99% vs 100% Comparison between regions showed a great variability in all studied parameters.
Conclusions: Most extremely premature infants (<29 weeks GA) receive delivery room resuscitation in France including oxygenation, positive pressure support and intubation. However there is major regional heterogeneity and practices are not always consistent with current recommendations.

CHANGES IN DELIVERY ROOM MANAGEMENT OF THE EXTREMELY LOW BIRTH WEIGHT INFANTS OVER TIME: A SURVEY OF PRACTICE IN ITALY

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Background: Although the availability of recommendations devoted to neonatal resuscitation of extremely low birth weight infants (ELBWIs) has been progressively increasing in the more recent versions of the International Guidelines for Neonatal Resuscitation, there are no published studies that have evaluated changes in practice over time. Objective: To evaluate the consistency of practice and adherence to the International Guidelines in early delivery room (DR) management of ELBWIs in Italy and to identify changes in practice between two historical periods (2002 vs. 2011).
Methods: A questionnaire was sent to the directors of every Italian level III centre with on site delivery room in two different periods (2002 and 2011). Differences between the two periods were analysed using Fisher's exact and Student's t-tests.
Result: There was an 88% (n=76) and 92% (n=98) response rate in 2002 and 2011, respectively. During the study period, the DR temperature was unchanged, but the use of polyethylene bags/wrap for thermal loss prevention significantly increased from 7% to 55% ($p<0.001$). The units using 100% oxygen concentrations to initiate resuscitation of ELBWIs significantly decreased from 55% to 6% ($p<0.001$); the availability of a pulse oxymeter (from 55 to 93%, $p<0.001$) and the use of target saturations (from 70 to 84%; $p<0.001$) significantly increased in the surveyed centres. The approach to respiratory management was significantly changed for the majority of the examined issues: positive pressure ventilation (PPV) administered through a T-piece resuscitator (from 17 to 79%; $p<0.001$); endotracheal tube as initial interface for PPV (from 22 to 3%; $p<0.001$); use of PEEP during PPV (from 34 to 90%; $p<0.001$); use of sustained lung inflation (from 0 to 68%; $p<0.001$). From 2002 to 2011, the percentages of ELBWIs who received chest compressions at birth decreased from 22% to 16% ($p<0.001$); no differences were found in the percentages of ELBWIs who received medications in DR (9% vs. 9%; $p=0.55$).
Conclusions: In Italy, the DR management of ELBWIs significantly changed over time, suggesting a good compliance with the International Guidelines. The availability of new evidence based recommendations and national protocols may have contributed to these results. However, some relevant interventions were not uniformly followed by the surveyed centres. Factors contributing to such discordance remain unclear and need to be investigated in future studies.

ACCURACY OF DELIVERY ROOM HEART RATE AUSCULTATION AT THE POINT OF NEED IN PRETERM INFANTS

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Background: International guidelines reflect heart rate (HR) as the most useful measure of the need for resuscitation in newborns [1-3]. These guidelines recommend HR is assessed every 30 seconds using a stethoscope. However, previous studies have demonstrated that manual HR assessment is inaccurate in simulation and well, term infants [4, 5]. Attempts to overcome this have resulted in exploration of HR measurement using pulse oximeter (PO) and/or ECG, both with disadvantages including delay in obtaining reliable signal, motion artefact and risk of cold exposure [6, 7]. There are no published studies evaluating accuracy of stethoscope assessment of HR in preterm infants at birth. We hypothesised that accurate assessment of preterm HR, at the point of need, could be obtained by trained healthcare professionals.
Patients & Methods: The study was conducted at two regional referral hospitals for neonatal intensive care; written informed consent was obtained from mothers with threatened preterm delivery. At birth, a digital stethoscope with real-time recording, was used by the attending team to assess HR as per resuscitation guidelines. At each assessment the attending team were asked to state the HR either as an absolute value or range (<60, 60-100, or >100bpm). Poor quality or insufficient audio of <6 seconds, therefore inadequate to allow accurate averaging was not included in analysis. HR was calculated from measurement of the visual waveform with simultaneous review of audio signal. Statistical analysis was performed with SPSS 20 and in all cases $P<0.05$ was considered statistically significant.
Result: 26 preterm infants were recruited: median gestation 32+3 (range 25+1-35+3) and birth weight 1.67kg (range 0.52-5.28kg). Duration of the initial assessment of HR was 13s (IQR 9-20s) with no detectable difference according to grade or profession of assessor. There were a total of 114 HR assessments [median listening time 10s (IQR 6-17s)] of which 82 assessments with clear audio were analysed (median 4 per baby, range 1-16). HR ranges were >100bpm (n=69), 60-100bpm (n=13) and <60bpm (n=3). 69 assessments were given as HR range and the remaining 13 were categorised into respective ranges for analysis. Overall, the attending team correctly identified the HR range in 73 (89%) of infants.
Conclusions: Though previous studies have commented on the inaccuracy of delivery room HR assessment by stethoscope, this is the first description of data from actual preterm infants in the delivery room. Our figure of 89% for correct HR assessments is significantly better than figures quoted from simulated auscultation. Clinicians may be better at evaluating actual cardiac sounds in a real life scenario, than in an artificial environment. The digital stethoscope may also offer better clarity of sound than a traditional stethoscope. However, this data would support that the stethoscope should remain gold standard for evaluation of HR in the crucial 1st minutes of life, particularly in light of the technical difficulties in obtaining reliable pulse oximetry tracings during this crucial period.

EVALUATION OF THE LIFESTART TROLLEY TO PROVIDE NEWBORN RESUSCITATION AT THE MATERNAL BEDSIDE.

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Background: International guidelines for resuscitation at birth state that the umbilical cord should be left intact for at least one minute, but if a baby requires resuscitation, then resuscitative measures take priority. With conventional resuscitation equipment it is difficult to provide resuscitation with the umbilical cord intact. This means that the umbilical cord is clamped quickly in the babies who may derive most benefit from deferred cord clamping . The Lifestart trolley is a small, mobile resuscitation trolley that has been developed to allow the provision of resuscitation at the maternal bedside, with the cord intact. It has been introduced into clinical practise at our hospital. We have performed an evaluation of its use.
Patients and Methods: All staff providing newborn resuscitation were instructed in the use of the trolley. The trolley was set up to provide resuscitation for any baby who was likely to require resuscitation at birth. Clinicians were completed proforma detailing the interventions provided and any difficulties encountered after each use.
Results: 48 babies have been resuscitated on the trolley to date. Median (range) gestation and birth weight were 36 (25 to 41) weeks and 2720 (520 to 4080) grams with 7 below 32 weeks and 11 babies below 2000g. 26 were delivered by caesarean section and 22 by vaginal birth. 2 deliveries (3 babies) were twins. Reasons for paediatric attendance at the birth included malformation in 7 (2 gastroschisis, 5 congenital heart disease), prematurity in 9 and concerns about potential fetal asphyxia in 13. No baby had a temperature below 36oC after resuscitation. Airway management was successful in all babies; 17 received mask ventilation and 7 were intubated. Surfactant was administered to 6 babies. None required cardiac compressions or resuscitation drugs. The umbilical cord was found to be too short to allow the baby to reach the trolley with the cord intact in 9 babies. These were typically the smallest babies. Clinicians providing the resuscitation reported no major difficulties in assessing the baby or providing any resuscitation measure, although they did make some design improvement suggestions. Informal feedback from the parents of the babies who were resuscitated on the trolley was extremely positive.
Conclusions: The Lifestart trolley allows newly born babies to be resuscitated successfully and safely at the maternal bedside after birth. In most babies, this can be performed with the umbilical cord intact. Feedback from the clinicians using the trolley in this evaluation will inform improvements in the design of the trolley which we hope will allow all babies to be resuscitated with an intact umbilical cord. Informal feedback from the parents of the babies has been very positive. A formal qualitative study of parents views on the use of the trolley is being undertaken. This abstract presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research funding scheme (RP-PG-0609-10107). The views expressed in this abstract are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

BEDSIDE RESUSCITATION OF PRETERM INFANTS WITH CORD INTACT IS ACHIEVABLE USING STANDARD RESUSCITAIRE.

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Introduction/Background: Deferring cord clamping for very preterm infants may be beneficial. Current practice for a preterm infant requiring assessment or resuscitation following birth is for the umbilical cord to be cut as soon as possible and for the infant to be carried to a resuscitaire usually situated away from the delivery bed. As part of the CORD trial, a pilot study to test the feasibility of a large UK trial to assess the effect of timing of cord clamping for preterm birth before 32 weeks gestation, we sought to establish how we could deliver assessment and stabilisation of the preterm infant at the bedside using standard resuscitation equipment. This has the potential benefit of making bedside stabilisation more available to the preterm patient population and allowing parents the opportunity of seeing or touching their baby at birth.
Patients and Methods: We looked at the resuscitaires in use in our service and using preterm and delivery manikins evaluated what steps would be necessary to be able to use these resuscitaires to provide bedside assessment and resuscitation for very preterm infants.
Results: The following steps are required to be able to provide bedside assessment and stabilisation for a vaginal birth, 1) Check resuscitation equipment to confirm it is functional. 2) Move resuscitaire next to the birthing bed and align longitudinally. 3) Drop barriers on the resuscitaire facing the birthing bed. 4) Secure resuscitaire in this position - lock wheels of the resuscitaire and birthing bed. 5) Adjust height of resuscitaire and birthing bed so that they are level. 6) Slide the moveable resuscitation mattress half way across so that it is adjacent to the mother's thigh. 7) Rotate overhead heater through 45 degrees so that the radiant heater warms the moved resuscitation mattress. For caesarean section the additional care is required to preserve the sterile field. This is accomplished by draping the resuscitation mattress with sterile drapes and ensuring that the clinical team performing the assessment and stabilisation are scrubbed. We have two types of resuscitaires in our service the Hill Rom Air-shields and the Fisher & Paykel CosyCot . Both are able to comply with the above requirements needed to provide safe assessment and stabilisation of preterm infants located at the bedside. The CosyCot mattress does not have a firm base so we replace this with a spare Air-shield mattress which consists of a foam mattress with a firm base. Simulation training sessions and video training material have been used to facilitate the introduction of this new approach to providing beside assessment and stabilisation. We will present the results from the service evaluation we are undertaking to assess the clinical acceptability of this approach.
Conclusion: With minor adjustments standard resuscitation equipment is able to meet the requirements for a suitable environment for bedside assessment and resuscitation of preterm births.

EXIT PROCEDURE: A CASE SERIES FROM LIVERPOOL WOMEN'S HOSPITAL

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Introduction: Ex utero intra-partum treatment (EXIT) procedure can be used to stabilise the foetal airway while foeto-maternal circulation is preserved to optimise foetal outcome at birth in foetuses having airway obstruction. We present 3 cases where EXIT procedure was used successfully at birth. EXIT Procedure: Ex utero intra-partum treatment (EXIT) procedure is a highly modified caesarean delivery and requires an experienced multi-disciplinary team. The goal is to partially deliver the baby, but maintain placental support to be able to perform surgery before the baby is completely delivered. Mother is given general anaesthesia to relax the uterus. Mother & foetus are extensively monitored. A haemostatic stapling device is utilised to prevent bleeding from the uterine edge. Foetus receives transplacental anaesthesia and additional anaesthesia delivered intramuscularly if needed. Foetus's head is delivered, so that foetus is still sustained by placenta. The first patient had Congenital high airway obstruction syndrome (CHAOS) caused by cricoid atresia. Antenatal foetal MRI scans showed enlarged hyperechogenic lungs, ascites with flattened diaphragms and mediastinal compression. The trachea was identified and either an atresia or stenosis at laryngotracheal junction was suspected. Mother had threatened preterm labour at 27+5 weeks and presented at her local secondary hospital nearly 50 miles from the treating centre . Mother was transferred to the treating centre and a specialised airway team (consisting of Consultant Paediatric ENT surgeon and Paediatric Anaesthetist with logistic support) was called. Cord prolapse developed, so an emergency caesarean section was performed. Subglottic atresia was recognised at birth using fibreoptic laryngobronchoscopy. An airway was secured using a tracheotomy at 14 minutes after the delivery of the baby; the umbilical cord was cut at 17 minutes of age. To our knowledge this is the youngest gestational age at which an EXIT procedure has been done successfully. The second patient had left sided cystic hygroma. Antenatal scans showed large left sided facial & neck mass. At 39 weeks elective caesarean section was performed with EXIT procedure and airway established by endotracheal intubation at 1 minutes of age by the Paediatric Anaesthetist and cord cut at 2 minutes. The third patient had left sided cervico thoracic tumour (infantile myofibromatosis). Antenatal scans showed large left sided neck swelling. At 37 weeks elective caesarean section was performed with EXIT procedure and airway established at 7 minutes of age by Paediatric Anaesthetist and cord cut at 8 minutes. This procedure was facilitated by a novel resuscitation trolley (BASICS) which has been developed in our unit. The BASICS trolley provides a stable environment for initial stabilisation of the neonate without the need to cut the umbilical cord.
Conclusions: The salient points about CHAOS are early diagnosis, detailed foetal assessment and an expert team to establish foetal airway at birth in a specialised centre. EXIT procedure is an excellent strategy for establishing an airway in a controlled manner such that the foetus continues to be oxygenated through the placenta while the procedure is performed.

A RANDOMISED TRIAL OF USING GESTATIONAL AGE OR WEIGHT TO ESTIMATE NEONATAL ENDOTRACHEAL TUBE DEPTH OF INSERTION (ISRCTN40879573)

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Background: In newborns, the measurement at the lips at which an oral endotracheal tube (ETT) is secured - the insertion depth (ID) - is most often estimated using their weight. Cohort studies suggest that estimating ID using gestational age is more accurate.
Objective: To determine whether estimating ID using gestational age, compared to birth weight, results in more correctly placed ETTs (i.e. tip of ETT between upper border T1 and lower border T2) on chest x-ray.
Design/Methods: Infants without congenital anomalies who were intubated orally in the NICU were eligible for inclusion. Enrolled infants were randomised to have ETT ID estimated according to gestation (Table 1) or using weight [ID (cm) = 6 + weight (kg)].
Table 1 Corrected gestation (weeks) ETT length at lip (cm) 23 - 24 5.5 25 - 26 6.0 27 - 29 6.5 30 - 32 7.0 33 - 34 7.5 35 - 37 8.0 38 - 40 8.5 41 - 43 9.0 Randomisation was stratified by gestational age (< 28 weeks, 28+). ETT position was determined on chest x-ray by one Consultant Paediatric Radiologist who was masked to treatment allocation. Secondary outcomes were measured and data were analysed using the 'intention to treat' principle.
Results: Ninety infants were enrolled and the groups were well matched for demographic details (Table 2). The proportion of correctly placed ETTs was not significantly different between the groups (Table 3). We found no significant differences between the groups in the secondary outcomes we measured.
Conclusions: Estimating ID of ETTs in newborns using gestation did not result in more correctly placed ETTs.
Table 2. WEIGHT (N = 49) GESTATION (N = 41) P value Gestational age at birth (weeks) 29 (27, 37) 29 (27, 36) 0.985* Day of life enrolled 2 (1, 5) 1 (1, 3) 0.525* Birth weight (g) 1340 (933, 2885) 1530 (820, 2830) 0.211* Weight at study (g) 1460 (990, 2885) 1530 (820, 2830) 0.211* Male, n (%) 21 (43) 24 (56) 0.204# *Independent t-test for medians, #Fisher's exact test Table 3. WEIGHT (N = 49) GESTATION (N = 41) P value ETT tip T1 - T2 on CXR, n (%) 25 (51) 16 (39) 0.293# Extubated before CXR, n (%) 4 (8) 3 (7) 1.00# ETT secured at estimated depth, n (%) 22 (45) 10 (24) 0.05# Difference secured - estimate (cm) 0.0 (0.0, 0.1) 0.0 (0.0, 0.0) 0.259* ETT tip high, n (%) 4 (8) 10 (24) 0.043# ETT tip low, n (%) 20 (41) 15 (37) 0.828# ETT adjusted after CXR, n (%) 16 (33) 16 (39) 0.659# Unequal lung expansion on CXR. n (%) 5 (10) 4 (8) 1.000# Air leak, n (%) 6 (12) 5 (12) 0.989# Pulmonary haemorrhage, n (%) 0 (0) 1 (2) 0.456# Oxygen at 28 days, n (%) 25 (51) 13 (32) 0.087# Oxygen 36 weeks, n (%) 15 (31) 6 (15) 0.080# Death before discharge, n (%) 3 (6) 6 (15) 0.291# *Independent t-test for medians, #Fisher's exact test

IS IT TIME TO REVIEW GUIDELINES FOR ETT POSITIONING IN THE NICU? (SCEPTIC - SURVEY OF CHALLENGES ENCOUNTERED IN PLACEMENT OF ENDOTRACHEAL TUBES IN CANADIAN NICUS)

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Background: Accurate positioning of the endotracheal tube (ETT) is essential to prevent associated morbidity. There are limited data regarding ideal placement of the ETT tip and many methods have been proposed to estimate the depth of insertion. These may not always be accurate, particularly at the extremes of gestation. T1-T2 is referred to as a mid tracheal position in the literature. Data suggest that the use of gestational age guidelines may result in more accurate placement of the endotracheal tube tip at mid trachea and hence reduce the need for repositioning and incidence of uneven lung expansion. Therefore, gestation based guidelines have been adopted in many jurisdictions including the UK, Europe, Australia and New Zealand. Objective: To examine current opinions, practices and challenges in regard to endotracheal tube placement in Canadian Neonatal Intensive Care Units (NICUs).
Design/Methods: Staff neonatologists, neonatal fellows, respiratory therapists (RTs) and nurse practitioners (NPs) across Canada were invited to participate in an anonymous online survey. Clinical directors in all Canadian Neonatal Network affiliated NICUs and all Neonatal-Perinatal Program Directors were contacted and asked to disseminate the survey invitation to the aforementioned groups. Consent was implied by participation. Email reminders were sent at three and five weeks after initial email invitation.
Result: A total of 207 responses were received of which 85.5% were complete. The representation of the RT's was the highest (47%) within the respondents. The majority of respondents (86%) worked in Level 3 NICUs. Most respondents performed between 5 and 14 intubations per year. The most common reported complications related to incorrect ETT placement were unequal surfactant administration, differential air expansion and atelectasis. Accidental extubations were noted to occur 'occasionally' by 71% of respondents. The majority of respondents (87%) used ‘weight +6' formula and 'Aim to black line' to estimate the depth of insertion of oral ETT. Almost two thirds of respondents reported the estimation of depth of insertion as challenging in infants with a birth weight <750g. Only 22% however believed that the narrower gestation age based guidelines may give better estimation of the depth of ETT insertion. While the vast majority of respondents (92%) identified the ideal ETT tip placement to be mid tracheal, preferred position on Chest X ray (CXR) varied amongst respondents , only 35% referred to T1-T2 as ideal. A significant proportion of respondents believe that ETT placement could be improved with more precise ETT markings (every 5mm).
Conclusions: Canadian practitioners report challenges in ensuring optimal endotracheal tube placement in extremely low birth weight infants. In addition, while respondents agree that mid-tracheal placement is optimal, opinion varies as to the corresponding position on CXR. Further research should focus on developing more effective guidelines for ETT tip placement in the extremely low birth weight infants. The use of gestational age based guidelines may optimise placement within this group.

THE RELATIONSHIP BETWEEN SUCCESSFUL INSERTION OF A NEONATAL-SIZED I-GEL AND A HEALTH CARE PROVIDER'S PROFESSION OR EXPERIENCE

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Background: ILCOR's 2010 guidelines recommend using a laryngeal mask (LMA) during resuscitation of newborns weighing >2000 g or delivered after 34 weeks gestation if facemask ventilation and tracheal intubation are unsuccessful or unfeasible. The i-gel (Intersurgical Ltd., Wokingham, UK) is a relatively new disposable supraglottic airway device made from a soft, gel-like elastomer and having a non-inflatable cuff. Several studies have reported that the i-gel is safe and effective for airway management in pediatric and adult patients. Moreover, the present study found the neonatal-sized i-gel easier to insert and more effective than the traditional LMA in a bench-top setting.
Objective: The purpose of this study was to assess the relationship between a health care provider's profession or experience and insertion of the neonatal-sized i-gel into a neonatal mannequin to consider its clinical use in a neonatal resuscitation setting. Methods/Designs: Participants included health care providers and nursing students who had participated in the Japanese version of the neonatal cardiopulmonary resuscitation (NCPR) course, which was based on ILCOR's 2010 guidelines. After participants read the device manufacturer's instructions, they were instructed to insert a neonatal-sized i-gel into a neonatal resuscitation mannequin. Under blind conditions, a non-clinical investigator measured the time between insertion and the point when participants judged the insertion successful. We used a respiratory function monitor to measure lung flow and pressure by ventilating the neonatal mannequin with a self-inflating bag. Successful insertion was defined as > 20 mmHg lung pressure. We assessed the relationship between successful insertion or insertion time and the participant's profession, duration of service in their profession, and the duration of participation in the NCPR course.
Result: Participants in this study included 22 medical professionals (6 doctors, 6 midwives, 8 nurses, and 2 nursing students). The successful insertion rate was high (95%, 21/22). We observed no differences between successful insertion or insertion time and participant profession, duration of service in profession, or duration of participation in the NCPR course.
Conclusions: In this study, the rate of successful insertion of a neonatal-sized i-gel was high. Moreover, the insertion time was not affected by the health care provider's profession or experience. These results suggest that all health care providers, including inexperienced providers, can successfully use the i-gel for airway management in neonatal resuscitation.

HIGHER SUCCESS RATE AND OPERATOR SATISFACTION WITH I-GELÂ„¢ LARYNGEAL MASK AIRWAY COMPARED TO FACE MASK: A MANNEQUIN STUDY OF NEONATAL RESUSCITATION IN UGANDA

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Background: Previous work showed the laryngeal mask airway (LMA) is effective for administering positive pressure ventilation (PPV) in neonates. Recently, a new neonatal LMA (I-gelâ„¢) has become available. The I-gel is cuffless, making its positioning potentially faster and easier in comparison with other LMA models. These advantages may be crucial in a low-resource setting where neonatal resuscitation is frequently performed by personnel with limited experience in airway management. We aimed to compare the performance (ease of insertion and time to establish effective PPV) of personnel involved in neonatal resuscitation with limited experience in airway management when using I-gel and face mask (FM) in a neonatal airway management mannequin. The quality of the two devices, as perceived by participants, was also evaluated.
Methods: Health-care providers involved in neonatal resuscitation at Mulago National Referral Hospital (Kampala, Uganda) were given a brief supervised training with the two devices. Every participant was then observed positioning each of the two devices (I-gel and FM) in 3 consecutive occasions. Success rate and insertion time (IT) were recorded by a single unblinded observer. A 5-point scale was used to rate participants' perceived quality.
Result: A total of 25 health-care providers participated in the study. I-gel allowed reaching effective PPV at the first attempt in all the three consecutive occasions. With the FM, however, there were significantly more failures in reaching effective PPV ($p<0.001$) at 1st , 2nd and 3rd attempt: 7/25 (28%), 2/25 (8%) and 5/25 (20%), respectively. The mean IT was similar with the I-gel as compared with FM at the 1st (6.2+2.3 vs. 8.3+4.7 sec; $p=0.18$), 2nd (5.2+1.1 vs. 9.9+14.1 sec; $p=0.68$) and 3rd (4.5+1.0 vs. 6.6+5.9 sec; $p=0.38$) occasion. The satisfaction perceived by the participants was significantly superior with I-gel as compared with FM (4.7+0.4 vs. 3.3+0.8; $p<0.001$).
Conclusions: Neonatal uncuffed LMA was superior to FM in establishing effective PPV; furthermore, quality perceived by the operator was higher with neonatal I-gel than with FM. These mannequin data could provide a useful guide for planning potential future clinical research on neonatal resuscitation in low resource countries.

FACIAL MEASUREMENTS TO DETERMINE OPTIMAL FACE MASK SIZE FOR RESPIRATORY SUPPORT IN PRETERM INFANTS

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Background: Preterm infants often receive positive pressure ventilation or CPAP via a mask. International and Australian Resuscitation Council guidelines and teaching resources recommend that 'the appropriate size of face mask must seal around the mouth and nose but not cover the eyes or overlap the chin'. The aim of this study was to measure relevant dimensions of preterm infants' faces and to compare them to commercially available neonatal face masks (Laerdal 50 mm diameter, Fisher&Paykel 35, 42 and 50 mm diameters).
Method: Preterm infants 24 to 33 weeks gestational age (GA) were studied. Infants were positioned with their heads in 'sniffing' position and the jaw neutral. A measured scale was placed level with the face. Photographs were taken from the front and side. Images were analysed using 'Image J software', a Java-based image processing program developed at the National Institute of Health. The distance from the nasofrontal grove to the mental protuberance (NGTMP) was calculated which equates to the diameter of an optimal fitting mask.
Result: 103 infants were recruited and photographed in their first 72 hours after birth.
Results are shown in table 1. Measurements were repeated at corrected ages (CA) until 33 weeks CA.

Gestation age weeks	Number of infants	Birth weight mean (SD) g	NGTMP Frontal mean (SD) mm	NGTMP Lateral mean (SD) mm
24	10	648 (82)	32 (2)	33 (3)
25	8	722 (124)	36 (3)	35 (2)
26	9	941 (180)	36 (3)	37 (3)
27	9	973 (216)	37 (4)	37 (2)
28	12	1102 (183)	38 (4)	39 (4)
29	12	1082 (302)	40 (4)	38 (4)
30	12	1617 (216)	41 (2)	42 (3)
31	10	1637 (335)	39 (4)	41 (2)
32	11	1838 (178)	43 (4)	43 (4)
33	10	1839 (392)	42 (5)	43 (4)

Those measurements did not show a statistical significant difference when compared to the corresponding GA after birth. GA Infants Birth weight NGTMP Frontal NGTMP Lateral weeks n mean (SD) g mean (SD) mm mean (SD) mm 24 10 648 (82) 32 (2) 33 (3) 25 8 722 (124) 36 (3) 35 (2) 26 9 941 (180) 36 (3) 37 (3) 27 9 973 (216) 37 (4) 37 (2) 28 12 1102 (183) 38 (4) 39 (4) 29 12 1082 (302) 40 (4) 38 (4) 30 12 1617 (216) 41 (2) 42 (3) 31 10 1637 (335) 39 (4) 41 (2) 32 11 1838 (178) 43 (4) 43 (4) 33 10 1839 (392) 42 (5) 43 (4)
Conclusions: Preterm infants' faces are smaller than many of the available 50 mm face masks. Neonatal resuscitation masks with external diameters 35 and 42mm are the most appropriate sized masks available for very preterm infants.

PREDICTORS OF UNFAVOURABLE THERMAL OUTCOME DURING EMERGENCY RETRIEVALS OF NEWBORN INFANTS

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Background And Aim: Maintenance of normal body temperature is essential for the wellbeing of the neonate. Temperature control in newborns has been studied extensively during the first hours of life, but large-scale reports on how temperature is regulated and maintained thereafter, are few. Neonates requiring transportation to another hospital are known to be at risk, as maintenance of normal body temperature is often a challenge during transfers. We aimed to identify predisposing factors for unfavourable thermal outcome during emergency retrievals of neonates.
Methods: The Newborn Emergency Transport Service (NETS Victoria, Australia) database was reviewed for retrievals performed between 1st July 2007 and 30th June 2009. Unfavourable thermal outcome was defined as temperature <36.5°C or >37.5°C on arrival at the receiving hospital.
Results: The study sample consisted of 1261 transported infants. The mean gestational age at birth was 35.7 weeks (SD± 4.5, range 23-42) and mean corrected gestational age at transfer was 37.1 weeks (SD± 5.4 range 23-83). Mean birth weight was 2678 grams (SD± 1020, range 422-5890) and mean weight on transport was 2851 grams (SD± 1064, range 500-6800). Respiratory support (mechanical ventilation or continuous positive airway pressure) was provided for 53% of patients. Normothermia (36.5°C to 37.5°C) on arrival at the receiving hospital was achieved in 78% of all transports. The strongest predictor of unfavourable thermal outcome was an abnormal temperature at the start of the retrieval: OR 8.04, CI 95% 5.91-10.95 (p<0.001), followed by very low transport weight (<1500g) OR 2.49, CI 95% 1.63-3.80 (p<0.001), and respiratory support: OR 1.81, CI 95% 1.29-2.54 (p=0.001). Antibiotics, inotropes, analgesia, sedation, muscle relaxation, central catheters or peripheral arterial lines were not significant predictors of outcome when temperature at the start of the retrieval, weight at transport and respiratory support were adjusted for as cofactors. Mode of transport (road 77%, fixed wing aircraft 19%, rotary wing 4%) and season/outside temperature were not associated with thermal outcome.
Conclusion: Abnormal temperature at the start of the retrieval, very low transport weight and respiratory support were strong predictors of unfavourable thermal outcome during neonatal emergency transports.

HEAT LOSS PREVENTION IN VERY PRETERM INFANTS IN DELIVERY ROOM: A PROSPECTIVE, RANDOMIZED, CONTROLLED TRIAL OF POLYETHYLENE TOTAL BODY SKIN WRAPPING.

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Background: Hypothermia after delivery is a world-wide problem associated with morbidity and mortality. Polyethylene occlusive skin wrapping covering the infant's body up to the neck reduces postnatal heat loss in very preterm babies and represents the standard of care recommended by the International Guidelines for Neonatal Resuscitation. The use of a polyethylene head cap will also reduce heat loss and its efficacy is comparable to that obtained with the wrap. It is unknown if the combination of body and head protection with a polyethylene wrap will reduce postata thermal loss.
Methods: Multicenter randomized trial conducted with infants <29 weeks gestation at three level III hospitals in Veneto Region Italy from january 2011 to july 2012. Exclusion criteria included presence of congenital anomalies with open lesions and babies whose deliveries were non attended by the neonatal team. In the total body wrapping group the body and the head of the infant were covered with a polyethylene wrap quickly after birth. Infants in the wrap group (control group) were put into a polyethylene bag up to their necks. Elegible infants were assigned to the total body wrap or to the control group according to a computer-generated, randomized sequence. Bilance in blocks of 6 subjects. The randomised al location was concealed in a double-enclosed, opaque, sealed and sequentially numbered envelopes prepared at University Hospital of Padua and then distributed to participating centers. In the delivery room, the next sequential randomization envelope was opened only when the infant was considered to be elegible by the attending neonatologist. The assigned procedure (total body wrap or wrap up to the neck) was then performed. Multiple births were separately randomized. Outcomes The primary outcome measure was axillary temperature on admission to the NICU and again one hour later. Secondary outcomes included mortality before hospital discharge, presence of major brain injury, blood gas analysis and serum glucose concentration on NICU admission.
Results: Of the 84 infants screened for the study 4 were excluded because the neonatal team did not attend the delivery or because the parents refused to partecipate. One infant who was randomly assigned to the control group died in the delivery room and was not included in the analysis. Baseline characteristics of infants and their mothers were similar in both groups. infants completed the study. Median axillary temperature at NICU admission and 1 hour later were comparable between the two groups (p=.001 and p=.0008 respectively)
Conclusions: Covering the entire body with a polyethylene wrap is comparable to covering the body up to the shoulders to prevent postata thermal losses in very preterm infants. These results suggest that the actual standard of care (covering the body up to the shoulders) remains to be recommended.

GRAVITY AND PLACENTAL TRANSFUSION FOR TERM BIRTH

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Introduction: Placental transfusion may be influenced by a range of factors, including gravity. During Caesarean sections (CS) with spinal anaesthesia it is common practice for Obstetricians to show the newborn infant to the Mother immediately at birth. Due to the configuration of sterile drapes this usually requires raising the baby above the drapes shielding the Mothers abdomen from her view. If this is done whilst the cord is intact, it may impact on placental transfusion.
Methods: To measure placental transfusion babies were weighed during the first two to three minutes of life with the umbilical cord intact using high quality pharmacy scales (Mettler-Toledo). At birth the baby was placed on the scales. For CS births the scales were positioned on a trolley next to theatre bed by the Obstetrician. The position of the baby relative to the woman's abdomen was recorded and adjusted by raising or lowering the theatre bed to an equivalent height. The infant was monitored by an experienced neonatologist using saturation monitoring and assisted by a research midwife.
Result: 45 term and 7 preterm infants were weighed. In 2 CS cases, due to the operating Obstetrician needing the theatre bed to be lower, the baby was initially weighed with the scales above the mother. Although these positions were quickly adjusted to be level, weight curves show that blood initially transfused into the placenta from the baby.
Conclusions: Placental transfusion at birth appears to be a dynamic process that may be affected by simple technical arrangements such as the position of the baby relative to the mother. As the practice of deferred umbilical cord clamping is recommended by national and international obstetric and neonatal guidelines (e.g. WHO guidelines, RCOG Guideline "Green-top 52' and ILCOR, 2010), consideration should be given to how it is carried out. The practice of raising the baby to show to the Mother whilst the cord is intact can have a major impact on placental transfusion. This may be harmful for the infant, especially if followed by immediate cord clamping.

CLINICAL PRESENTATION AND OUTCOME OF NEONATES BORN WITH FETOMATERNAL HAEMORRHAGE IN A TERTIARY NEONATAL INTENSIVE CARE UNIT IN UNITED KINGDOM

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Background: Fetomaternal haemorrhage (FMH) refers to the entry of fetal blood into the maternal circulation before or during delivery. Antenatal FMH is a pathological condition with a wide spectrum of clinical variation. Secondary to the resultant anaemia, FMH may have devastating consequences for the fetus such as neurological injury, stillbirth, or neonatal death. Presentation is frequently without an evident precipitating factor. Recognition may become apparent only after injury has occurred, if at all. Although the placenta is considered a barrier separating the maternal and fetal circulations, bidirectional trafficking of cells across the placenta is a physiological event. Most investigations have focused upon fetal nucleated blood cells, which have been identified in minute quantities in the maternal circulation throughout normal pregnancy. Sometimes, however, FMH involves a large volume of blood. A FMH of 20 mL/kg, which represents 20% of the fetoplacental blood volume, is considered massive because it has been associated with significant fetal/neonatal morbidity or mortality.
Aims: To evaluate the incidence, clinical presentation and outcome of all neonates who demonstrated fetomaternal haemorrhages > or = 25 ml and to assess possible predictors of large fetomaternal haemorrhage and outcome.
Methods: Retrospective data analysis of 5 year period from Jan 2008 to Dec 2012. Clinical data included antenatal events, condition at birth, haematology results, treatment and outcome. RESULTS: Total number of infants born with FMH during the study period was 51. Incidence 1.7 per 1000 Births. 11(21%) infants were identified with FMH more than 25mls. 9 infants were born at term and 2 were preterm. 4 infants had mild FMH (25 to 50 mls), 3 infants had moderate FMH (50 to 100mls), and 4 infants had severe FMH >100mls. Pre-delivery concerns (Eg: Fetal bradycardia, fetal distress) were noticed in 6 (54%) infants. 6 (54%) infants were born in poor condition needing resuscitation. 3(27%) infants needed Blood transfusion immediately after birth. 3 infants had admission Haemoglobin (Hb) <5 g/dL, 1 infant had Hb between 5 to 10 g/dL, and 6 infants had Hb> 10 g/dL. (In one infant admission Hb was not available) Adverse outcome occurred in 3 (27%) infants. (2 infants died, 1 infant had abnormal neurological signs on follow-up) 3 (75%) out of 4 infants with severe FMH >100mls had overall good outcome. 1 (33%) out of 3 infants with Hb <5 g/dL at birth had overall good outcome. Outcome can be better predicted by postnatal presentation and initial haemoglobin.
Conclusion: The incidence of fetomaternal haemorrhage in our study period is 1.7 per 1000 births. Adverse outcome amongst neonates with large fetomaternal haemorrhage is high. Outcome is better predicted by initial haemoglobin than volume of fetomaternal haemorrhage as per the Kleihauer test.

EVALUATION OF PLATELET AGGREGATIVE CAPABILITY AT CARDIOVASCULAR SYSTEM DISEASES IN CHILDREN

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The platelet aggregation function takes part in the body defense reactions at various diseases due to ADP, histamine, serotonin, growth factors and other substances contained in platelets. Interaction of platelets with each other and vascular endothelium are stimulated by thrombin, ADP, thromboxane A2 and inhibited by prostacyclin and nitric oxide.
Aim: to determine functional peculiarities of the platelet hemostasis component at cardiovascular diseases in children. Materials and
Methods: 19 patients with cardiomyopathy and 18 patients with metabolic syndrome of 2-16 years of age in both study groups. Average age - 9.6 years. The healthy group was comprised of 16 healthy children. The platelet aggregative function was analyzed in whole blood using the Multiplate (VD, Germany) device with thrombin, ADP, arachidonic acid in all children.
Result: statistically significant differences have been revealed between platelet aggregation with thrombin (p=0.026) in the patients from study groups. No statistically significant differences have been revealed between platelet aggregation with arachidonic acid and ADP (significance levels - p=0.161 and p=0.369, accordingly). Tendency to platelet hyperaggregation with thrombin (value median - 87U; 95% CI: 31-145) has been noted in most patients (57.8%) with cardiomyopathy. Thrombin test median in healthy children - 80U; 95% CI: 59-95. Platelet hypoaggregation with ADP (median - 28.5; 95% CI - 13-69) and arachidonic acid (median in both cases - 35U; 95% CI - 5-73) has been observed in patients with metabolic syndrome. Arachidonic acid test's median in healthy children was 58.5U; median of aggregation with ADP - 45.5U. The data allows to assume altered platelet aggregation qualities; this may favor microcirculation disorder and, thus, ischemic alterations.
Conclusions: given the possibility of complications in platelet hemostasis component, inclusion of antiaggregants with different points of application, vasoprotectives and metabolic drugs into the therapy is an obligatory condition for the therapy rendered to patients with cardiomyopathy and metabolic syndrome.

MICROSAMPLING REDUCES RED BLOOD CELL TRANSFUSIONAL NEED IN VLBW INFANTS

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Background: VLBW infants are the most transfused patients in NICU. The incidence of serious hazards of red blood cells (RBC) transfusion was estimated to be threefold for infants less than 12 months compared to adults.
Aim: to evaluate if the reduction of phlebotomy losses by the use of microsampling limits the transfusional need in VLBW.
Methods: We conducted a cross-sectional retrospective analysis of all VLBW neonates admitted to our NICU between January 1, 2004, and December 31, 2012. The use of microsampling for laboratory evaluations (blood count, CRP, transaminases, ammonium, creatinine, BUN, Tri-Glycerides) has been implemented since January 1, 2007. We compared blood loss volumes and RBC transfusional needs before and after this date. T-test and Wilcoxon test were used for statistical analysis.
Result: 404 VLBW were born between January 1, 2004 and December 31, 2012 (122 and 282 before and after January 1, 2007, respectively; M:F=0.9 vs 1.2, p=0.7). No significant difference was found for GA (weeks) and BW (grams) between the two groups (median with 5 th /95th percentiles for GA: 26.8, 23.8-28.4 vs 27, 24.4-28.8, p=0.34; and for BW: 852.5, 510-1270 vs 864, 550-1285, p=0.06). Mean blood volume (ml) collected for laboratory testing was 8.12 vs 2.84 ($p<0.001$); 3.27 vs 0.95 ($p<0.001$) and 0.925 vs 0.173 ($p<0.001$) in the first, second and third week of life, respectively. The percentage of RBC transfused infants was significantly different before and after January 1, 2007: 79.5% vs 64% ($p<0.001$); the transfusion rate (number of transfusions/neonate by median with 5 th /95th percentiles) was: 4 (1-9) vs 2 (1-8), p= 0.03. The day of life at the first transfusion was (mean±SD) 7.4 ± 6.7 vs 12.9 ± 11.1, p= 0.01. The percentage of transfused neonates was 61.8% vs 51.4% ($p<0.001$) in the first week of life, and 80% vs 71% ($p<0.001$) after their first week of life. During the analyzed period no variations were performed neither in transfusional guidelines, neither in laboratory evaluations indications, neither in iron and nutritional supplementation.
Conclusions: We confirmed the role of iatrogenic blood loss in the development of anemia of prematurity and the effectiveness of microsampling to prevent RBC transfusion in VLBW.

HAEMOGLOBIN AT BIRTH AND BLOOD TRANSFUSION IN PRETERM INFANTS

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Introduction: Blood transfusion (BT) is one of the most commonly used interventions in neonatal medicine [1]. The three categories of infants who receive blood transfusion are: (1) peri-partum blood loss, (2) significant cardiopulmonary disease e.g. to keep haematocrit >40% and (3) haemoglobin (Hb <7 g/l) or haematocrit (Hct <23%) below a predetermined level [2].
Methodology: Aim: To evaluate the relationship between Hb at birth and blood transfusion Inborn preterm infants (23 to 32 weeks of gestation) in a tertiary neonatal unit were studied from January 2006 to September 2012. Data collected: demography (gestational age, birth weight and sex), type of delivery, fetal distress, APH, birth Hb and blood transfusion (BT) details. Data was collected from blood bank and clinical databases (EPR, SEND and WinPath). Birth Hb - measured within 4 hours after birth Data was analysed using SPSS 18.0. A regression analysis was performed to find out the correlation between Hb at birth and BT. Study was approved by the hospital R&D department.
Result: 918 infants were eligible; 28 excluded because of missing data. Of the 890 infants included 518 received blood transfusion (BT). The mean birth Hb was 15.8 g/dl (SD 2.59). The birth Hb was significantly associated with gestational age ($p<0.001$, 95% CI 0.352 to 0.467), birth weight ($p<0.001$), ethnicity ($p<0.001$), APH [mean 15.99 (SD 2.5) vs. 15.23 (2.6) g/dl; $p<0.001$], foetal distress [15.95 (2.5) vs. 14.60 (2.7) g/dl; $p<0.001$], mode of delivery [vaginal - 15.35 (2.6) vs. caesarean - 16.11 (2.6); $p<0.001$] and receiving a BT (OR 1.404, $p<0.001$; CI 1.313 to 1.500). On logistic regression analysis birth Hb was significantly (OR 1.213, 95% CI 1.116 to 1.317; $p<0.001$) associated with receiving a BT. Further analysis on restricting to the infants who received BT (n - 518), the birth Hb was significantly associated with gestational age ($p<0.001$, 95% CI 0.253 to 0.441), birth weight ($p<0.001$, 95% CI 0.001 to 0.002), Sex ($p<0.001$), ethnicity ($p<0.001$), APH ($p = 0.041$, 95% CI 0.022 to 0.986), foetal distress ($p= 0.006$, 95% CI 0.238 to 1.388) and type of delivery ($p < 0.001$). The birth Hb was also significantly associated with frequency ($p<0.001$: CI 0.65 to 0.27) and total volume of BT ($p<0.001$; CI -9.769 to -4.067) received. On multivariate regression analysis, the birth Hb was significantly associated with gestational age ($p<0.001$, 95% CI -0.918 to -0.362) and birth weight ($p<0.001$, 95% CI -0.007 to -0.003) but not with frequency ($p=0.130$; CI -0.318 to 0.041) and total volume of BT ($p=0.126$; CI 4.787 to 0.592).
Conclusions: Lower birth Hb was an independent risk factor of receiving a blood transfusion in preterm infants of =32 weeks of gestation but not with frequency or total volume of blood transfusion.
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HAEMOGLOBIN AT BIRTH AND SHORT-TERM OUTCOMES IN PRETERM INFANTS

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Introduction: Delayed cord clamping has demonstrated increased haemoglobin (Hb), blood volume at birth1 and improved short term outcomes2. Hb at birth and its relation with short-term outcomes of preterm infants has not been explored.
Methodology Aims: To evaluate the relationship between Hb at birth and short term outcomes in preterm infants. Inborn preterm infants (23 to 32 weeks of gestational age) from January 2006 to September 2012 in a tertiary neonatal unit were studied Data collected: gestational age (GA), birth weight, sex, ethnicity, mode of delivery, fetal distress, APH, admission temperature, chorioamnionitis, Hb at birth (measured within 4 hours of birth); and outcome variables - blood transfusion (BT) details, Intra-ventricular haemorrhage (IVH), Necrotising enterocolitis (NEC), Retinopathy of prematurity (ROP), Broncho-pulmonary dysplasia (BPD), length of Level 1 care & total neonatal unit (NNU) stay and mortality. Data was collected from blood bank and clinical databases (EPR, SEND and WinPath). Data was analysed using SPSS 18.0. Logistic regression analysis was performed to assess the relationship between Hb at birth and the outcome measures. The study was approved by the hospital R&D Department.
Result: 918 infants were eligible; 28 excluded because of missing data. The mean GA was 28.3 (SD 2.68) wks, birth weight 1139.6 (SD 413.9) g and 50.6% infants were male. Mode of delivery: vaginal - 40.7% & C-section - 59.3%. The mean Hb at birth was 15.8g/dl (SD 2.59) and admission temperature 36.6 (0.7)0 C. Ethnicity: Caucasian-35.8%, Black-37.2%, Asian-14.5% & Mixed/unknown-12.5%. 12.1% of infants had fetal distress & 26.4% APH. The significant confounders of Hb at birth were gestational age, birth weight, ethnicity, APH, chorioamnionitis, foetal distress and mode of delivery ($p<0.01$). On univariate analysis, low Hb at birth was significantly associated with BT, IVH, NEC, ROP, BPD, length of Level 1 care & total NNU stay and mortality ($p <0.01$). On multivariate logistic regression analysis, low Hb at birth was independently associated with BT (OR=0.786, 95% CI 0.718 to 0.861, $P<0.01$) and mortality (OR = 0.854, 95% CI 0.769 to 0.947, P=0.03). Hb at birth was not associated with BPD (p=0.770, 95% CI 0.937 to 1.091), NEC (p=0.271, 95% CI 0.892 to 1.032), IVH (p=0.084, 95% CI 0.874 to 1.008), ROP (p=0.611, 95% CI 0.906 to 1.060), length of Level 1 care (p=0.305) and total NNU stay (p=0.747).
Conclusions: Low Hb at birth was significantly associated with mortality and an increased likelihood of requiring blood transfusion but not with BPD, NEC, IVH, ROP and length of NNU stay in preterm infants.
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PLATELETS FOR NEONATAL TRANSFUSION - STUDY 2 PLANET-2: A RANDOMISED CONTROLLED TRIAL TO COMPARE TWO DIFFERENT PLATELET COUNT THRESHOLDS FOR PROPHYLACTIC PLATELET TRANSFUSION TO PRETERM NEONATES.

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Introduction: Neonatal thrombocytopenia is common, with around a quarter of neonates admitted to Neonatal Intensive Care Units (NICUs) developing thrombocytopenia. Bleeding is frequent, particularly in preterm neonates, ranging from cutaneous bleeding, bleeding from the endotracheal tube, oozing from the skin at puncture sites, and bleeding through the nasogastric secretions through to more severe pulmonary or intracranial hemorrhages. Intraventricular and periventricular hemorrhage (IVH-PVH) is a particular issue with concern for neurodevelopment outcomes. In addition, platelet transfusions are frequently prescribed in neonates; such that previous studies estimate that 25% of neonates whose platelet counts fall below 150 x109/L receive one or more transfusions and this increases to 50% in extremely low birth weight (birth weight <1000g) neonates A trial assessing clinically relevant outcomes in relation to the platelet count thresholds currently used as triggers for transfusion has never been undertaken in preterm neonates with severe thrombocytopenia.
Objectives: PlaNeT-2 aims to assess whether a higher prophylactic platelet transfusion threshold is superior to the lower thresholds in current standard practice in reducing the proportion of patients who experience a major bleed or death up to study day 28.
Methods: Platelets for Neonatal Transfusion - study 2, (PlaNeT-2) is a 2-stage, randomised, parallel group, superiority trial. PlaNet-2 compares clinical outcomes in preterm neonates (<34 weeks gestation at birth) randomised to receive prophylactic platelet transfusions to maintain platelet counts at or above either 25 x109/L or 50 x109/L. The primary outcome measure is the proportion of patients who either die or experience a major bleed up to and including study day 28. 660 infants will be randomised
Results and conclusions: The relationship of thrombocytopenia to bleeding and the role of prophylactic platelet transfusion are ill defined.. Defining thresholds of clinically significant thrombocytopenia by platelet count in peripheral blood takes no account of changes in platelet function, which differ between neonates and older children and adults, nor the capacity of bone marrow to increase platelet production or produce more metabolically active platelets. Not surprisingly, platelet transfusion practice in neonates is highly variable. The uncertainty in defining optimal platelet transfusions is primarily due to the weak evidence base to support practice in this area. The only randomised controlled trial to assess a threshold level for the effectiveness of neonatal prophylactic platelet transfusions looked at moderate thrombocytopenia (defined as 50-150 x109/L) and found it was not detrimental to short-term neonatal outcome. The inclusion criteria for this trial did not consider infants under 33 weeks and practice in the early 1990s has changed considerably over the last two decades.This trial will help define optimal platelet transfusion support for severely thrombocytopenic preterm neonates by evaluating the risks and benefits of two different prophylactic neonatal platelet transfusion thresholds.

A NOVEL TECHNIQUE- CONTINUOUS ARTERIO-VENOUS EXCHANGE (CAVE) VS CONVENTIONAL PULL-PUSH TECHNIQUE OF PARTIAL EXCHANGE TRANSFUSION IN NEONATES WITH POLYCYTHEMIA- A DOUBLE-BLINDED RANDOMIZED CONTROLLED TRIAL

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Background: Partial exchange transfusion (PET) is performed in neonates with polycythemia to lower hematocrit and hyper-viscosity. Conventionally PET is performed by pull-push (PP) method. However, active pull and push are associated with several drawbacks discomfort, pain, disturbance in hemodynamics, frequent blockage of cannula, ischemia of limb and intracranial bleed. We propose a novel technique- Continuous arterio-venous exchange (CAVE), which involves spontaneous and gradual letdown of blood from intra-arterial cannula in a graduated container and simultaneous continuous infusion of saline in peripheral vein by infusion pump thus avoiding above-said complications. We planned this study to investigate whether CAVE technique would lead to decrease in intra-procedural pain scores by 60% as compared to pull-push technique among neonates undergoing PET for polycythemia.
Method: This, double blind randomized controlled trial, was conducted in a level III neonatal intensive care unit of Northern India from July 2011 to February 2012. Neonates (>320/7 weeks), aged 0 to 28 days requiring partial exchange transfusion for polycythemia [symptomatic polycythemia (hematocrit =65%) or asymptomatic neonate with hematocrit >75%] were eligible. Neonates with major congenital malformations and negative Modified Allen's test were excluded. We performed stratified randomization (for gestation) with blocking. Eligible neonates were randomly assigned to either Pull-push group or CAVE group in 1:1 ratio. Blinding was achieved by video recording the entire procedure, editing to blur the site of cannula insertion, and calculating the pain score through video recordings. Two trained neonatal fellows, independently performed N-PASS scoring on these recorded and edited videos in a blinded manner. The N-PASS scores was assigned every one minute till the end of procedure starting from baseline and the average of scores by two scorers was used for analysis. Two groups were compared for pain scores by repeated measures analysis of variance (RM-ANOVA).
Result: Twelve neonates were randomized to CAVE group and 10 to Pull-push group. Baseline variables were comparable between two study groups. The median (IQR) time for partial exchange transfusion in CAVE group [16 (9, 29) min] was significantly greater than Pull-push group [10 (6, 12) minutes], p=0.016. We compared the two groups till 12 minutes, as procedure got finished in majority of neonates in Pull-push group by 12 minutes. There was a trend of reduced pain scores in CAVE group as compared to Pull-push group till 12 minutes (p=0.057). However in 'post-hoc' analysis comparing pain scores in initial 7 minutes, pain scores in CAVE group were significantly less as compared to Pull-push group (p=0.03). PCV dropped similarly in two groups. Procedure related complications like limb erythema, gangrene, cannula blockade and IVH in <34 week infants were similar in two groups.
Conclusions: CAVE technique of partial exchange transfusion was associated with a trend of lower procedure-related pain as compared to conventional pull push technique among >32 week neonates undergoing partial exchange for polycythemia. CAVE technique was associated with significantly prolonged duration of procedure as compared to conventional pull-push technique and was equally efficacious.

NR OF RETINAL BRANCHING POINTS CORRESPONDS TO HEAD SIZE IN INFANCY AND ADULTHOOD IN SUBJECTS BORN PRETERM

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Background: Preterm infants have an increased risk for abnormal retinal development. Aim: We aimed to investigate the influence of head size on retinal branching points in children and adults born preterm at different postnatal ages and in a small group of adult subjects born full-term but with standard deviation scores (SDS) below -2 SDS (SGA).
Design/Methods: 37 children and 13 adults born very preterm (gestational age (GA)<32 weeks) and 17 adults born full-term but below -2 standard deviation score (SDS) for weight (SGA) were studied. They were examined at (mean age±SD) children: 4.7 ± 0.4 years and adults: 25.5 ± 1.7 years respectively, with eye fondus photo in which the number of retinal branching points could be estimated. The results were correlated to head circumference (HC) standard deviation scores (SDS) at postnatal weeks 34 and 36.5 and 2 y in children and to HC at birth in adults.
Result: The number of retinal branching points correlated with HCSDS at all measurements that is, postmenstrual age of 34 (r=0.51, p=0.003), 36 weeks (r=0.44, p=0.012) and at 2 years of age (r=0.65, p=0.043). In adult subjects retinal branching points correlated to HC at birth (r=0.43, p=0.022).
Conclusions: The number of retinal branching points is prospectively correlated to head circumference at birth and in infancy in children born very preterm and also in adult subjects born very preterm or full-term SGA. These correlations indicate a dependence of gradual head growth on the development of branching of retinal vessels.

INFANTILE HEMANGIOMAS AND RETINOPATHY OF PREMATURITY: COMMON MECHANISMS OF PATHOGENESIS?

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Introduction: Retinopathy of prematurity (ROP) is an eye disease that affects the retina of the preterm infant and can cause impairment of vision. Infantile hemangiomas (IHs) are benign vascular tumors that develop in infancy. Studying IH and ROP may further increase our understanding of the mechanisms of normal or abnormal vasculogenesis.
Methods: We undertook the present study to examine the concordance between IH and ROP in populations of preterm infants in the U.S. and Hungary. Clinically collected data from infants with gestational ages less than 32 weeks born between May 1, 2007 and December 31, 2010 were analyzed. A total of 897 infants with gestational ages less than 32 weeks were admitted to the NICUs at Iowa and Pécs, 684 subjects were eligible for the study (236 from Pécs and 448 from Iowa). Their data were entered into a shared database and were analyzed by center and then combined through meta-analysis.
Results: There were no significant demographic differences between populations. After univariate analysis of potential covariates in the Iowa and Pécs populations, hyperglycemia, transfusion, infection, breast feeding, postnatal corticosteroids, gestational age, birth weight, highest bilirubin, and days on oxygen were all related significantly to IH or ROP. These variables were entered into a logistic regression model. After stepwise regression, hemangioma remained in the logistic regression model in each population but showed only a trend toward significant relation to ROP. When the corrected associations from the two populations were combined through random effects meta-analysis, a significant relationship between IH and ROP was detected (OR=1.84, 95% CI 1.08-3.12).
Conclusions: These combined results suggest that IH and ROP do not occur independently in preterm infants. Further study of these conditions and their association may shed new light on the role of abnormal vasculogenesis in these disorders and on common mechanisms of pathogenesis in IH and ROP.

THE EFFECT OF CHORIOAMNIONITIS ON RETINOPATHY OF PREMATURITY: A META-ANALYSIS

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Background: Preterm labour and delivery, the leading identifiable causes of retinopathy of prematurity (ROP), have been shown to be associated with maternal infections like chorioamnionitis. Maternal intrauterine infection induces cytokine production in the fetal brain and this elevated blood and brain cytokine levels from maternal infection may disrupt the blood-brain barrier. It has also been shown that increased cytokine levels in the first 72 hrs of life are linked with development of severe ROP. Thus perinatal inflammation and infection may have a deleterious effect on the developing blood vessels in the retina, making them vulnerable to the development of ROP. OBJECTIVE: To conduct a systematic review and meta-analysis of the association between chorioamnionitis (CA) and retinopathy of prematurity (ROP) in preterm infants.
Methods: The authors searched Medline, Embase, CINAHL, Cochrane Central Register of Controlled Trials and PubMed, reviewed reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Paediatric Research 1990 to 2012) and seeking results of unpublished trials, and contacted the primary authors of relevant studies. Studies were included if they had a comparison group, examined preterm infants, and reported primary data that could be used to measure the association between exposure to CA and the development of ROP. Two reviewers independently screened the search results, applied inclusion criteria and assessed methodological quality. One reviewer extracted data and a second reviewer checked data extraction. Studies were combined with an OR using a random effects model.
Results: We identified 1249 potentially relevant studies from the electronic databases. Twenty seven studies (10590 babies) were included. Studies were published between 1997 and 2013 (median year 2011). The pooled unadjusted OR showed that CA was significantly associated with ROP (any stage) [OR=1.55(95% CI:1.21 to 1.98);p= 0.0004]. There was substantial heterogeneity [I^2 = 70.5%(95% CI:54.4% to 79.2%)] but no significant publication bias [Egger:bias=0.73(95% CI:-0.67 to 2.14);p=0.29] among the studies. CA was also found to be significantly associated with severe ROP (stage > 3) [OR=1.29(95% CI:1.12 to 1.47);p=0.0002;I^2=73.5%(95% CI:53% to 82.7%)]. No publication bias was noted among the subgroup of severe ROP as well [Egger:bias=0.32(95%CI:-1.71 to 2.36);p=0.74].
Conclusions: Chorioamnionitis was significantly associated with both ROP (any stage) as well as severe ROP (> stage 3). However oxygen therapy, which is an independent risk factor for ROP may largely vary in different GAs and in different units over different time periods. This could not be accounted for in the analysis and could play an important confounding factor. The effect of genetic variation affecting the pathogenesis of ROP was also taken into account in almost none of the studies. Finally there was substantial heterogeneity across the studies in the magnitude and direction of associations. This was primarily due to wide variation in the definition of chorioamnionitis among the studies. Hence a more careful evaluation in future taking into the account all possible confounding factors would give us a more comprehensive and true picture of the effect of chorioamnionitis on development of ROP in preterm infants.

IMPORTANCE OF TIME PERCEPTION ON THE VARIABILITY OF CAPILLARY REFILL TIME ASSESSMENT BY PAEDIATRIC STAFF

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Introduction: Accurate assessment of capillary refill time (CRT) forms an essential part of the cardiovascular assessment of children in early warning scores and international guidelines. A number of studies have examined CRT in well individuals and demonstrated marked variation depending on important variables, including: temperature, age, sex and ambient lighting (Pickard 2011). There is marked intra- and inter-observer variability with the assessment of CRT and this may reflect the published studies not controlling for these variables. The calculation of passing of time by internal time perception varies between individuals (Allman & Meck 2012). Manual calculation of heart rate during newborn resuscitation is known to be inaccurate (Voogdt 2010) which could be a result of internal time perception by the resuscitator. As yet, no one has studied the importance of individual time perception on the variability of CRT assessment which typically takes place over a few seconds. Hypothesis: Internal (i.e. manual counting) time perception alters the assessment of CRT in comparison to an external (i.e. stopwatch) measurement when other variables are removed.
Methods: Using a digital video camera we captured 6 CRT assessments in children (age 2-7). A total of 8 video clips (including 2 repeat clips for internal reliability) were shown to paediatric health care professionals (HCPs) based at a University Children's Hospital. They were asked to calculate the CRT using the standard bedside method (manually counting the time, MC) and using a stopwatch (SW). When manually assessing, participants were asked to give the result in one second windows (e.g. <2s, 2-3s, 3-4 s etc). For each assessment we compared the differences between MC and SW methods. Cronbach's a was used for intra- and inter-observer reliability. Ethical approval was given by the University of Nottingham, Faculty of Medicine Ethics Committee.
Result: A total of 74 HCPs participated in the study (25 clinicians, 49 nurses/allied health professionals) completing a total of 1184 assessments. Cronbach's alpha for MC (video 1=0.54, video 2=0.48) and SW (video 1=0.56 and video 2=0.63) demonstrated intra-observer reliability was poor. MC inter-observer reliability was unacceptable (mean=0.26, CI 0.12-0.41). Overall, only 36% of MC and SW assessments by HCPs agreed. HCPs calculated the CRT shorter with the SW method, compared with MC, in 52% of assessments. Only 12% calculated the CRT longer with the MC method. When using a normal CRT of <3s to guide cardiovascular management, these differences could result in different supportive therapies in up to 39% of cases (mean=18, CI 6-30%).
Conclusions: Assessment of CRT in children by paediatric HCPs, after removing key clinical and environmental variables known to affect it, has poor intra- and inter-observer reliability. Worryingly, we have demonstrated, for the first time, that bedside manual counting of CRT could result in a large number of children being managed differently compared to when the assessment is timed with a stopwatch. With the increasing use of early warning score systems, we need to re-evaluate the use of CRT as a component of the assessment of cardiovascular stability in children if we are to improve paediatric care. Funding: Nottingham Hospitals Charity.

24H NIRS MEASUREMENTS IN PRETERM AND TERM NEONATES: IMPACT OF ARTEFACTS

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Background: Near infrared spectroscopy (NIRS) is a continuous and non-invasive method to measure the regional oxygen saturation (rSO2) Aim of this study was to analyse artefacts during a 24h measurement of cerebral regional (crSO2) and peripheral regional (prSO2) oxygen saturation in preterm and term neonates and to analyse the influence of these artefacts on crSO2and prSO2.
Methods: The NIRS measurements were performed with the INVOS Cerebral/Somatic Oximeter (Somanetics Corporation; Troy, Michigan, USA). Sensors were placed on two different regions: fronto-parietal left (crSO2) and right forearm (prSO2). crSO2 and prSO2 were measured over a period of 24h beginning in the first 6h after birth. Sampling rate was 10values/minute. The peripheral arterial oxygen saturation (SpO2) was measured by pulse oximetry (IntelliVue MP50 Monitor; Philips, Amsterdam, the Netherlands) on the right hand. Artefacts were excluded from data according 3 criteria: C1: missing values, C2: abrupt changes in rSO2 over 15% with abrupt return to baseline within one minute and C3: rSO2 = SpO2 values. For C1 and C2 original data were used. For C3 mean values of minutes were compared. If rSO2 was = SpO2 data of the whole minute were excluded. To analyse the influence of artefacts on rSO2 values of the 24 hours period two datasets were generated and compared: original data revised with C 1 and original data revised with C1, C2 and C3
Results: Measurements were performed in 31 preterm and 9 term neonates. In crSO2 measurements artefacts occurred according C1 in 7.37%, according C2 in 0.03% and according C3 in 1.50%. In total artefacts occurred in 8.89% of the crSO2 measurement time. In prSO2 measurements artefacts occurred according C1 in 10.83%, according C2 in 0.07% and according C3 in 6.89%. In total artefacts occurred in 17.78% of the prSO2 measurement time. The comparison of datasets revealed no significant difference in mean crSO2 (78.58±1.25% and 78.54±1.24, p=0.90) and prSO2 (83.74±0.89% and 83.50±0.87, p=0.35). CONCLUSION In these long-term 24-hours measurements mean rSO2 values were not significantly influenced by artefacts. However, in 8.89% (crSO2) and 17.78% (prSO2) of the measurement time artefacts were observed. Therefore rSO2 has to be interpreted with caution in short-term measurements.

PREVALENCE OF IRON DEFICIENCY ANEMIA IN INFANTS BORN VERY LOW BIRTH WEIGHT PRETERM AT 1 YEAR CORRECTED AGE AND RISK FACTORS

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Background: Studies assessing the prevalence of anemia in very low birth weight preterm infants are scarce. Objective: To determine the prevalence of iron deficiency anemia and iron deficiency at one year corrected age (CA) in very low birth weight preterm, and evaluate risk factors for iron deficiency anemia.
Design/Methods: A cohort of infants with birth weight < 1500 g and gestational age < 34 weeks in prophylactic use of iron were followed up to twelve months CA. Anemia diagnosis was hemoglobin < 11g/dL; iron deficiency was ferritin <10mcg / l, transferrin saturation < 10% and MCV < 80fL. Following data were analyzed: number of pregnancies, maternal age, alcohol or drug addiction, gestational diabetes, chronic hypertension or preeclampsia, chorioamnionitis,UTI,family income,education,birth weight, gestational age, adequacy for birth weight, Apgar scores at 1 and 5 minutes, length of stay, type of delivery, amino acids in the first 24 hours of life, early and late onset sepsis , meningitis, NEC, erythropoietin, transfusion of packed red blood cells, exchange transfusion, PIVH and PVL, PDA, SNAPPE II, BPD, apnea, ROP, hemoglobin levels at discharge, feeding at 6 and 12 months' CA (breast milk or not supplemented with cow's milk or infant formula), hospitalization during the first year, weight, head circumference, body mass index and length at 12 months CA, use of zinc sulfate. Exams were obtained at one year CA.
Result: 310 children were studied: prevalence of anemia was 26.5% (95% CI 21.8- 31.6%), iron deficiency was 48% (95% CI 39.0-56.9%). Maternal education, family income, number of children, alcoholism by a family member, and use of cow´s milk at six months CA were significantly associated with the presence of anemia in bivariate analysis.Increased consumption of cow's milk at 6 months (RR = 1.687;95% CI 1.146-2.483) lower maternal age (RR = 0.953;95% CI 0.923-0.983), the high number of pregnancies (RR = 1.256;95% CI 1.122-1.406) and being born small for gestational age (RR = 1.578;95% CI 1.068-2.331) were independently associated with anemia after adjustments.
Conclusions: Prevalence of anemia is high at 1 year CA. Low maternal age, more pregnancies, low birth weight for gestational age, and consumption of cow's milk at six months CA increase the prevalence of anemia. Food and environmental education strategies may impact on lower prevalence of anemia at follow-up after discharge.

HEPCIDIN CONCENTRATION IN CORD BLOOD OF TERM AND PRETERM INFANTS CORRELATES WITH GESTATIONAL AGE AND FERRITIN

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Background: Hepcidin, first described in 2001, plays a crucial role in regulating iron homeostasis. This peptide hormone binds to the iron exporter ferroportin on the basolateral membrane of enterocytes, macrophages, hepatocytes and syncytiotrophoblasts inhibiting iron efflux. In future, hepcidin, which can also be measured in urine, could serve as a non-invasive iron status parameter for monitoring individualised iron supplementation e.g., in preterm infants. The aim was to establish gestational age-specific reference ranges of hepcidin in cord blood and to determine perinatal factors with impact on the hepcidin concentration.
Patients and Methods: Hepcidin concentration (Hep(S)) as well as complete blood count, ferritin, CRP and IL-6 were measured in cord blood of 162 infants (24+1/7 to 41+6/7 weeks of gestational age). Data are shown as median (interquartile range) along with Spearman´s rank correlation coefficients and p-values by Wilcoxon-Mann-Whitney test.
Result: Hep(S) in infants was 75 (39,125) ng/mL and detectable also in extremely premature infants. Higher Hep(S) were observed with increasing gestational age ($r = 0.51$, $p<0.0001$). Gestational age specific Hep(S) values were: < 30 weeks. 30 (17, 60) ng/mL, n=19; 30-36 weeks, 54 (34, 78) ng/mL, n=56; > 36 SSW, 107 (72, 153) ng/mL, n=87. There was a correlation between Hep(S) und ferritin ($r = 0.67$, $p<0.0001$); Hep(S) was lower in term infants with depleted iron stores (ferritin < 40 ng/L) [36.5 (10, 80), n = 11] compared to non-iron-depleted term infants [115.9 (80, 155), n = 72, $p<0.0005$]. In term infants with an umbilical artery pH<7,15, Hep(S) was higher [130 (116, 198) ng/mL] compared to term infants with an umbilical artery pH>7.15 [97 (68, 145) ng/mL, p= 0.02)]. There was a trend towards higher Hep(S) in term infants after spontaneous vaginal delivery [121 (86,153) ng/mL] compared to term infants delivered by elective caesarean section [94.9 (47,122) ng/mL, p=0.05] what can be explained by higher cytokine levels in infants after spontaneous vaginal delivery. The highest Hep(S) (437 ng/mL) was observed in a preterm infant with early onset sepsis, a positive blood culture and high initial IL-6 levels (1760 ng/L). In a subgroup analysis excluding infants with infection, with perinatal acidosis or after spontaneous vaginal delivery (n=48), we observed even stronger correlations between Hep(S) and gestational age ($r = 0.70$, $p<0.0001$) and between Hep(S) and ferritin ($r = 0.86$, $p<0.0001$).
Conclusions: Even extremely preterm infants already synthesize hepcidin, possibly for regulation of intrauterine iron homeostasis. Hepcidin concentrations increase with gestational age and there is a good correlation between hepcidin and ferritin. Consequently, hepcidin may serve as an iron status parameter in preterm infants but the influence of perinatal factors, e.g. sepsis, on Hep(S) should be taken into account.

EFFECTS OF DELAYED VERSUS EARLY CORD CLAMPING ON IRON STATUS AND NEURODEVELOPMENT AT 12 MONTHS OF AGE - A RANDOMIZED TRIAL

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Introduction: By waiting to clamp the umbilical cord for 3 minutes, the newborns blood volume can be expanded by up to 30 ml/kg. Consequently, delayed cord clamping in term newborns is associated with higher hemoglobin at 2-3 days after birth and higher ferritin at 4-6 months. To date, no trial has reported on iron status or neurodevelopmental outcome after 6 months of age. Objectives: To investigate effects of delayed umbilical cord clamping, as compared to early, on iron status and infant development at 12 months of age.
Study design: Term infants (n = 382) were randomly assigned to delayed (=180 sec) or early (=10 sec) umbilical cord clamping. Follow up at 12 months of age included evaluation of iron status (ferritin, transferrin saturation, transferrin receptor, reticulocyte hemoglobin equivalent and mean cell volume) and parental assessment of neurodevelopment by the Ages and Stages Questionnaire.
Result: At 12 months 347 infants were assessed. The two randomization groups did not differ in ferritin (inter quartile range); 36 (26-50) µg/l in the delayed clamped group versus 35 (23-50) µg/l in the early clamped group, p=0.3. Nor did groups differ in neurodevelopment measured as ASQ total score; delayed clamped scored 230 (205-260) and early clamped scored 240 (215-255), p=0.3. In total, 13 had iron deficiency; 5 (3.4%) in the delayed group compared to 8 (5.4%) in the early, p=0.5. Only one infant had iron deficiency anemia. Predictors of ferritin levels were infant sex and ferritin in umbilical cord blood. Predictors of ASQ were infant sex and breastfeeding within one hour after birth. For both outcomes, being a boy was associated with lower results. Interaction analysis showed that delayed cord clamping was associated with a 5 points higher ASQ score among boys, but a 12 points lower score in girls, out of a maximum of 300 points.
Conclusions: Delayed cord clamping increases neonatal hemoglobin levels and improves iron status at four months of age, but does not affect ferritin levels or neurodevelopment assessed by ASQ in a selected population of healthy term born infants. However, minor effects on neurodevelopment may not be possible to demonstrate with the size of the study population and the chosen method for assessment. The current data indicate that effects of delayed cord clamping may differ according to infant sex and that boys may benefit more from delayed cord clamping than girls.

IRON STATUS IN INFANTS BORN AFTER 32 TO 37 WEEKS OF GESTATIONAL AGE; PRELIMINARY RESULTS OF THE IPI STUDY

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Background: Infants born prematurely are susceptible to iron deficiency (ID) because of insufficient iron storage due to premature delivery, rapid growth after birth and frequent blood sampling during the first weeks of life. ID in infants may have a long-term detrimental influence on mental and psychomotor development. An iron intake of 2 to 3 mg/kg/day is recommended by the ESPGHAN. Standard practice in the Netherlands is to provide iron supplementation only in infants born < 32 weeks gestational age (GA). We hypothesized that the iron content in the diet of preterm infants born > 32 weeks is insufficient to fulfill the increased iron demands. The aim of this study is to assess to iron status in infants born after 32 to 37 weeks GA during the first six months of life.
Methods: Prospective cohort study in infants born in between 32 and 37 wk GA. Iron status (mean corpuscular volume (MCV), zinc protoporphyrin (ZPP), plasma ferritin (Fer) and Hb content in reticulocytes (Ret-Hb)) was assessed in the first week of life and at the postnatal age of 1 ½, 4 and 6 months. Low iron stores were defined as Fer < 12 µg/L. Iron deficient erythropoiesis was defined as ZPP > 0,75 µmol/mol heme or Ret-Hb < 1,6 fmol (< 26 pg) at the age of 6 months.
Results: Until now 180 infants were included in the study. Median GA and birth weight (range) were 34,9 weeks (32,0 - 36,9) and 2192 g (1195 - 3910) respectively. Iron status was available in 98, 101, 89 and 89 infants at the age of 1 week, 1 ½ , 4 and 6 months respectively. Low iron stores were present in 1, 6 and 8 infants at the age of 1 ½, 4 and 6 months (1%, 6% and 9% respectively). Iron deficient erythropoiesis was present in 26 infants (29,2%) aged 6 months. There was a significant correlation between Fer, MCV, ZPP and Ret-Hb after birth and the same parameters during follow-up (p-values <0,05). Lower Fer values after birth were observed in infants with a lower GA and birth weight (p-value 0,01 and <0,01 respectively). At the age of 1 ½ and 4 months lower Fer values were observed in twins (44 µg/L and 28 µg/L) compared to singletons (123 µg/L and 88 µg/L) (p-value < 0,01 and 0,03 respectively). Faster weight gain was associated with lower Fer values at the age of 1 ½ and 4 months.
Conclusion: Low iron stores and iron deficient erythropoiesis are frequently observed in infants born after 32 to 37 weeks GA. Infants born with low iron stores at birth continue to have lower iron stores later in life.

EFFECTS OF IRON SUPPLEMENTS AND PERINATAL BACKGROUND ON FETAL HEMOGLOBIN DISAPPEARANCE IN INFANTS.

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Introduction/Background: Due to its high affinity for oxygen, fetal hemoglobin (HbF) is the main hemoglobin produced by the fetus. After birth, the production is switched to adult hemoglobin (HbA).Concurrently after birth, iron and hemoglobin metabolism undergoes rapid changes and rearrangements to meet the requirements of erythroid expansion. However, it is not known whether the switch from HbF to HbA is affected by iron status. Furthermore, the influence of other environmental and perinatal circumstances is not fully clear. In this study, we investigate whether iron supplementation affects the disappearance of HbF after birth in low birth weight infants, a group with increased risk of iron deficiency. We also explore other perinatal background factors and their impact on HbF-disappearance.
Patients and
Methods: This was originally a randomized, double blinded, controlled trial of iron supplementation to low birth weight infants (2000-2500 g). The present study is based on secondary analysis of HbF and its predictors. Included infants (285) were stratified by sex and randomized into three intervention groups receiving the following doses of iron supplementation: 0 mg/kg/day (placebo), 1 mg/kg/day or 2 mg/kg/day from 6 wk to 6 mo of age. Blood samples were obtained at 6 wk, 12 wk and 6 mo of age. Each blood sample was analyzed for iron status indicators and hemoglobin (Hb). HbF-fraction was determined using electrophoresis and HbF-concentration was calculated from Hb and HbF-fraction. Perinatal background data was collected at inclusion.
Results: Mean total Hb (SD) decreased from 107.4 (12.0) g/L at 6 wk to 107.2 (7.1) g/L at 12 wk followed by an increase to 117.7 (9.5) g/L at 6 mo of age. At 6 mo of age there was a significant difference between the intervention groups with mean Hb (SD) of 113.2 (8.2) g/L, 118.8 (8.4) g/L, and 122.5 (9.7) g/L in the placebo,1 mg, and 2 mg-group respectively, suggesting an increased synthesis of hemoglobin in iron replete infants between 12 wk and 6 mo of age. For absolute HbF-concentration there was no significant effect of intervention. Mean (SD) HbF was 81.2 (16.8) g/L, 37.0 (13.8) g/L and 8.1 (5.6) g/L at 6 wk, 12 wk and 6 mo respectively. In univariate linear regression analysis, we examined the correlation between HbF and iron status indicators as well as other perinatal background variables. In those, only age at examination and post-conceptional age turned out as significant predictors of HbF-concentration. In a multivariate model, the only remaining predictor of HbF was post-conceptional age ($r= 0.352$, $p<0.001$ at 6 wk, $r=0.510$, $p<0.001$ at 12 wk, $r=0.292$, $p<0.001$ at 6 mo of age).
Conclusion: Our hypothesis, that iron availability during the phase of rapid erythroid expansion from 6 wk to 6 mo of age would affect the synthesis or disappearance of HbF, was rejected. Our results suggest that iron supplements only stimulate HbA production. The lack of correlation between HbF and perinatal background factors together with a strong significant correlation between post-conceptional age and HbF, suggests that the hemoglobin switch is pre-programmed in the fetus and independent of the circumstances at birth and thereafter.

THE INTERACTION EFFECT OF C-REACTIVE PROTEIN AND MALNUTRITION ON LOW PLASMA SELENIUM IN CRITICALLY ILL CHILDREN

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Background: as an essential trace element, selenium is involved in immune function, antioxidant defenses and thyroid function (1). Low plasma selenium concentrations are frequent in critically ill patients. However, whether this is due to systemic inflammation or to a selenium-deficient state is still not clear (2). We aimed to determine the factors associated with low plasma selenium in critically ill children, while taking into account the inflammatory response and nutritional status.
Methods: a prospective cohort study was conducted in 173 children who had plasma selenium assessed at admission and on the 5th day of ICU stay. Outcome variable: a plasma selenium concentration below the median value of 0.30 µmol/L during this period (low plasma selenium). Main explanatory variables: age, sex, malnutrition (according to WHO growth standards), sepsis, C - reactive protein (CRP), serum lactate, serum albumin, and clinical severity scores (Pediatric Logistic Organ Dysfunction - PELOD), and the revised Pediatric Index of Mortality (PIM 2). The effect of explanatory variables on the outcome was analyzed by using Generalized Estimating Equations (GEE) with binomial distribution, which allows to include the correlation between admission and 5th day responses.
Result: malnutrition and CRP were associated with low plasma selenium. There was a significant interaction effect between these two variables (p=0.035). At CRP values equal or lower than 40mg/dL, malnutrition is independently associated with low plasma selenium (odds ratio=3.25, 95% CI 1.39-7.63; p=0.007, odds ratio=2.98, 95% CI 1.26-7.06; p=0.013 and Odds ratio=2.49, 95% CI 1.01-6.17; p=0.049, for CRP=10, 20 and 40mg/dL, respectively). This effect decreases as CRP increases and loose significance at CRP values > 40 mg/dl (odds ratio=2.09, 95% CI 0.79-5.53; p=0.140 at CRP=60mg/dL and odds ratio=1.75, 95% CI 0.60-5.07; p=0.306 at CRP=80mg/dL. Similarly, the effect of CRP on low plasma selenium was significant for well-nourished patients (odds ratio=1.012; 95% CI 1.006-1.019, p<0.001), but not for the malnourished (odds ratio=1.003; 95% CI 0.99 - 1.008, p=0.157).
Conclusions: there is an interaction effect of CRP and malnutrition on low plasma selenium. This should be considered when interpreting plasma concentrations as an index of selenium status in patients with systemic inflammation, as well as in studies on micronutrient supplementation.
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VITAMIN D DEFICIT IN OVERWEIGHT CHILDREN AND ADOLESCENTS

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Introduction: Recent studies show that vitamin D deficit is a common health problem in all age groups, with particular interest in risk groups such as children and adolescents with high body mass index (BMI). For this matter, we aim to determine the prevalence of 25-hydroxyvitamin D (25(OH)D) deficit in children and adolescents with BMI superior to the 85th centile.
Methods: Transversal and descriptive study involving children and adolescents aged 9-17 years followed in the Pediatric Nutrition Consult in a level 2 district hospital. All subjects were submitted to a standardized questionnaire, anthropometric, puberty (Tanner stages) and analytical assessment, including levels of 25(OH)D, lipid and phosphocalcic metabolism, insulin and fasting glucose. All individuals with secondary obesity were excluded. Statistical analysis with SPSS v17 (significance with p value <0.05).
Result: We evaluated 106 individuals with a mean age of 12.5 years, 50% were female. Deficiency of 25(OH)D (<20ng/ml) was found in 43.4% and insufficiency (20-40ng/ml) in 48.1%. Analyzing the sample by BMI categories, 28.3% were overweight and 71.7% obese. Statistically significant differences were found related to anthropometric parameters (weight, height, waist perimeter, p <0.001), systolic blood pressure (p = 0.018), HDL-cholesterol (p = 0.027), insulin (p = 0.013) and HOMA-IR (p = 0.012). There were no statistically significant differences in the levels of 25(OH)D. Metabolic syndrome was identified in 9.4% of the sample, and statistically significant differences were identified in puberty stage (p = 0.048), systolic blood pressure (p = 0.001), HDL-cholesterol (p = 0.020) and triglycerides (p = 0003). Again, there were no statistically significant differences in 25(OH)D levels. Correlating the different variables studied, 25(OH)D level was positively associated with the number of exercise hours per week (r = 0.279, p = 0.016), no significant correlation was found in the remaining variables.
Conclusions: It is noteworthy that 91.5% of the sample has insufficient levels of 25(OH)D, of which almost half had deficient levels. 25(OH)D levels appear to be associated with greater physical activity, with no significant association with the other variables studied, probably due to the very high prevalence of 25(OH)D deficiency. These results urge for a profound reflection on the need for systematic screening of the 25(OH)D levels and its supplementation, at least in this population. However, more studies are needed involving its assessment in eutrophic population.

CUMULATIVE DIETARY AND SUPPLEMENTAL VITAMIN D INTAKE IN PRETERM INFANTS: HOW MUCH VITAMIN D IS ENOUGH?

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Background: Vitamin D (25OHD) plays an important role in skeletal and non skeletal health. 25OHD deficiency is common in premature infants. Controversies still exist among institutions on reference daily intake for Vitamin D especially in at risk groups. Aim: To assess serum 25OHD status in preterm infants at birth and response to cumulative vitamin D intake during their hospital stay.
Methods: Serum 25OHD levels were evaluated using the Elecsys Vitamin D Total automated competitive binding protein assay from preterm (< 32 weeks gestation) infants at birth, before commencement of oral additional vitamin D supplementation and at discharge from the hospital.
Result: 38 VLBWs were included in this study and had 106 samples taken. Their mean gestational age (SD) was 28 ± 2 weeks and birth weight 1.2 ± 0.4 kg. Average daily Vitamin D intake from birth to discharge was 620.9 IU/L which comprised TPN (120 ± 39 IU/day), Fortified Breast milk/Formula (300.9 ± 120 IU/day) and Vitamin D supplement (200 IU/day). 25OHD levels increased from 25.7 ± 17nmol/L at birth to 36.3 ± 19nmol/L, p=0.02, during only TPN and to 59 ± 25.6nmol/L, p=0.0001, at discharge (duration 7 weeks).
Conclusions: Vitamin D plays a key role in skeletal health and inadequate nutrition in premature infants can lead to poor growth and increased morbidity. There is paucity of data to guide vitamin D intake in preterm infants. However the IOM recommends 400 IU/day, while ESPGHAN recommends 800 - 1000 IU/day. In this cohort of preterm infants, 200 IU/day of vitamin D supplementation in addition to fortified feeds resulted in a cumulative average daily intake of vitamin D up to 620.9 IU which was adequate to raise 25OHD level >50nmol/L.

FISH OIL SUPPLEMENTATION IN PREGNANT DIET AND VISUAL DEVELOPMENT OF CHILDREN: DIFFERENTIAL EFFECT DEPENDING ON GENDER

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Objective and Study: Docosahexaenoic acid (DHA) has putative roles that relate to visual function, including signal transduction and neurotransmission, therefore, DHA deficiency during pregnancy could be related to delay in the cognitive and visual development. However, many controversies can be found in the scientific literature regarding visual acuity and DHA supplementation and they can be attributed to the multiple factors and different conditions of the studies such as gestational age, mother´s diet, timing, way of the supplementation, and newborn´s sex. The aim of the current study was to elucidate the effect of DHA supplementation on visual development of the newborn, taking into account the gender of infants. **Methods**: 80 women were randomly assigned to one of the following intervention groups: A) Control Group (n=40): They received 2 glasses/day of the control dairy drink, and B) Supplemented Group (n=40): The women received 2 glasses/day of the fish-oil supplemented dairy drink (400mg DHA/day). Dietary intervention began in the sixth month of pregnancy and concluded at the end of breastfeeding. During all this time women from both groups received a controlled diet under the supervision of a dietician. At 2.5 and 7.5 months of life of infants (n=54), pattern-reversal visual evoked potentials (VEPs) were measured at different angles (2°, 1°, 30', 15', 7.5'). The results are expressed as latency (P1, in miliseconds). **Results:** There were no differences between groups in latency. However, when only boys (n=27) were considered, latency at 7.5m was significantly lower in group B ($P<0.05$ at 7.5'). In addition, when considered just the supplemented group (n=28), latency at 7.5m was significantly lower in boys compared to girls ($P<0.05$ at 15' and also at 7.5'). CONCLUSION The effects of a dairy drink enriched in DHA on visual development of children depend on the gender being more evident in boys than in girls. More studies are needed to further elucidate these differences and the mechanisms involved.

CHOLINE DEFICIENCY IN PRETERM INFANTS - POSTNATAL DECREASE IN PLASMA CONCENTRATION AS AN INDICATOR OF CHOLINE UNDERNOURISHMENT

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Background: Choline is an essential nutrient. It is a component of phosphatidylcholine (Ptd'Cho) und sphingomyelin (SPH) required for membrane formation and lipid containing secretions (surfactant, bile, lipoproteins), and of the neurotransmitter acetylcholine. Ptd'Cho of very low density lipoproteins (VLDL) from the liver contributes to the supply of the central nervous system and other organs with essential fatty acids like docosahexaenoic acid (DHA). In both animals and humans, choline deficiency impairs cognitive development. Choline requirement depends on growth rate, and is inversely related to body weight. In utero, choline is actively transported across the placenta, resulting in fetal plasma concentrations (35µmol/L) 3fold those of the pregnant mother. Choline uptake into peripheral organs including the brain is proportional to plasma concentration. However, plasma choline levels of preterms are unknow, while decreased concentrations may impact on overall and cognitive development.
Objective: To determine choline concentrations in cord blood and postnatal blood samples of preterm infants during neonatal intensive care.
Patients and Methods: Cord blood EDTA plasma of preterm and term (N=177; 24-42wk postmenstrual age [PMA]) and residual plasma of clinically indicated blood samples (N=162 of 56 preterm infants (27.9[23.4-35.0]wk PMA) were extracted with chloroform:methanol. Choline concentrations were assessed with electrospray ionization tandem mass spectrometry. Data are indicated as medians (25th/75th percentile).
Result: Choline concentration in cord plasma was 41.4 (31.8-51.2)µmol/L and was inversely correlated (r=-0.35, p<0.0001) with PMA: 24-27w: 47.1 (32.0-60.0)µmol/L; 37-42w: 34.9 (29.4-41.3) µmol/L. In postnatal plasma of preterm infants choline dropped within 48h from 42,5 (26.6-52.0) (N=13) to a constant level of 20.7 (16.0-27.0)µmol/L (d2-d84; N=149; P<0.001), irrespective of PMA at delivery.
Conclusions: In fetal plasma choline concentration is higher during the period of rapid growth in early third trimester compared to end gestation. Postnatally, plasma choline drops within 48h to about 50% of intrauterine levels. As choline uptake into tissues correlates with plasma concentration, and as this decrease occurs at a time where choline should be much higher, this may contribute to the impaired cognitive development of preterm infants. Further studies on choline supplementation and its effect on (neuro)development are required.

CALCIUM, PHOSPHORUS AND MAGNESIUM IN SMALL FOR GESTATIONAL AGE (SGA) INFANTS IN CORD BLOOD AND AT 72H OF AGE

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Background: Fetal growth restriction (FGR) is couse of many disorders in neonatal period and later life, including hormonal and metabolic consequences. The aim of our study was to investigate the electrolyte status in SGA infants at birth. Patients and
Methods: In this prospective cross -sectional study we determined calcium, phosphorus and magnesium in cord blood (CB) and at 72h of age (d3) in two groups of infants:1.) SGA group- 50 term neonates from singleton pregnancies with birthweight (BW) below 10th percentile and 2.) AGA (appropriate for gestational age) group- consists of 48 helthy, term, gestational age matched infants with BW between 10th and 90th percentile.
Result: mean CB levels of ionisated calcium were significantly higher in AGA group (1,41±0,12 vs. 1,32±0,16 mmol/l, p< 0,01), while mean magnesium levels were higher in SGA CB (0,87± 0,18 vs. 0,77± 0,12 mmol/l, p<0,01). Mean cord serum phosphorus levels did not differ between SGA and AGA groups (1,82± 0,52 vs. 1,80± 0,36 mmol/l, p>0,05). D3 calcium (1,07±0,23 vs. 1,01±0,16 mmol/l, p>0,05) and magnesium (0,94±0,18 vs. 0,89±0,15 mmol7l, p>0,05) levels were comparable between SGA and AGA groups. Significantly higher d3 phosphorus levels were found in SGA neonates (2,41± 0,47 mmol/l vs. 1,81± 0,52 mmol/l p<0,01).
Conclusions: A lower CB calcium level in SGA newborns is probably related to reduced nutrient supply in fetuses with FGR. Increased CB magnesium levels in SGA infants might be in connection with development of insulin resistance in later life although in our study difference between groups disappeared at d3. Our data showed that SGA infants, beside disturbances in lipid and glucose metabolism, also have and electrolyte difference in first days of life.

PLASMA PHOSPHOLIPID ALTERATIONS IN PRETERM INFANTS AS INDICATORS OF ESSENTIAL FATTY ACID IMBALANCE AND UNDERNOURISHMENT

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Background: Polyunsaturated fatty acids (PUFA), namely docosahexaenoic (DHA) and arachidonic (ARA) acid, are essential to human brain development and as precursors for resolvins and eicosanoids. DHA and ARA are enriched in the placenta and actively secreted into the fetal circulation, whereas linoleic acid (LA) is retained in the maternal organism. This preferential DHA and ARA supply to the fetus via placenta is abolished after preterm delivery. In postnatal plasma, DHA is predominantly, and ARA to a large degree, present in several molecular species of phosphatidylcholine (PC). Plasma turnover of DHA- and ARA-PC exceeds that of other PC components, highlighting the importance of phospholipids for the distribution and homeostasis of these essential PUFA. In contrast, fatty acid composition of phosphatidylethanolamine (PE) in plasma reflects liver tissue resources, as PE is a physiologic plasma membrane component. Its ARA and DHA serve as precursors for DHA- and ARA-PC of lipoproteins being secreted by the liver. Objective: To determine the postnatal changes in plasma PC and PE species in preterm infants, as they are fed on lipids high in LA, but low in DHA and ARA. Patients and
Methods: Preterm infant plasma (N=171 from 56 patients, 23-35wk postmenstrual age [PMA], postnatal d1-103), cord plasma (N=194) and maternal serum (N=121) (24-41wk PMA each) were extracted with chloroform:methanol. PC and PE species were quantified using electrospray ionization tandem mass spectrometry. Data are medians and 25th/75th percentiles.
Result: Total plasma PC was increased in postnatal blood of preterm infants (2.35[1.91-2.79]mmol/L) compared to cord blood (1.15[0.97-1.41]mmol/L) throughout the PMA range studied. Maternal blood PC was 3.30[2.84-3.89]mmol/L. This also applied to total PE, which was a minor component, comprizing less than 4% of PC in plasma of preterm infants and cord blood. The higher PC concentrations in preterm infant plasma were due to a postnatal increase in LA-PC ($r=0.59$;$p<0.0001$), which was at the expense of the DHA- and ARA-PC fraction ($p<0.0001$). Consequently, PC composition in postnatal plasma was similar to that of maternal rather than fetal plasma throughout the PMA range studied ($p<0.0001$), with high LA-PC and low DHA- and ARA-PC. This similarly applied to PE components, showing a rapid postnatal decrease in PUFA-PE ($p<0.001$).
Conclusions: In preterm infants, plasma phospholipids increase shortly after delivery. This is due to an increase in LA-PC at the expense of DHA- and ARA-PC. The decrease in ARA- and DHA-PE suggests a postnatal depletion of hepatic PUFA pools. These molecular changes, presumably based on inadequate LA, ARA and DHA supply, might contribute to impaired neurodevelopment. Whether this implies a revision of our feeding approach during neonatal intensive care requires further study.

DO GENDER AND PERINATAL FACTORS AFFECT THE REDOX STATE OF THE TERM NEWBORN AT BIRTH AND WITHIN THE FIRST 48H?

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Background: Oxidative stress is an unbalance between pro-oxidant and antioxidant factors that leads to increased levels of reactive oxygen and nitrogen species, which can cause cellular and tissue damage. Newborns are especially sensitive to oxidative stress, and numerous factors around the moment of birth can potentially modify this delicate balance. Early sex-differences regarding newborn oxidative stress have been so far poorly investigated. Many studies have aimed at determining to which extent factors like the birth mode, type of anesthesia or maternal background, actually affect neonatal redox state, sometimes with small samples of newborns, or conflicting results. Objective: To assemble a large group of participants in which to study whether gender has a significant role on neonatal redox state. To investigate the effect that different factors around the time of birth may have on the neonatal redox state. Patients and
Methods: All newborns above 35 gestational weeks born in our institution from October 2012 - March 2013 were elegible for study. 374 newborns (185 females and 189 males) met the inclusion criteria and consented to participate. The gestational history was retrospectively questioned, and the perinatal evolution was prospectively registered in detail until the time of hospital discharge. Blood samples were extracted at birth (cord arterial and venous blood) and, in a subgroup of patients, at 48h postnatal life (by heel puncture); and urine from the first and second day was collected. The acid-base status in umbilical venous and arterial blood was measured. The levels of total antioxidant capacity (TAC), MDA and carbonyl group in blood and urine, and those of glutathione and nitric oxide in plasma were analyzed (only TAC and glutathione ratio in blood samples by the time this abstract was sent in). A p value of less than 0.05 was considered statistically significant.
Result: Our data show no significant gender differences in the glutathione ratio at birth in arterial cord blood or at 48h postnatal life and no significant sex-differences in the levels of TAC at birth. However, male newborns seem to have a significantly higher level of TAC in plasma at 48h (males 1.47mM, SD 0.44, females 1.37mM, SD 0.34, $p<0.05$). Concerning gestational and birth history, so far we have not found any factor which significantly affects glutathione ratio or TAC. The venous cord glutathione ratio was significantly correlated to partial oxygen pressures in venous cord blood. The glutathione ratio at 48h postnatal life was significantly higher in the newborns with higher partial oxygen pressure in arterial and venous cord blood.
Conclusions: Our data suggest that there are no sex differences in the glutathione ratio and TAC levels at birth. Male newborns had a higher level of plasma TAC at 48h. We found a significant correlation between the partial oxygen pressure at birth and the glutathione ratio in venous cord blood and at 48h postnatal life.

FOCAL CONGENITAL HYPERINSULINISM: ADENOMATOUS HYPERPLASIA OF PANCREATIC ENDOCRINE CELLS. IMMUNOHISTOCHEMICAL ANALYSIS OF P57 EXPRESSION.

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Background: Congenital hyperinsulinism (CHI) is a rare genetically heterogeneous disorder characterized by profound hypoglycemia due to inappropriate insulin secretion. Two histologically and genetically forms are recognized due to ATP-sensitive K-channel defects: a diffuse form, which involves the whole pancreas and a focal form, with an area of adenomatous hyperplasia within an otherwise normal pancreas. Focal CHI is due to a somatic K-channel mutation on chromosome 11p15.5, generally inherited from the father, and a loss of heterozygosity (LOH) of the corresponding region on maternal chromosome. In this maternal region resides the P57 KIP2 gene. This gene is involved in regulation, as inhibitor, of cell proliferation. Focal CHI is curable with limited pancreasectomy. Aim of our study is to analyze the P57 KIP2 expression in 6 cases of focal CHI: 4 inside the pancreas and 2 with the aspect of an exophitic polyp on the surface of the pancreas.
Methods: Six children, 2 males (10- and 13-month-old) and 4 females (age range from 10- to 61-month-old) showed a clear areas of increased F-fluoro-L-Dopa PET uptake within the head (2 cases), the uncinate process (1 case), the isthmus (1 case) and, apparently, 2 outside the pancreas. On the surgery, the four children with inside adenomatous hyperplasia needed several intraoperative frozen sections to ensure complete excision; on the contrary, the exophitic forms were easily identified on naked eye and the adenomatous hyperplasia was confirmed on frozen section. Immunohistochemistry for P57 KIP2 was performed on formalin-fixed paraffin-embedded tissue. Microsatellite markers were used to demonstrate LOH in focal lesion compared to adjacent normal pancreas.
Result: All lesion were composed of large endocrine cells with dispersed abnormal nuclei. In two cases there were satellite lobules in the nearby normal pancreas. On immunohistochemistry, in all samples P57KIP2 expression was lost in the lesion, whereas it was normal outside the islets of Langerhans. Microsatellite marker, D11S909, showed loss of maternal 150 bp allele in DNA in focal adenomatous hyperplasia compared to adjacent normal pancreas.
Conclusions: Focal CHI is caused by specific loss within affected ß-cells of a portion of the maternal allele of 11p15, which contains the p57KIP2 gene. p57KIP2 has been shown to be paternally imprinted in several tissues. Loss of p57KIP2 expression within the focal CHI lesion suggests that the gene is also imprinted in human ß-cells. This relatively simple immunohistologic stain can be used to confirm LOH of the maternal allele in these lesions and may be of use in differentiating focal HI from other forms of hyperinsulinism.

MALNUTRITION AS A PREDICTOR OF DEVELOPMENT AND OUTCOME OF ACUTE KIDNEY INJURY IN CHILDREN WITH CRITICAL ILLNESS.

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Background: Acute kidney injury (AKI) is an important, independent risk predictor of mortality in critical illness (1, 2). Identification of factors interacting with the development and outcomes in AKI is deemed necessary for the clinical management of critically ill patient. Nutritional status is one of these factors. We aimed to investigate the interaction between malnutrition and AKI and its effect on the outcomes of children admitted to a pediatric intensive care unit (pICU).
Methods: we prospectively evaluated children who were admitted to the pICU between September 2011 and December 2012. Patients with evidence of end-stage renal disease were not included. Outcome variables were: a) 28-day mortality, b) need for dialysis, c) pICU-free days (the number of days alive from ICU discharge to day 28 after study enrollment), d) free-ventilator days (the number of days between successful weaning from mechanical ventilation and day 28 after study enrollment). Exposure variables: malnutrition on admission (WHO growth standards), clinical severity scores (Pediatric Logistic Organ Dysfunction - PELOD), and the revised Pediatric Index of Mortality (PIM 2), and development of AKI (according to the pRIFLE criteria) during the first 14 days in ICU stay.
Result: Of 98 patients enrolled (median age=19 months, interquartile range =50 months, 63 males) 35% (34/98) developed AKI and 40% (39/98) were malnourished. Among the malnourished, 49% (19/39) developed AKI, while this complication occurred in 25% (15/59) of the well-nourished, resulting in a risk ratio of 1.9 (95% CI=1.1 - 3.3, $p<0.05$). The overall 28-day mortality rate was 10% (10/98). AKI was associated with a higher risk of mortality (8/34 versus 2/64 cases, RR=7.5, 95% CI 1.7 - 33.5). Concurrent malnutrition and AKI occurred in 19% (19/98) of patients producing a non significantly higher mortality risk (RR=9.4, 95% CI 1.5 - 58.0). Malnutrition increased the risk for dialysis (RR=5.3 95% CI 1.2 - 24.2), a complication that occurred in nine out 98 patients. AKI was associated with significantly more pICU-free days ($p< 0.016$) and free-ventilator days ($p <0.0001$), however concomitant malnutrition did not affect either of these outcomes.
Conclusions: Malnutrition and AKI are common in children admitted to the ICU. Malnutrition is associated with increased risk of developing AKI and need for dialysis. A larger sample size of patients will be necessary to confirm whether concomitant AKI and malnutrition are associated with higher mortality.
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REMOTE ISCHEMIC POSTCONDITIONING IN A PIGLET MODEL OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Aim: To characterize the effects of remote ischemic postconditioning (RpostC) after hypoxic-ischemic encephalopathy (HIE) in a piglet model. Background RPostC is the application of controlled limb ischemia after an initial ischemic insult, resulting in remote tissue protective effects thought to be mediated by blood-borne factors. RPostC has been shown to reduce myocardial infarct size and it is speculated that RPostC may protect against brain damage following ischemia.
Methods: Fifty-two piglets (18 hours old) were instrumented for continuous monitoring. FiO2 was lowered to 4%, then adjusted over a 45-minute period to suppress aEEG to < 7uV. Piglets were randomized at 1-hour post hypoxia to RpostC (4 cycles of 5 minutes ischemia in both hind legs induced by external compression) or no intervention.
Primary outcomes: 1) Histological brain examination at 72h. 2) MRI: a) infarct size by high-resolution MRI volumetry b) diffusion-weighted imaging c) deep gray matter lactate/N-acetyl aspartate and lactate/creatinine ratios.
Results: and perspectives At present 40 piglets have been examined and data analysis is ongoing. Hypoxic piglets demonstrated acidosis, hypotension and neurologic abnormalities. Final results presented at the meeting will contribute to the evaluation of RpostC as a potential neuroprotective intervention after HIE.

RELATIONSHIPS BETWEEN LOW PCO2 AND DIFFUSION TENSOR IMAGING MRI VARIABLES IN HYPOCARBIC BABIES: A PILOT STUDY

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Introduction: We postulate that brain MRI findings reflect specific mechanisms of neonatal brain injury. Here we explore the relationship between neonatal hypocarbia and findings on brain imaging. Hypocarbia is associated with vasoconstriction and with poor neurodevelopmental outcome. To date there has been no reported study that compares variables derived from diffusion tensor imaging (DTI) on magnetic resonance imaging (MRI) with the extent of hypocarbia in ventilated neonates. Aim: To conduct a pilot study of the hypothesis that DTI variables reflect the extent of hypocarbia among babies with hypocarbia within 24 hours of birth.
Methods: Ventilated neonates were eligible for enrolment in the LAMB Study (Liverpool Archive of MRI in Babies (Neonates) after parental consent between December 2011 and January 2013. Basic demographic details and biochemical details were collected from the electronic patient data management system. Subjects for this analysis were selected if at least one blood gas within 24 hours of birth showed a pCO2 less than 4 kPa, irrespective of source. DTI measurements were performed using a 3 Telsa MRI scanner (Philips Achieva XL). Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were measured in 9 regions of the brain (with bilateral or anteroposterior replicates as appropriate) giving 32 measurements. Statistical analysis was performed using IBM SPSS 21 statistical package. Spearman's Correlation coefficient was calculated between lowest pCO2 and duration of hypocarbia in the first 24 hours of birth and DTI variables. In this exploratory study a significant result was defined as having an effect on the same part of the brain on both the sides with a $p<0.05$.
Result: MRI of the brain was done on 81 babies. A pCO2 of < 4 kPa was found in 23/81 (28%) who had a median (range) gestational age (GA) at birth of 38 (23, 42) and median (range) postmenstrual age (PMA) at scan of 42 (36,45). Correlation coefficient (p-value) between lowest pCO2 and FA was: right posterior cerebral white matter = 0.532 (0.009); left posterior cerebral white matter = 0.510 (0.013); cerebellar vermis = 0.584 (0.004). These FA variables were not associated with GA at birth or PMA at scan. None of the other DTI results showed significant correlation with the lowest pCO2 on day 1. Duration of low pCO2 on day 1 did not show any significant correlation with DTI variables.
Conclusions: The extent of hypocarbia within 24 hours of birth was correlated with the FA of the cerebellar vermis and of the posterior white matter on both sides. We have not adjusted for multiple testing. However, the bilateral finding suggests that the absolute value of early hypocarbia is associated with reduced myelination at term equivalent in the posterior white matter. We speculate that this brain region is vulnerable to the vasoconstrictive effects of hypocarbia and that FA in this region may identify cases of brain injury due to hypocarbia.

GLOBAL AND REGIONAL BRAIN TISSUE VOLUME ALTERATIONS IN EXTREMELY PRETERM INFANTS AT TERM-EQUIVALENT AGE

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Background: It is known that preterm birth has negative consequences on brain development even in the absence of significant brain lesions. In this respect, several studies have demonstrated global and regional volumetric brain alterations in preterm samples using different approaches. However, studies investigating alterations on global and regional brain volumes in extremely preterm infants (EPT) (<27 weeks of gestational age) at term-equivalent age, and using voxel-based morphometry (VBM) are not currently available. This study aims (1) to investigate global and regional brain volume alterations between EPT infants at term and term-born controls by using automatic segmentation and VBM-DARTEL and (2) to examine the effect of immaturity (categorized into two gestational age groups, =25+6 and 26+0-26+6 weeks), mild white matter (WM) abnormalities qualitatively defined on MRI (signal abnormalities, reduction in WM volume, ventricular size, thinning of the corpus callosum, myelination), intraventricular haemorrhage (IVH) I-II on neonatal ultrasound, and patent ductus arteriosus (PDA) ligation.
Patients and methods: Forty-seven infants born <27 weeks of gestational age without focal brain lesions and 15 healthy born-term controls underwent conventional structural MRI at term. Automatic segmentation of 3D T1-weighted images using neonatal probabilistic atlases (grey matter, white matter -myelinated and unmyelinated-, deep grey matter -basal ganglia and thalamus-, cerebellum and brainstem) and VBM-DARTEL in SPM v8 was used. Analyses were adjusted for gestational age at birth and intracranial volume as appropriate. Family-wise error (FWE) correction ($p < 0.05$) was applied. To validate the automatic segmentations, the images of five randomly chosen subjects were manually segmented using ITK-SNAP. The Dice overlap coefficient between the automatic and manual segmentation showed a good agreement of at least 0.8 for all structures.
Results: Global brain volumes were reduced at a global level in EPT infants compared to controls with no significant difference in the cerebrospinal fluid volume. At regional level, EPT infants showed extensive areas of decreased grey matter volumes bilaterally distributed predominantly in the cortical temporal lobe, extending to the frontal, parietal and insular lobes. Smaller WM volumes were observed in the temporal lobes, adjacent to grey matter reductions. Decreased volumes were also seen in the deep grey matter, cerebellum and brainstem. Increased volumes in both cortical grey matter and WM were found predominantly in the occipital and parietal regions. In the preterm group immaturity, IVH grades I-II, and PDA ligation were related to globally and regionally decreased volumes. Mild WM abnormalities on MRI at TEA did not affect global or regional volumes.
Conclusions: Extremely preterm infants without focal brain lesion had significant global reductions on brain volumes comprising the grey matter, WM, deep grey matter, cerebellum and brainstem, compared to healthy term-born controls. At regional level the EPT infants exhibited regional decreased volumes primarily in the cortical grey matter. Degree of immaturity, low-grade IVH, and PDA ligation were associated with differential patterns of volume reduction. Interestingly, regional increased volumes of grey matter and WM in areas subserving visual function were found in EPT compared to controls, suggesting experience of long-term visual stimulation.

INCREASED RATIO TAURINE/TOTAL CREATINE ON BRAIN MAGNETIC RESONANCE SPECTROSCOPY CAN BE A PREDICTOR IN NEONATAL ENCEPHALOPATHY.

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Background: Brain energy metabolism following perinatal hypoxia-ischaemia has often been studied using phosphorous and long echo time (TE) proton magnetic resonance spectroscopy (MRS). Short TE proton (1H) MRS detects additional metabolites; there is limited reporting of short-TE data in infants with neonatal encephalopathy (NE). Aims To assess short-TE (30 ms) thalamic 1H MRS in the first month after birth in babies with NE and relate to MRI abnormality, early clinical predictors of outcome and long-term neurodevelopmental outcome.
Methods: Thirty-six infants with NE, gestational age 39.9 ± 1.5 weeks (range 35-42), underwent MRI with long- and short-TE MRS at age 8.2 ± 4.5 days between 2010-2011. Early clinical predictors of outcome were retrospectively collected from medical records; these included APGAR scores, lowest pH and base excess on blood gas, initial resuscitation and amplitude integrated electroencephalogram pattern within the first 6 hours and at 24 hours of life. T1 and T2-weighted MRI were graded as being normal or having mild or moderate-severe injury according to basal ganglia signal intensity; Barkovich score >2 was considered moderate-severe. Localised 1H magnetic resonance spectra (TE 30 ms) were taken from basal ganglia and analysed using LCModel, which fits exemplary metabolite spectra, rather than individual peaks, to estimate concentrations of metabolites. Neurodevelopmental outcome measures were collected between 9-25 months age. Moderate-severe disability was defined as cerebral palsy (CP) unable to walk or walking with aids, deafness, hearing impairment requiring aids, cortical blindness or cognitive score<=80 on Bayley Scales of Infant Development (BSID-III).
Results: Nine babies scored maximum for basal ganglia (Barkovich score 4) on MRI (moderate-severe injury) and 27 had a normal or mildly abnormal MRI for BGT. Twenty-eight babies underwent therapeutic hypothermia (64.8 ± 21.8 hours); all were re-warmed before scan. Twenty-eight babies were followed-up. In the moderate-severely abnormal MRI group, 2/7 babies died and 5/7 were had moderate-severe disability at follow-up. In the mildly abnormal MRI group (n=21) , only 1 baby was classified as having moderate-severe disability (hearing aids). We found statistically differences between the normal/mildly abnormal and moderate-severly abnormal MRI groups for base deficit, delayed onset of respiratory effort, Lactate/NAA, NAA+NAAG/Cr ratios, Cognitive BSID-III scores and motor impairment ($p<0.005$). Taurine/creatine+phosphocreatine (Cr), myo-Inositol/Cr and glutathione/Cr ratios were derived accurately (standard deviation <20%, individual metabolite fits) with LCModel. Taurine/Cr was significantly higher in the group with moderate-severely abnormal MRI. There was no interseverity statistical difference in myo-Inositol/Cr or glutathione/Cr. As expected lactate/NAA was also raised in infants with abnormal MRI, but did not correlate with taurine/Cr ($p>0.05$). Discussion Thalamic taurine was increased in babies with a moderate-severe BGT pattern of NE. Taurine is an inhibitory amino acid with a number of cytoprotective properties including GABA agonist activity and suppression of inflammation. Levels have been found to be significantly increased in CSF in babies with NE correlating with poor neurological outcome. A rodent stroke model has shown neuroprotective properties of both endogenous and exogenously-administered taurine. Raised taurine may suggest involvement of different neurotoxic pathways to lactate increases.

CHARACTERIZATION OF CEREBRAL WHITE MATTER DAMAGE IN NEONATAL ENCEPHALOPATHY USING 1H MR SPECTROSCOPY, DIFFUSION WEIGHTED MR IMAGING AND T2 RELAXOMETRY.

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Background: Thalamic proton (1H) magnetic resonance spectroscopy (MRS) is sensitive and specific biomarker of adverse neurological outcome in neonatal encephalopathy (NE). On conventional MR imaging NE can result in basal ganglia (BG) predominant, white matter (WM) predominant and global injury patterns. We hypothesized that WM MRS would provide a quantitative measure of white matter injury and correlate with imaging abnormalities in NE. Patients and
Methods: The local Ethics Committee approved this study. 37 term infants with NE underwent MRI (conventional T1 and T2, quantitative diffusion tensor imaging and T2 relaxometry) with two single voxel (1.5 x 1.5 x 1.5 cm3) point-resolved 1H MRS measurements, one in the thalamus and one in the posterior white matter at a mean postnatal age of 7 (range 1-20 days). Metabolite ratios were quantified using AMARES algorithm. BG and WM injury on MRI was classified using the Barkovich scoring system and the MRS data compared. Region of interest were positioned in the posterior white matter to measure T2, mean diffusivity (MD) and fractional anisotropy (FA) values.
Result: BG predominant and global patterns were associated with increased Lac/NAA, Lac/Cho and Lac/Cr and a decrease in Naa/Cr compared to babies with normal scans or with watershed injury. With BG predominant injury WM MRS ratios were similar to those with normal MRI. Watershed and global injury (ie white matter injury) resulted in a significant increase in Cho/Cr in the posterior white matter voxel ($p<0.05$). In addition global injury resulted in significant increase in all lactate-containing ratios ($p<0.05$). Cho/Cr and tNAA/Cho correlated significantly with T2 ($r = -0.69$; $p<0.01$) ($r = -0.45$; $p<0.05$) and MD values ($r= 0.46$; $p<0.01$) ($r= 0.39$; $p<0.05$). T2 values correlated significantly with MD ($r = 0.42$; $p< 0.05$) and FA values ($r = -0.64$; $p< 0.05$). There was no significant difference in T2 values between the different groups. MD values were significantly higher in Normal or BG involvement groups than in global injury or watershed involvement groups ($p<0.05$).
Conclusions: Combined thalamic and white matter proton MRS demonstrates different changes in peak metabolite ratios according to the predominant pattern of injury. Watershed predominant injury led to increased Cho/Cr, suggesting astrogliosis, but did not increase lactate ratios whereas global severe injury increased both Cho/Cr and Lac ratios in the WM.

MAGNETIC RESONANCE IMAGING IN NEWBORN INFANTS AFTER THERAPEUTIC HYPOTHERMIA FOR NEONATAL ENCEPHALOPATHY: ALL IS NOT AS IT SEEMS

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Background: Therapeutic hypothermia (TH) for infants with hypoxic ischaemic encephalopathy (HIE) is now a standard of care. There is a coordinated, regional approach to the management of these infants across the East of England encompassing early recognition and transfer for TH to one of three tertiary-level neonatal intensive care units (NICUs) and timely magnetic resonance imaging (MRI). The aim of this study was to investigate the implementation of MRI guidelines across the region.
Methods: We studied babies who underwent TH for suspected HIE in our three regional NICUs in the 17-month period January 2011 to May 2012 inclusive. We examined: (1) whether MRI was undertaken, (2) timing of MRI scan, (3) MRI findings, and proportion with abnormalities on MRI consistent with the initial clinical diagnosis of HIE.
Results: Data was available for 110 of 111 eligible babies. 95/110 (86%) completed 72 hours of TH. MRI was performed in 88 out of 110 (80%) infants. 60 (55%) infants had MRI between day 7-14 of life as per regional guidelines. 22 (20%) infants did not undergo MRI (withdrawal of intensive care, n=7; TH discontinued early as infant did not fit cooling criteria, n=4; infant repatriated to local unit before MRI undertaken, n=9; transferred for neurosurgical intervention, n=1; unknown, n=1). 23 (21%) infants underwent MRI in the first week of life. Reasons for early imaging included informing decision to withdraw intensive care (n=7) and clinical suspicion of pathology other than HIE (n=3). 5 infants had MRI after day 14. Of 88 infants imaged, 31 (35%) had normal scans. 39 (44%) infants had changes consistent with the clinical diagnosis of HIE. 29 (33%) infants had unexpected or incidental findings on their MRI either in addition to changes consistent with their clinical diagnosis of HIE (n=11, 13%) or as the sole finding (n=18, 20%). Unexpected findings included arterial infarction, n=4; features consistent with venous sinus thrombosis, n=3; multiple focal lesions suggestive of another pathology, n=2; and congenital abnormalities, n=4 (1 infant had features consistent with a diagnosis of lissencephaly, 2 infants had abnormalities of cerebellar vermis and one infant had unusual appearances warranting genetics review and investigations). In 10 infants these additional findings prompted consideration of further investigations or influenced discussions regarding prognosis.
Conclusions: The majority of infants referred for TH underwent MR imaging at the recommended time. Withdrawal of care was one of the primary reasons for infants either not undergoing an MRI or having an early MRI. In our series, unexpected MRI findings were present in nearly a third of infants referred for TH and led to changes in clinical management in a significant number of these infants. Whilst a timely diagnosis of HIE ensures early commencement of TH, it is vital not to overlook other potential causes of neonatal encephalopathy in these infants. It may also be prudent to ensure MRI is undertaken in all infants referred for TH prior to transfer back to the referring unit to ensure alternative diagnoses are not missed

CORRELATIONS BETWEEN A MARKER OF PERINATAL ILLNESS SEVERITY (CRIB-2 SCORE) AND DIFFUSION WEIGHTED MRI VARIABLES IN PRETERM BABIES: A PILOT STUDY

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Introduction: An understanding of when brain injury develops among extremely preterm neonates will facilitate the development of better treatments. We postulate that selected imaging variables indicate the timing of brain injury. Since brain injury is likely to occur when babies are sick we initially explored whether a marker of illness severity at a particular age is associated with imaging findings. Aim: To conduct a preliminary assessment of the hypothesis that a marker of perinatal illness severity (CRIB -2; clinical risk index for babies - version 2) is associated with findings on diffusion tensor imaging (DTI) derived from magnetic resonance imaging (MRI) performed close to term.
Methods: Parents of newborn preterm babies were approached about participation in the LAMB Study (Liverpool Archive of MRI in Babies (Neonates) between December 2011 and January 2013. Basic demographic details and the components of the CRIB-2 score were collected from the electronic patient data management system. Brain MRI was performed on a 3 Tesla Philips Achieva XL MRI scanner at near term age. High resolution DTI was performed using 32 gradient directions, and fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were measured in 9 regions of the brain (with bilateral or anteroposterior replicates as appropriate) giving 32 measurements in all. Spearman's Correlation coefficient was calculated between CRIB-2 score and FA & ADC (IBM SPSS 21). In this preliminary study a significant result was defined as having an effect on same part of the brain on both the sides with a $p<0.05$.
Result: A total of 25 babies born at less than 32 weeks or less were recruited into the LAMB study. Brain MRI was obtained in 24 babies who had a median (range) gestational age at birth of 27 weeks (23,32) a median (range) CRIB-2 score of 9 (2, 15) and a median (range) corrected gestational age at imaging of 42 (36, 45). Correlation coefficients (p-value) between CRIB-2 and ADC were as follows. Globus pallidus: right -0.604 (0.002); left 0.439 (0.032). Anterior white matter: right -0.456 (0.025); left -0.551 (0.005). Posterior white matter: right -0.502 (0.012);left -0.443 (0.03). Correlation coefficient between CRIB-2 and cerebellar vermis FA: 0.611 (0.002, 23). Globus pallidus and posterior white matter ADC were correlated with gestational age at birth, but CRIB-2 was the only significant association on ANOVA. None of the other DTI variables correlated with the CRIB-2 score.
Conclusions: These preliminary findings suggest that some DTI variables reflect poor condition at birth. Although we have not adjusted for multiple analyses the findings are consistent between sides in this sample. Acute changes in ADC often reflect infarction and resolve in the days after an insult. These data were obtained several months after the birth of these babies and may reflect sequelae, such as gliosis, arising in the days before and after birth at extreme prematurity. We speculate that DTI of particular brain areas specifically reflects perinatal causes of brain injury associated with preterm birth. These surrogate outcomes may be valuable ways to assess strategies designed to prevent perinatal brain injury.

DESIGNING STIMULATION PROTOCOLS TO MAXIMIZE SENSITIVITY IN NEONATAL FMRI

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Introduction/Background: In neonatal intensive care units, MRI is increasingly used to assess structural changes in the brains of infants with suspected injury. However, the outcome of relevance to everyday life is not the degree of structural injury, but the degree of cognitive or behavioral impairment. Even in adults that acquire brain injury, it is hard to predict from structural changes what cognitive deficits will result, and in infants the tremendous plasticity available during development make this relationship even more imprecise. As a result, there is increasing interest in supplementing structural imaging with a more direct measure of neurocognitive function from functional MRI (fMRI). However, there are important methodological issues that remain to be addressed. fMRI measures the brain's response to stimulation (e.g., sounds or flashes). fMRI does not measure neural activity directly, but the hemodynamic response evoked by neural activity. The timing of the response, relative to the neural activity, changes dramatically during early human development (Arichi et al, 2012). While in adults, brief stimulation is followed a few seconds later by an almost entirely positive fMRI response, in term infants there is a positive fMRI response followed by a negative response of approximately equal size. Patients and
Methods: The current study models the sensitivity of fMRI to different stimulation protocols in adults and preterm/term infants. We quantitatively compare signal-to-noise ratios by characterizing the spectra of noise in 3T fMRI data from five healthy adults and five neonates of term equivalent age.
Results: We find that protocols have quite different sensitivities and interact with age, such that slow stimulation cycles (common in adult fMRI experimental designs) yield reduced power in neonates. Furthermore, in the existing literature, analyses have assumed the neonatal hemodynamic response to be the same as the adult one. To assess the impact of this, we calculated the statistical power when the actual and modeled responses were mismatched. Our simulations show that substantial signal loss is to be expected when long blocks and a mismatching hemodynamic model is used (e.g., 90% loss for 45s on/off blocks).
Conclusion: Selection of age-specific stimulation protocols and analysis methods is critical for successful fMRI in neonates. Reference Arichi, T. et al. (2012).Development of BOLD signal Hemodynamic Responses in the Human Brain. NeuroImage 63(2):663-73.

IS MRI IN THE FIRST DAYS OF LIFE AN ACCURATE TOOL TO IDENTIFY HYPOXIC-ISCHEMIC LESIONS? CORRELATION BETWEEN EARLY AND LATE MRI.

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Background: MRI performed in the second week of life predicts outcome in infants with HIE. However, especially in the era of therapeutic hypothermia, there is a need for an early and accurate identification of infants who will have very severe impairment if they survive. As reported in the recent cooling trails, two-thirds of deaths followed treatment withdrawal. If decisions are delayed, there is a risk that the neonate will survive with very severe long-term disabilities. End of life decisions are relying more and more on the results of MRI performed in the first days of life. In this scenario, it is uncertain whether early MRI findings reflect brain damage seen in later MRI in newborns with HIE treated with hypothermia. Aim. To evaluate the correlation between MR images performed in the first 6 days of life and the ones obtained in the second week in infants with hypoxic-ischemic encephalopathy treated with hypothermia. Setting. Level III Neonatal Intensive Care Unit in Barcelona, Spain. Design. Prospective observational study. Methods. All consecutive term infants with HIE meeting the criteria for therapeutic hypothermia were included. Two sequential MRI studies with conventional T1/T2 sequences were planned: an 'early' study, including DWI, in the first 7 days of life and a 'late' study during the second week of life. Two neuroradiologists who were blinded to the clinical condition of the infants reviewed MRI and DWI scans using a scoring system designed by Rutherford et al.
Results: Fifteen neonates with moderate and 25 with severe HIE were included. Forty-eight MRI scans were obtained in the 40 newborns (29 early and 19 late scans). Sixteen infants died (15 with severe encephalopathy) at a median age of 76 hours (range 30-144 hours). Six infants died before a scan was performed and five were too instable to perform an early MR. Finally, fifteen infants underwent two sequential MR scans, 7 with moderate HIE and 8 with severe HIE. These infants were not significantly different to the rest of the cohort in terms of perinatal factors. The average scanning age in hours was 94.5 ± 28.9 and 288.9 ± 60.9 for the early and late scans, respectively. Findings on early conventional MR scans highly correlated with those on the late scans (rs 0.940; $p < .001$). DWI scores on early scans correlated with both early (rs=0.869; $p< .001$) and late conventional MRI scores (rs= 0.866; $p < .001$).
Conclusions: In infants with HIE treated with hypothermia, MRI performed in the first week of life can accurately depict hypoxic-ischemic lesions seen in later scans. MRI may provide valuable prognostic information in the first days of life for clinicians to orientate care and give information to parents in the hypothermia era.

ASSOCIATION OF HYPOTHALAMIC HAMARTOMAS AND CORTICAL DYSPLASIAS IN CHILDREN: REVIEW OF 14 CASES.

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Objectives: Hypothalamic hamartomas (HH) are developmental malformations associated with precocious puberty (PP) and gelastic seizures (GS). Role of HH in GS induction was approved in the last decade by ictal SPECT studies showing HH hyperperfusion and by stereotactic depth recording of seizures onset within hamartoma. Surgical treatment of HH for intractable epilepsy is increasingly advocated in present time. One of the main factors determining of surgical success is the absence of coexisting cortical dysplasias or other epileptogenic changes. In the literature, controversy exist regarding the frequency and epileptic significance of malformations of cortical development associated with HH. This study aim to describe the high resolution (HR) MRI findings in children with HH.
Methods: A total 14 children with neuroimaging and clinical (GS and PP) evidence of HH syndrome were retrospectively reviewed. All patients were followed by HR MRI at age from 2 to 15 years. Studies were performed using either 1.5 T or a 3.0 T MRI scanners. Images were analyzed independently by three pediatric neuroradiologists and findings were agreed by consensus. The MR protocol consisted of sagittal view FSE (slice thickness 1.2 mm and interslice gap 0.1 mm); axial view FSE (st-1.5 mm; g-0.1 mm); sagittal view conventional SE (st-2 mm; g-0.5); axial and coronal view FSPGR (contiguous section 0.5 mm). Dedicated coronal view images targeted to the hippocampus and anterior temporal lobe were acquired perpendicular to the long axis of the hippocampus and included the FSE (contiguous 2 mm section) and FLAIR (contiguous 3 mm section). Contrast medium was not administrated as part of imaging protocol in our center, but 8 contrast-enhanced previously obtained images were reviewed. RESULTS: Images of the all 14 patients were included in this analysis. The size of HH ranged from 14 to 55 mm in maximum diameter. For the 8 patients with contrast enhancement no enhancement of HH were observed. Malformations of cortical development were revealed in 6 cases (42%). In two cases there were small nodular subependimal neuronal heterotopias in the walls of lateral ventricles; in one case it was regional polymicrogyria of left fronto-parietal lobe; and subtle focal cortical dysplasias were identified in the rest 3 cases.
Conclusions: Despite of conventional opinion about rare associating between HH and cortical dysplasias we revealed it in almost half of our patients group. Standard MR protocols may be insufficient to evaluate of cortical malformation (especially small size ones) in children with HH. HR MRI protocol may depict greater detail providing important information in children with HH. Our dates proposed the HH as a part of dyplastic continuum of the brain and determined necessity of HR MRI in such patients.

STRUCTURAL MAGNETIC RESONANCE IMAGING IN THE DIAGNOSIS OF EPILEPSY IN CHILDREN.

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Introduction: Magnetic resonance imaging is a standard technique in the diagnostics of epilepsy. The frequency of children epilepsy is 0.7-1%. Often seizures develop in early childhood, and for further treatment it's important to determine the cause of seizures. Patients and
Methods: In the period from 2008 to 2012 the structural MRI was performed for 205 children (119 boys, 86 girls) enrolled in the Institute with a first seizure. MRI examination was done on high field MRI scanner (Achieva 3T, 8ch HeadSense coil) in the first 24 hours after a seizure event, with average patient age around 1.2 years. The MRI study protocol included ?2TSE, FLAIR, ?2*FFE, EPI DT, 3D PC ?R?, pre- and post-contrast 3D ?1TFE.
Results: Structural MRI didn't find brain lesions for 49 from 205 children (23.9%), for them cause of seizures were dehydration or fever. According with MRI results for 156 (76.1%) children causes seizures were: ?. Malformations due to abnormal neuronal and glial proliferation or apoptosis -39; II. Malformations due to abnormal neuronal migration - 21; III. Malformations due to abnormal cortical organization- 14; IV. Malformations of cortical development, not otherwise classified - 17; V. Secondary posthypoxic sclerosis and atrophy - 25 VI. Vascular malformations and hemorrhagic disease of newborn - 34 VII. The effects of intrauterine infection - 6
Conclusion: The pathologies of the children brain development as well as cortical syndromes can be established by MRI. Comparison of MRI and clinical data accurately determine the cause of epilepsy in children after the first seizures, and allow to select the most appropriate treatment.

1H MRS EVALUATION OF THE STEM CELLS THERAPY EFFECTS ON NEURONAL INTEGRITY IN BRAIN OF CHILDREN WITH LONG -TERM EFFECTS OF SEVERE TRAUMATIC BRAIN INJURY.

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Background: Marker of neuronal integrity N-acetylaspartate (NAA) was measured in different loci of brain in children with long -term effects of severe traumatic brain injury (TBI) before stem cells therapy and after it using single voxel 1H MRS.
Materials and Methods: Patients (in age of 8 - 17 years) with severe neurological deficit (Glasgow Coma Scale score 3) were treated in 6 - 23 months after severe TBI with injections of the cord/placental blood cells suspension. The cells (in the dose of 5×106 per 1 kilo of weight) were injected twice with time interval of 14 days. Brain metabolites were measured at the 45th and 15th day before the treatment and up to the 15th, 45th, and 150th day after the end of therapy. Philips Achieva 3T scanner was used. Localisation of spectroscopic voxel (the volume was 3cm3) was achieved by PRESS (echo time TE = 35 ms, repetition time TR = 2000 ms). The spectra were obtained in normal appearing white matter of temporal and frontal lobes, as well as in the frontal cortex and in hippocampus.
Results: According to the data of statistical analysis of signal intensities of NAA, glutamine+glutamate, choline containing compounds, creatine+creatine phosphate, mioinositol normalised to unsuppressed water signal intensity, the levels of above mentioned metabolites were stable before the treatment. After stem cells therapy NAA increased reliably at the 45th day and remained at the same level up to the 150th day in cortex and in white matter of temporal lobe.
Conclusion:NAA increase reflects an increase of neuronal integrity in temporal lobe cause by stem cells therapy. This effect is probably due to neurotropic factors penetrated through blood brain barrier in contrast to the cells. The raise of neuronal integrity coincided with positive dynamic in improvement of cognitive and motor functions.

1H MRS IN THALAMUS OF CHILDREN IN VEGETATIVE STATE AFTER TRAUMATIC BRAIN INJURY.

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Background: The aim of this study was to identify possibilities and diagnostic value of 1H MRS in thalamus for outcome prognosis in children being in vegetative state after traumatic brain injury (TBI). Materials and methods The study was performed on magnetic resonance scanner Phillips Achieva 3?. Bilateral 1H MRS of uninjured thalami was made in 15 children being in vegetative state (group I) after TBI. The group of 7 healthy age matched children was studied as the controls (group II). Spectroscopic voxel (volume of 3 cm3) was localised by PRESS (echo time TE = 35 ms, repetition time TR = 2000 ms). The patients of group I were classified into two subgroups according to neurological outcome: subgroup Ia (n = 7) - the patients came back to consciousness, subgroup 1b (n = 8) - the patients remained in a vegetative state. Statistical analysis of signal intensities of N-acetylaspartate (NAA), glutamine+glutamate, choline containing compounds, mioinositol normalised to creatine+creatine phosphate signal intensity was performed. Intergroup differences were estimated with Mann-Witney criterion.
Results: 1H MRS revealed metabolic disorders in thalami of the patients. NAA in group of patients was statistically significantly lower (? <0,001), than in the control group. NAA is known as neuronal marker and reflects the level of neuronal integrity. For subgroup I? NAA/Cr = 1.80 ± 0.26, for subgroup Ib NAA/Cr =1.17 ± 0.25, for the control group NAA/Cr = 2.67 ± 0.26. In subgroup Ia NAA /Cr was statistically significantly higher than in the subgroup Ib (? <0.002), however it was lower than in the control group (? <0,001). MRI revealed brain stem injuries in 5 (62.5%) patients of subgroup Ia and in 4 (57.1%) patients of subgroup Ib. No correlation (correlation coefficient R = 0.7) between brain stem injuries and neurological outcome was found.
Conclusion:1H MRS was found to be helpful in neuronal damage and axonal injury evaluation in the patients being in vegetative state. N??/Cr is the reliable criterion of thalamus state.

MRI DIAGNOSTICS OF SECONDARY ISCHEMIC CHANGES IN CHILDREN BRAIN INJURIES.

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Background: The most common type of traumatic brain injury (40% of the total) is the brain matter contusion. MRI diagnostics allows to differentiate primary and secondary changes for the brain injury and to plan appropriate treatment by identifying areas of edema and secondary ischemia. Patients and
Methods: MRI was performed for 132 children aged from one month to 17 years in the first 24 hours after TBI (Achieva 3T, 8ch SenseHead Coil). The study protocol included: ?2TSE, FLAIR, ?2*FFE, EPI DTI, 3D PC MRA, pre- and postcontrast 3D TFE.
Results: From total 132 cases of children brain injuries around 48.5% were corresponded to mild injury, 23.5% - average and 28% - severe. For mild and average brain contusions the proposed study protocol can reliably identify areas of edema and secondary ischemia of brain matter. For severe brain injuries due to the presence of hemorrhagic component and magnetic susceptibility artifacts it's appropriate to use 3D high-resolution techniques with Gd- contrast enhancement.
Conclusion: The detection of secondary changes in the brain matter significantly reduces the risk of brain matter damage expansion. The use of contrast agents increases the sensitivity of MRI study in cases of severe injury.

GADODIAMIDE APPLICATION IN MAGNETIC RESONANCE IMAGING IN CHILDREN WITH ACUTE VASCULAR PATHOLOGY OF THE BRAIN.

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Background: Incidence of stroke ranges from 2 to 13 cases per 100,000 children each year. Ischemic strokes are registered slightly more often than hemorrhagic ones. The death rate for this pathology reaches 36%. We evaluated the diagnostic value of contrast enhanced MRI for diagnosis of acute vascular pathology of the brain in children.
Patients and **Methods:**We diagnosed 30 children aged from 1 month to 17 years, who admitted to our institute with suspected acute vascular pathology of the brain in 2010-2011. All studies were performed on Philips Achieva 3T MR scanner with a use of standard protocols, which were supplemented with contrast enhanced angiography and T1-weighted images. Gadodiamide was administered intravenously in a dosage of 0.2 ml\kg. All studies were performed as soon as possible from the moment of admission.
Results: We have diagnosed a wide range of vascular abnormalities in examined patients. Ischemic strokes were diagnosed in 4 patients (traumatic occlusions), arterial aneurisms - in 7, arterio-venous malformations - in 5, venous angiomas - in 4 and traumatic sinus thrombosis - in 7 children. In three children we diagnosed a relatively rare pathology - Moyamoya Disease. Only two of 4 arterial occlusions, one of 4 venous angiomas, two of 7 arterial aneurisms and three sinus thromboses were clearly visible at unenhanced images.
Conclusion:MRI with intravenous contrast enhancement allows to diagnose with high accuracy a wide range of acute vascular pathology of the brain in children. The use of this technique in many cases eliminates the invasive method of diagnosis, which is not available in all children hospitals, and accompanied by a significant radiation exposures - direct angiography.

RED BLOOD TRANSFUSION IS A RISK FACTOR IN DEVELOPING NECROTIZING ENTEROCOLITIS IN VERY LOW BIRTH WEIGHT INFANTS IN A INTENSIVE CARE UNIT IN SOUTH OF BRAZIL

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Background: Necrotizing enterocolitis (NEC) is a multifactorial disease that results from the interaction between the loss of integrity of the intestinal mucosa and the host response to this damage. This is the most prevalent emergency of the gastrointestinal tract in the neonatal period. Its incidence is highly variable, affecting 2% to 22% of newborns with very low birth weight (< 1,500 g) and with high mortality (10-44%). Several factors are associated with the development of NEC, including early initiation of enteral feeding, duration of parenteral nutrition, use of postnatal corticosteroids, and the presence of umbilical catheter. It is also known that there is a relationship with red cells transfusions. This study evaluates the prevalence of NEC in the intensive care unit and correlates it with factors associated with increasing the risk of developing the disease. Patients and
Methods: All the very low birth weight infants (VLBW) admitted to the neonatal intensive care unit of the ULBRA / SSMD Hospital in the period of January to December 2012 were included in the study. We evaluated the correlation between NEC and the duration of total parenteral nutrition (TPN), birth weight, enteral feedings, asphyxia and blood transfusion. Data analysis was performed with SPSS 18.0, using the Student t test, Mann-Whitney, chi-square test, McNemar, with a significance level of 5%. Cases that met the criteria of Bell's classification stage 1 were considered NEC. The ethics committee of the institution approved the study.
Result: 62 VLBW were admitted into the unit during the study period. Of these, 27.4% developed NEC, 52.9% with birth weight less than 1000g and 47.1% of the group of birth weight greater than 1000g. There was an increased risk for NEC in premature infants with longer TPN (RR = 1.05, 95% CI: 1.02 to 1.08, p = 0.02) and in the group with preterm birth weight < 1000g (RR = 2.36, 95% CI: 1.07 to 5.20; p= 0, 033). There was an increased risk for NEC in those infants submitted to blood transfusion (RR = 2.25, 95% CI: 0.9 -5.6, p = 0.083).
Conclusions: VLBW submitted to blood transfusion, longer duration of TPN and birth weight <1000g have a higher risk in developing NEC.

ASSOCIATION OF RED BLOOD CELL TRANSFUSIONS AND NECROTIZING ENTEROCOLITIS IN PRETERM INFANTS

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Introduction: Necrotizing enterocolitis (NEC) is one of the most common surgical diseases of preterm infants, with significant short- and long-term morbidity and mortality. Although the etiology remains unclear, recent studies suggested an association between red blood cell transfusion (RBCT) and NEC in premature neonates. Aim: To characterize NEC in infants admitted to a neonatal intensive care and evaluate the association between RBCT and NEC.
Methods: Retrospective design, with data obtained from a computerized database and review of the medical records. The study population included infants admitted to the neonatal intensive care unit at Maternidade Bissaya Barreto (MBB) between 1995 and 2012 (18 years), with diagnosis of NEC. Infants with congenital anomalies of the digestive tract and NEC grade I of Bell's criteria were excluded. NEC after transfusion was defined as NEC occurring in the 48 hours after RBCT.
Result: Of the 4937 infants admitted between 1995 and 2012, 31 met the inclusion criteria. These 31 infants had a median weight of 885g (470-2850 g) and median gestational age of 27 weeks (24-34 weeks). The median age of enteral feeding beginning was 3 days (1-8 days) and 72% started with breast milk. At diagnosis 87% had enteral feeding, 55% with breast milk, 15% with preterm formula and 30% with a combination of breast and formula milk. 13 infants had patent ductus arteriosus at the time of diagnosis. The median age of diagnosis was 11 days (3-40days) and 29,7 weeks of post-menstrual age (25,1S- 34,6S). 52% of these infants had advanced NEC (grade III of Bells' criteria). 17 infants (55%) underwent surgical intervention. There were 19 deaths (61%) and almost two thirds of NEC deaths occurred <7 days from diagnosis (median 3 days). In this study 8 infants (26% - Group 1) didn´t receive any RBCT preceding NEC diagnosis, whereas 13 (42% - Group 2) received an RBCT within 48H of NEC diagnosis and 10 (32% - Group 3) more than 48H before diagnosis. In group 1 the median age of diagnosis was 5,5 days, 75% of infants had advanced NEC, 6/8 underwent surgery and 2/8 died. In group 2 the median age of diagnosis was 11 days, 46% had advanced NEC, 7/13 underwent surgery and 8/13 died. In group 3 the median age of diagnosis was 15,5 days, 40% had advanced NEC, 4/10 underwent surgery and 9/10 died. Discussion: This study confirms the high mortality in infants with NEC. In our study, 74% had a RBCT and in 42% that occurred within 48h of NEC diagnosis. These results suggest, as already discussed in the literature, that anemia and/or RBCT may increase the risk of NEC in preterm infants. We need more prospective studies, with larger numbers, in order to evaluate the potential influence of transfusions on the pathogenesis of NEC.

RED BLOOD CELL TRANSFUSION AND NECROTIZING ENTEROCOLITIS IN VLBW: WE DO NOT FIND ANY ASSOCIATION

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Introduction: Necrotizing enterocolitis (NEC) is an important cause of morbidity and mortality in premature infants. The mean prevalence of NEC is about 7% among infants with a birth weihgt < 1500g (VLBW) and the rate mortality is estimated between 20-30% especially in infants requiring surgery. The etiology of NEC is multifactorial; several studies have suggested a possible role for red blood cell (RBC) transfusion in the pathogenesis of NEC when administered up to 48 hours before the onset of symptoms. Aim of our study was to evaluated the association between RBC transfusion administered up to 48 hours before disease and NEC in our NICU.
Patients and Methods: We reviewed retrospectively the medical charts of VLBW admitted to our NICU between 1/1/2007 and 31/12/2012. For each patient birth weight (BW), gestational age at birth (GA), day of life at onset of symptoms, each RBC transfusion, NEC stage = 2 according to modified Bell's criteria, the need for surgical procedure and NEC related mortality were recorded. Outborn patients, patients with genetic disease and newborns who died within the first 24 hours of life were excluded.
Results: In the study period 765 newborn were admitted to our NICU. 142 patients were excluded because they did not meet the inclusion criteria; statistical analysis was conducted on 623 very low birth weight. NEC was diagnosed in 13 patients (2%) with a mean BW of 1028g (± 325 g), mean GA of 28 (± 2.8 weeks); mean age at onset was 33 (± 11) days of life. Surgery was performed in 5 patients (39%) while 8 patients (61%) were medically treated. None of the patients with NEC received RBC transfusion up to 48 hours before the onset of the disease.
Conclusion: Our findings differ from those reported in various previous studies concerning the association between RBC transfusion and NEC. We did not record NEC related to previous RBC transfusion. We speculate that this result may be related to RBC products. During the study period we employ fresh (< 5 days), leuco-depleted RBC units. These procedures reduce the exposure to biological mediators accumulated during storage and the risk of sensitization to donor human leukocyte antigens due to repeated exposure to tha same donor. These practices could reduce the activation of immune system related to transfusion and consequently the incidence of NEC transfusion related. Prospective studies are necessary to understand the possible association between RBC transfusion and NEC.

CONVENTIONAL LABORATORY PARAMETERS IN THE EARLY PREDICTION OF NEED FOR SURGERY IN NECROTIZING ENTEROCOLITIS.

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Background: Necrotizing enterocolitis (NEC) is a serious gastrointestinal emergency that predominantly affects preterm infants. Due to a lack of prognostic tools, prediction of the course of the disease is a great challenge for physicians. The aim of this study was to assess the predictive abilities of early conventional laboratory parameters for the need for surgery in NEC.
Methods: Retrospective analysis (January 1990-January 2010) of all neonates diagnosed with NEC (Bell stage =2) admitted to our neonatal intensive care unit (NICU). We retrieved laboratory values that were performed as routine patient care, including CRP, platelet count, leukocyte count, pH, and glucose from patient files at baseline (first blood sample upon diagnosis of NEC), 12h and 24h after initial diagnosis. NEC requiring surgery was considered as surgical NEC; NEC which was treated conservatively was considered as medical NEC. Study endpoint was defined as gastrointestinal surgery during the first NEC episode. We related the course of the laboratory values to the need for gastrointestinal surgery using multilevel statistics, which takes missing values into account. Next, we categorized those laboratory parameters that had shown significant differences between surgical NEC versus medical NEC into 3 or 4 classes (for example pH<7.25; pH 7.25-7.30; pH>7.30), and computed odds ratios (OR) for each of these classes regarding the risk of gastro-intestinal surgery.
Results: Of the 168 neonates included in the study, mean gestational age was 31.6 weeks (range: 25.0-42.6) and mean birth-weight 1503 grams (530-4435). Mean postnatal age at NEC onset was 12 days (1-66). Surgery was performed in 78 patients (46%). Mean interval between diagnosis and surgery was two days (range 0-19). Missing laboratory values occurred, resulting in a mean of 92 (66-135) laboratory results being available for each parameter at each of the 3 time-points. At NEC onset, we found significant ORs for pH 7.25-7.3 (OR 4.9 [95% confidence interval: 1.5-16.1]), pH<7.25 (OR 3.9 [1.2-12.5]), plasma glucose >6 mmol/l (OR 2.7 [1.1-7.1]), and leukocytes <5 x109/ml (OR 3.0 [1.1-8.0]). At 12h after diagnosis, we found significant ORs for pH 7.25-7.3 (OR 3.9 [1.2-13.1]), pH<7.25 (OR 8.2 [2.2-29.9]), plasma glucose >6 mmol/l (OR 3.1 [1.1-8.9]), leukocytes <5 x109/l (OR 3.8 [1.1-12.5]), platelets 50-100 x109/l (OR 3.3 [0.9-12.2]), and platelets <50 (OR 4.3 [1.1-18.3]). At 24h after diagnosis, we found significant ORs for pH 7.25-7.3 (OR 5.0 [1.1-24.7]), pH<7.25 (OR 3.4 [1.0-11.9]), glucose >6 mmol/l (OR 4.2 [1.7-13.9]), and CRP>210 mg/l (OR 13.5 [1.3-138.6]).
Conclusion: Several conventional and readily available laboratory parameters might aid in the early prediction of progression of NEC to need for surgery. At NEC onset, acidosis, hyperglycemia and leucopenia may help to predict progressive disease. Thrombocytopenia only has predictive value for surgical NEC at 12 hours after diagnosis. Elevated CRP does not have predictive value for surgical NEC until 24 hours after diagnosis.

LOW CEREBRAL AND SPLANCHNIC TISSUE OXYGEN SATURATION IN PRETERM INFANTS WITH (SUSPECTED) NECROTIZING ENTEROCOLITIS PREDICT SEVERE DISEASE PROGRESSION

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Introduction/Background: Necrotizing enterocolitis (NEC) is a devastating disease and a major cause of mortality and morbidity in preterm infants. Early diagnosis and prediction of disease progression in NEC is challenging. We therefore aimed to relate the levels of cerebral, liver, and infra-umbilical oxygen saturation in preterm infants with (suspected) NEC to development of Bell stage III.
Patients and Methods: We included preterm infants between October 2010 and November 2012 that were suspected of developing NEC or that were recently diagnosed with NEC. Cerebral (rcSO2), liver (rlivSO2), and infra-umbilical (rintSO2) tissue oxygen saturation monitoring by means of near-infrared spectroscopy (NIRS) was started as soon as NEC was suspected or confirmed. Classifying preterm infants into the modified Bell stages was independently done after completion of the study by blinded experts, based on the most severe symptoms and radiographic signs observed during the disease period.
Results: Of the 38 infants enrolled, four were excluded (three infants had an incomplete dataset and one infant was diagnosed with a spontaneous intestinal perforation). Twenty three infants were diagnosed with Bell stage I (n=13) or II (n=10); median gestational age (GA) 28.7 wks, range 25.7-35.9. Eleven infants eventually developed Bell stage III; median GA 27.4 wks, range 25.0-34.0. Postnatal age was not significantly different between infants with Bell stage I-II and stage III. RcSO2, rlivSO2, and rintSO2 were significantly lower during the first 24 hours after inclusion in infants that developed Bell stage III compared to infants that developed Bell stage I-II (median rcSO2 55.0% vs. 69.8%, p=0.002, median rlivSO2 25.6% vs. 59.5%, p=0.035, median rintSO2 32.5% vs. 49.3%, p=0.038).
Conclusions: Low rcSO2, rlivSO2, and rintSO2 levels during the first 24 hours after the onset of NEC might help the clinician in identifying those infants that will go on to develop a severe disease progression of NEC, defined as Bell stage III.

NEONATAL PNEUMOPERITONEUM: COMPARISON OF THE SUPINE ABDOMINAL WITH THE SUPINE CROSS TABLE RADIOGRAPH IN DIAGNOSTIC ACCURACY

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Background: Intestinal perforation is a potentially fatal and not uncommon complication of neonatal gastrointestinal disorders, in particular necrotizing enterocolitis (NEC). Detection of free intra-abdominal gas on abdominal xray (AXR) remains the only, universally agreed, absolute radiological indication for surgery. There have been, however, relatively few studies that have assessed the accuracy of abdominal x-rays in diagnosis of intestinal perforation associated with NEC. In particular, no study in the literature has specifically compared the accuracy of the supine cross table lateral and horizontal radiograph with the standard supine antero-posterior (AP) AXR in the detection of free intra-abdominal gas in neonates . Aims We aimed to compare the accuracy of these different abdominal radiographic views (AP and cross table) in the diagnosis of neonatal intestinal perforation.
Methods: Retrospective review of all neonates (gestational age, M/F, birth weight) admitted to a tertiary neonatal intensive care and surgical unit (NICU) who received an AP and supine cross table horizontal or lateral AXR for possible intestinal perforation of any cause over a period of 2 years. The radiographs were anonymised and randomly mixed. Two paediatric radiologists and 2 neonatologists separately co-reviewed the x rays in particular to determine presence of free gas consistent with intestinal perforation. Radiological criteria evaluated as predictors of perforation included signs such as Cupola (football), Rigler's, continuous diaphragm, falciform ligament, outline of umbilical artery, urachus, unusual/ triangular pockets of air (in Morrison's pouch), gasless abdomen and on cross table views, the presence of air over liver and between bowel loops .
Results: 140 (70 AP and 70 corresponding lateral)films were reviewed. There were 7 perforations on the 70 lateral films identified. Perforations were noted on the corresponding AP in all films by the neonatal team and radiology team [6/7]. Neonatologists over diagnosed possible perforations in 2/70 radiographs. The neonatologists felt 8.6% of the films to be of poor quality and the radiographers felt 5.7% to be poor images.
Discussion: Intestinal perforation is a potentially fatal complication of neonatal gastro-intestinal disease, in particular NEC. Plain abdominal radiography remains the standard imaging tool however, there have been relatively few studies that have assessed the accuracy of abdominal x-rays in diagnosis of intestinal perforation associated with NEC and these have been performed mainly before the advent of digital imaging allowing image manipulation. In addition, there is only one specific study assessing the accuracy of the supine AP AXR compared to the cross table lateral in detection of pneumo-peritoneum), although the latter is often performed at the same time or as a further view if the AP AXR is equivocal incurring both extra radiation burden and handling of clinically unstable neonates. Our study seeks to determine the ‘added value' of this additional view. The vast majority of perforations 85% can be identified following careful examination of the AP film. The burden of positioning for an additional lateral film may be avoided in many critically ill neonates.

SPONTANEOUS INTESTINAL PERFORATION VERSUS NECROTIZING ENTEROCOLITIS IN VERY-LOW-BIRTH-WEIGHT NEONATES

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Idiopathic spontaneous intestinal perforation (SIP), a distinct clinical entity different from necrotizing enterocolitis (NEC), has an increasing prevalence in very-low-birth-weight neonates (VLBW) and it is associated with low morbidity and mortality. The aim of this study was to define neonates characteristics and potential risk factors that allow early diagnosis of SIP and the distinction from ECN. The medical records of 18 VLBW infants hospitalized in the NICU between 2007 and 2012 were retrospectively reviewed, 5 with SIP and 13 with NEC. The incidence of prenatal problems and antenatal medical treatment, gestational age and mean birth weight were equally distributed. Neonates with SIP had lower Apgar scores, although neonatal resuscitation, umbilical lines and hemodynamic support were similar for the two groups. Neonates with NEC were submitted to more blood transfusions (11/13), half of them (5/11) in the 24 hours preceding NEC (p0.002). The NEC group had done more days of antibiotic therapy previous to NEC (p0.046). The onset of the disease was earlier in neonates with SIP (p0.02), characterized by sudden abdominal distension (5/5) and pneumoperitoneum (5/5), without pneumatosis intestinalis (p0.015). The perforation was unique, always located in the terminal ileum, and the remaining bowel was normal. The histological examination revealed focal hemorrhagic necrosis and absence of coagulation necrosis, typical of ECN. Neonates with SIP were submitted to a less invasive surgery, with resection and primary anastomosis, and had a faster recovery after surgery, requiring shorter antibiotic therapy and getting full enteral feedings earlier (p0.005). The mortality rate was similar in both groups. SIP can be differentiated from NEC based on clinical, radiologic and intraoperative findings. The lack of low mortality rate in the SIP group can be related with the small number of cases in the SIP group.

SPONTANEOUS INTESTINAL PERFORATIONS VS NECROTISING ENETEROCOLITIS PERFORATIONS:10 YEAR EXPERIENCE OF A U.K. TERTIARY LEVEL PAEDIATRIC SURGERY CENTRE

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Background: The operative findings of necrotising enterocolitis perforations (NECPs) and spontaneous intestinal perforations (SIPs) are distinct. Therefore these patients may be managed differently perioperatively. Often there are clinical,radiological and biological distinctions as well. Identifying these preoperatively can be advantageous as SIPs tend to be operated earlier, may not need drainage and bowel continuity may be established at primary procedure. NECPs in contrast may benefit from drainage as a temporising measure, followed by laparotomy and bowel resection to a safe margin with stoma formation. Our aim was to identify pre- operative clinical and biological criteria that may help distinguish differences between newborns with NECPs and SIPs.
Methods: Retrospective case note study of neonates with intestinal perforation in a single tertiary-level Paediatric surgical unit over 10 year period 2002-2012. Classification was based on operative findings. We analysed multiple parameters (50), including day of life at perforation, timing of commencement of initial enteral feed, pre - operative platelet counts and C-reactive protein concentrations.
Result: 46 patients were identified, 18 in the SIP group and 28 in the NECP group. Of all the parameters analysed, the day of life at which perforation occurredwas significantly earlier in the SIP group. Median days: SIP6.0 vs NECP 12.5,p=0.0049 (Mann Whitney test). SIPs NECPs p - value Platelet 109 (51-238) 120 (5-334) 0.276 CRP 23 (7-254) 57 (3-271) 0.168 Data are median (range)
Conclusions: Our study shows that early perforation is in favourof SIP. In these circumstances we would recommend an early operation without peritoneal drainage, aiming at re-establishing bowel continuity. However, as shown, pre-operative distinction between these two entities is difficult because of overlapping features.

MORBIDITY AND MORTALITY ASSOCIATED WITH NEC IN A TERTIARY SURGICAL CENTRE

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Background: Necrotising enterocolitis (NEC) is the single most important cause of surgical gastrointestinal emergency in the neonatal intensive care unit (NICU) accounting for the majority of late neonatal deaths. As a regional surgical referral centre it is important to have data in order to counsel parents effectively regarding prognosis and possible course for their babies. Similarly, an estimate of resource requirements associated with the condition can help in financial planning for the NICU. This study aims to evaluate differences in outcome, specifically mortality, time to stoma closure, growth, use of parenteral nutrition and length of stay in babies with surgically versus medically managed NEC.
Methods Retrospective data were collected from 1st January 2009-31st December 2011 for all babies with a diagnosis of NEC. Data were non parametric and were analysed using the Mann Whitney U test or Chi squared test.
Results: From 2009-2011, 167 babies had a diagnosis of NEC (67 managed operatively vs 100 medically). 28% of operative babies had recurrent NEC. In the surgical group there were 73 episodes of surgically managed NEC. Mortality rate in this group was 42% (28/67) vs 7% (7/100) in the medical group, $p<0.01$. Of the 67 babies who had operative NEC, 58 had stoma formation and 9 had other surgical procedures (direct anastamosis, peritoneal drain, exploratory laparotomy for NEC totalis). The 58 babies with stomas were divided into two groups; a proximal group with stomas of the proximal ileum and above and a distal group with stomas placed in the distal ileum and below. In the proximal group the median birth gestation was 25 weeks compared to 31 weeks in the distal group. Mortality was significantly higher in the proximal group at 51% (14/27) vs 16% (5/31). 9 of the 14 babies who died in the proximal stoma group had NEC totalis with stoma formation for palliative care. The median age at re-anastamosis was 38 weeks in the proximal group vs 44 in the distal group, however the median time to stoma closure was 68 days in both groups. Weight centile at closure was ~0.4th centile in both groups. Earlier gestational age at closure was associated with a lower conjugated bilirubin (74 vs 107) which may be attributable to shorter duration of parenteral nutrition (25 vs 32 days) although this was not statistically significant. 20% of surviving operative babies (8/39) required parenteral nutrition for over 100 days. 5/8 of these babies had had recurrent NEC.
Conclusion: Operative NEC is associated with a high mortality rate particularly in infants of lower gestational age. Regardless of gestation at time of diagnosis or site of stoma, babies undergo re-anastomosis at a median time of 10 weeks following NEC surgery. There is also significant morbidity associated with operative NEC, particularly recurrent NEC, as the majority of these babies require significantly prolonged periods of parenteral nutrition with its associated costs and complications.

COST OF SURGICAL VS MEDICAL MANAGEMENT OF NECROTISING ENTEROCOLITIS

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Background: The incidence of necrotising enterocolitis (NEC) on neonatal units is increasing as advances in care allow greater numbers of premature neonates to survive. Care for these neonates takes place on the neonatal intensive care unit (NICU), high dependency unit (HDU) and special care baby unit (SCBU). Additionally they may require ventilatory support via a ventilator, administration of continuous positive airway pressure (CPAP) or additional oxygen. The tariffs for each level are on average £1034/day on NICU, £695/day on HDU and £457/day on SCBU. Total parenteral nutrition (TPN) usage adds an additional cost of £75/day. Aims To identify overall resource usage in infants with NEC.
Methods: We studied infants with NEC admitted to a tertiary neonatal surgical unit in the UK. NEC episodes were recorded based on clinical and radiological findings, number of days spent at each level of care, ventilation modality on each day and administration of parenteral nutrition. In babies with documented NEC episodes, we defined medical NEC as a neonate on IV antibiotics and simultaneous nil by mouth for at least 7 days. Surgical NEC was defined if operative intervention was required (bowel excision and stoma formation followed by closure). Student's T-test was used for statistical analysis.
Results: All infants with NEC over a three year period from 2009 to 2011 in a tertiary neonatal surgical unit were included. 99 infants were managed medically and 68 surgically. Neonates with surgical NEC spend a significantly greater proportion of admission on NICU compared to medical management (45% vs 27%, $p<0.001$). However in medical NEC neonates spend a higher proportion of admission on the HDU (38% vs 24%, $p<0.001$). The median length of stay in surgical and medical NEC was roughly similar (68.5 vs 76, $p=0.60$). Infants with surgical NEC also spend a higher proportion of days being ventilated (41% vs 20%, $p<0.001$) but a lower proportion of days on CPAP (43% vs 55%, $p<0.005$) and on oxygen (16% vs 25%, $p<0.001$). There was a significantly higher mortality rate in surgical neonates compared to medical neonates (42% vs 7%, $p<0.001$). Factoring in the cost of TPN, the total cost of care on the neonatal unit for surgically and medically managed neonates is roughly similar (£46,157 vs £50,192). If rates remain static NEC will cost £2.6 million in resources annually (£1 million from surgical NEC, £1.6 million from medical NEC).
Discussion: Our results show that surgically managed neonates utilise a higher proportion of intensive care resources reflected in the number of total NICU days (median 25 vs 15) and number of days requiring ventilation (median 13.5 vs 6). However, the significantly higher mortality rate in neonates with surgical NEC compared to medical NEC and increased overall length of stay in survivors contribute to similar overall service costs. If incidence rates remain static however, the service will spend £2.6 million on caring for neonates with NEC each year. NEC represents a considerable proportion of resource allocation in neonatal services.

MANAGING NEWBORN ILEOSTOMIES

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Introduction: Ileostomies are commonly performed on newborn infants with surgical abdominal emergencies. The two large groups of newborns who require an ileostomy are preterm infants with necrotising enterocolitis (NEC) 1 and term infants with a wide spectrum of surgical conditions. The surgical technique involved in the creation of an ileostomy is well defined but the early post-ileostomy management of the infant is less clearly documented with much of the skill and knowledge lying in the hands of neonatal surgical nurses. This study highlights the medical and surgical challenges encountered when managing newborns after an ileostomy.
Methods: Our objective was to identify the post-operative management and related problems in newborns and subsequently report on their optimal management. All infants who received an ileostomy March 2010-December 2011 were identified from the neonatal surgical logbook. In the case of each infant the case notes, operation details, fluid balance and nursing observation charts were obtained by chart review. Each infant's birth weight, gestational age, age at surgery and underlying condition was documented. The post-operative ileostomy progress of each infant was recorded as follows: stoma output, weight gain/loss, parenteral and enteral feeding, types of milks administered, catheter-related infections, surgical stoma, and medications prescribed. Excessive stoma output was defined as greater than 20mls/kg/dy.
Result: There were 16 cases of neonatal ileostomy during the study period which included 8 preterm infants (median gestational age 32 weeks IQR 31-35 weeks) with a median birth weight of 1670g (IQR 1100-3170g) and 8 term infants (median gestational age 40 weeks IQR 38-42 weeks) had a median birth weight of 3320g (IQR 2940g-3900g). Over the first 14 days there was no weight gain. By 21 days the infants were gaining 140 g/week. The stoma output was 5 mls/kg/dy during the first 7 days increasing to 17.5-20 mls/kg/dy. Weight gain or weight loss was closely related to the consistency and volume of the stoma output. Most of the complications were local stoma problems including stricture, prolapse, skin excoriation and cellulitis. Ten infants had a high stoma output >20mls/kg/dy (3 preterm, 7 term).This high stoma output was associated with sub-optimal weight gain. Three infants had catheter-related sepsis. 5 infants were fed exclusively breast milk (EBM) with 2 having combined EBM and donor EMB.
Conclusions: In summary this study provides an account of the progress and complications encountered by a cohort of newborn infants after an ileostomy. The critical issues are weight gain, stoma output local and systemic complications. The findings provide a template for the care of these infants. It sets out how the attending doctor or nurse should approach the management of these high risk infants in the early post-operative period.
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DECISION OF ENTEROSTOMY REVERSAL TIMING FOR PREMATURE INFANTS

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Background: For premature infants with advanced acute abdomen conditions, including necrotizing enterocolitis (NEC), spontaneous intestinal perforation (SIP) and meconium plug syndrome (MPS), creating a temporary enterostomy is thought as a safe surgical management. However, there is no consensus regarding the timing of enterostomy reversal. This study was aimed to determine the optimal timing of stoma closure based on an analysis of enterostomy repair complication.
Methods: All medical data regarding neonates who underwent a laparotomy for a suspected abdominal emergency and received also enterostomy repair in NICU of Seoul National University Children's Hospital from 2007 to 2012 were retrospectively reviewed.
Result: From 54 premature infants with median gestational age of 26+4 (range 23+1 to 35+5) weeks and median birth weight of 765 (range 460 to 2480) grams, indications for enterostomy were NEC (n = 32), SIP (n = 12) and MPS (n = 10). Median postmenstrual ages (PMAs) at stoma creation, repair and stoma duration were 27+1 (range 25+1 to 42+0) weeks, 42+2 (range 34+2 to 80+0) weeks and 13+5 (range 2+5 to 52+0) weeks, respectively. Median weight at stoma creation and repair were 805 (range 535 to 2830) grams and 2510 (range 910 to 7300) grams, respectively. In 35 patients (65%), stoma repair (SR)-related complications occurred. Most frequent were wound problem (n = 20, 37%) such as oozing, redness or bulging and paralytic ileus (n = 13, 24%). In SR complication group, weight at SR, PMA at SR and stoma duration were smaller (P = <0.001, 0.002 and 0.004, respectively). In multiple logistic regression analysis, significant risk factor of SR complication was weight (P = 0.032). SR complication group babies were ventilated longer after operation (P = 0.003), given more vasopressors (P = 0.01) and re-operation (P = 0.019). They required total parenteral nutrition (TPN) for more days (P < 0.001), also took longer to reach full enteral feeding (P = < 0.001), had a longer length of hospital stay after enterostomy reversal (P < 0.001), and their weight and height at corrected age of 10 months were significantly smaller (P = 0.015 and 0.001) compared to no SR complication group. In ROC curve, area under the curves for weight, PMA at SR and stoma duration are 0.834, 0.762 and 0.737, respectively. From these result, the cutoff value for weight, PMA at SR and stoma duration are 2660grams, PMA 43+4 weeks and 15 weeks.
Conclusions: In premature infants underwent the enterostomy creation surgery for their acute abdomens, maturation of babies, especially the weight, significantly impacts the postoperative outcome of enterostomy reversal. Unless seriously indicated, stoma repair should be deferred until at least weight greater than 2600 grams and PMA 43 weeks.

NECROTIZING ENTEROCOLITIS: A 22 YEARS STUDY IN A MEDICAL-SURGICAL NEONATAL CENTRE

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Aim: to assess outcomes of NEC in a tertiary referral neonatal intensive care unit.
Methods and Patients: Observational study, historical cohorts. Four cohorts of patients were enrolled over 22 years, divided in 4 periods: 1990-1994 (A), 1997-2000 (B), 2001-2004 (C) and 2005-2011 (D). Data were gathered from a published paper (A), free communications (B and C) and newly studied (D). NEC grade I was excluded (n=52). Gestacional age (GA), birth weight (BW), birth place, Bell´s modified classification stages, surgical intervention, length of stay (LOS), mortality, lethality and sequelae were studied. NEC - UCIN HDE A(1990-1994) B(1997-2000) C(2001-2004) D(2005-2011) Total Number A-17 B-25 C-24 D-48 Total - 114 GA(median, limits) A-35(30-41) B-30(23-40) C-30(24-37) D-28(24-40) - BW(median, limits) A-2045(800-4200) B-1203(612-3919) C-1045(519-3350) D-965(424-3060) - BW <1500g A-(6/17)35% B-(14/25)56% C-(15/24) 58% D- (32/48)66% E-(67/114) 58% BW <1000g A-(4/17)23% B-(10/25)40% C-(10/24)41% D- (23/48)48% E-(47/114) 41% Inborn/out born A-7/10 B-0/25 C-6/18 D- 6/42 Total-19/95 Bell's class (II/III) A- 4/13 B-4/21 C-9/15 D-7/41 Total 24/90 Surgically treated A-11 (64.7%) B- 22 (81.5%) C-15(62.5%) D-42(87,5%)Total-90(78.9%) Segmental Resection+Ostomy A-11 (91.6%) B-17(77.3%) C-12 (80%) D-31 (74%) Total-70 (77,7%) Segmental resection+ primary anastomosis A-0 B-2 C-0 D-4 Total-6 Peritoneal drain A-0 B-2 C-2 D-5 E-9 Peritoneal drain+ secondary laparotomy A-1 B-1 C-1 D-2 Total-5 Lenght of stay (days) median A-29.5(1-83) B-20(1-197) C-49(1-140) D-42 (2-157) Mortality rate A-5/17(29.4%) B-10/27(37%) C-8/24(33.3%) D-8/48(16.6%) Total-31/114 (27.2%) Lethality A-4/17(23.5%) B-4/25(16%) C-3/24(12.5%) D-6/48(12,5%) Total:17/114 (14.9%) Complications/Sequelae (Post NEC strictures/Short bowel syndrome) A-(1/0) B-(0/0) C-(24/3) D-9/6 Total - 43 (45.3%)
Conclusions: Mortality and lethality rates have decreased over the 22 years period. As a consequence higher rates of complications and sequelae were found. These findings ascertain the severity of the disease. Key Words: Necrotizing enterocolitis, newborn, lethality

THE EFFECT OF TRANSIENT HYPEROXIA ON REGIONAL CEREBRAL TISSUE OXYGENATION IN PRETERM AND TERM NEONATES.

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Introduction/Background: The ideal oxygenation level when treating preterm neonates with supplemental oxygen is a continuous matter of debate. Even short periods of hyperoxia may induce prolonged cerebral vasoconstriction, leading to potential tissue ischemia when FiO2 is reduced to achieve normoxia. We aimed to investigate the effect of brief hyperoxic exposures on the regional cerebral tissue oxygenation (rcSO2) and to evaluate whether any response was related to gestational age. Vasoconstriction should decrease rcSO2 if blood oxygen content and metabolism remain constant.
Patients and Methods: Inclusion criteria: Neonates with a postmenstrual age above 32 weeks, treatment with CPAP and a FiO2 below 0.3, and parental accept. The study group comprised of 19 infants with a mean gestational age of 35.3 weeks (± SD 2.3) and a birth weight of 2515g (± SD 678). Postnatal age at the time of investigation was 1.5 days (± SD 1.5). The INVOS 5100C Oximeter with the neonatal sensor 'OxyAlert' was used to measure changes in rcSO2 before, during and after a five-minute hyperoxic (FiO2= 1.0) exposure. This procedure was repeated after 20 minutes. Transcutaneous pCO2 (tc-pCO2) and arterial oxygen saturation (SaO2) were measured continuously during the study. Baseline values of rcSO2, SaO2 and tc-pCO2 were averaged over a 5 min period and compared with a similar period after oxygen exposure (paired t-test). This latter interval started 3 minutes after termination of oxygen exposure, when SaO2 had attained baseline levels. The differences in rcSO2 were related to changes in SaO2, pCO2 and postmenstrual age using multiple regression for repeated measures.
Result: There was a minor, though significant, increase in rcSO2 after the first hyperoxic exposure, mean difference 1.73% [95% CI 0.39, 3.06] (p=0.015). This increase, however, was not found after the second exposure where rcSO2 remained constant, mean difference -0.57% [95% CI -2.26, 1.11] (p=0.48).Tc-pCO2 decreased by a mean of -0,16kPa [95% CI -0.27, -0.05kPa] (p=0,009) during the first oxygen exposure and -0.15kPa [95% CI -0.27, -0.02kPa] (p=0.025) during the second. Pre- and post-hyperoxic SaO2 was not significantly different during the first oxygen exposure 0.36% [95% CI -0.33; 1.04] (p=0.29) nor during the second -0.043% [-0.71, 0.62] (p=0.89). Multiple linear regression revealed that variations in rcSO2 were attributable to changes in SaO2 (p=0.012); the small fluctuations in pCO2 did not achieve statistical associations. RcSO2 did not change systematically after oxygen exposure and the response was not related to gestational age (p=0.89).
Conclusions: We found no evidence that a brief hyperoxic exposure induces prolonged vasoconstriction in infants with a postnatal age above 32 completed weeks.

ASSESSMENT OF NEUROVASCULAR COUPLING IN NEONATES USING SIMULTANEOUS DOI AND EEG

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Introduction: Understanding the relationship between electrical and haemodynamic activity (neurovascular coupling) resulting from brain activation is an important prerequisite of functional brain imaging. An approach to studying neurovascular coupling in the newborn is to combine electroencephalography (EEG) with diffuse optical imaging (DOI). DOI uses near-infrared light, is non-invasive, and can produce both topo- and tomographic images of regional cerebral blood flow. The ability to elucidate healthy and pathological cortical activity using combined EEG-DOI could help better estimate future cognitive and motor deficits in premature and term-born infants.In this preliminary study we aimed to study resting state functional connectivity (RSFC) globally in the cortex of sleeping infants using combined EEG and DOI.
Patients and Methods: Eight babies born with a median gestational age of 37+3 weeks (range 35+1 – 41+5 weeks) were studied at a median gestational age of 38+3 weeks (range 36+2 – 42+2 weeks). All infants were recruited from the Neonatal Intensive Care Unit of the Rosie Hospital. Seven were healthy subjects or only had mild complications with no history of neurological pathology. The other, RSFC_006, showed burst suppression in line with hypoxic ischemic encephalopathy (HIE) during a clinical EEG scan at 1.5 hours of age. Subjects were scanned in their cots immediately after a feed and while quietly resting. The length of the scan typically lasted 30-60 minutes.A 13-channel EEG and continuous-wave DOI system with 16 sources and 16 detectors were used in parallel to acquire simultaneous data of neurovascular coupling. The EEG-DOI array was attached to the infant's head using a soft, skin-compatible cap that positioned each electrode, detector, and source relative to the 10-5 international cortical labeling system. The cap was designed to cover the entire surface of the head, including the frontal, parietal, temporal, and occipital lobes.Optical and EEG data were pre-processed and cleaned of motion artifacts. DOI data was bandpass filtered in the RSFC range (0.009-0.08 Hz) prior to time series correlation. Global signal regression (GSR) was used to eliminate noise in the optical data due to systemic physiology. Pearson's correlation coefficient r and z-scores were calculated for the time course of each channel in relation to every other channel. Channels were considered correlated when r > 0.5.

Table 1 - Subject Information

Subject Code	GA at delivery	GA at scan	Head circ. (cm)	Relevant clinical remarks
RSFC_001	36 1/7	39	33.5	Prematurity, duodenal atresia, ASD*, jaundice
RSFC_002	37	37 2/7	36.8	Healthy term infant
RSFC_003	38	38 4/7	35.5	Healthy term infant
RSFC_004	37 5/7	38 1/7	35.0	Healthy term infant
RSFC_005	35 1/7	36 2/7	31.8	Prematurity, IUGR†, RDS**
RSFC_006	38 1/7	39 4/7	33.9	IUGR†, jaundice, HIE‡ Grade 2, seizures
RSFC_007	41 5/7	42 2/7	35.5	Healthy term infant
RSFC_008	36	36 5/7	34.4	Prematurity

* = Atrial septal defect, † = Intrauterine growth retardation, ** = Respiratory distress syndrome, ‡ = Hypoxic ischemic encephalopathy

Results: Analysis of pilot optical data demonstrated connectivity maps in infant cortex. The region of the chosen seed, especially in frontal and parietal areas, typically correlated to other nearby channels and to homologous channels in the opposite hemisphere. GSR was found to be an effective method of reducing correlation false positives due to systemic physiology.
Conclusions: Our preliminary results imply that bimodal DOI and EEG recording can be a useful tool for investigating neurovascular coupling in infants at the cot-side. Further analysis of simultaneous optical and electric data from neonatal cortex could yield novel information about neurological connectivity and pathology in the developing brain. These results have the potential to help create a set of valuable imaging biomarkers for the management of infants with perinatal brain injury.

THE VALUE OF NEAR-INFRARED SPECTROSCOPY (NIRS) IN PRETERM INFANTS WITH POSTHAEMORRHAGIC VENTRICULAR DILATATION

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Background: Intraventricular haemorrhage (IVH) is still a major cause for brain injury in preterm infants. About 40% require treatment for posthaemorrhagic ventricular dilatation (PHVD) using serial lumbar punctures or the implantation of a decompressing drainage device. Little is known about changes in cerebral perfusion in preterm infants suffering PHVD. Near-Infrared Spectroscopy (NIRS) is a non-invasive tool for continuous bedside monitoring of cerebral oxygen saturation. Aim: To delineate the impact of progressive PHVD on regional cerebral oxygenation in preterm infants before and after ventricular decompression using NIRS.
Methods: We performed a prospective observational study using NIRS. Changes in cerebral regional oxygen saturation (rcSO2) were measured continuously for several hours before and after neurosurgical intervention to decompress PHVD by insertion of an external ventricular drainage (EVD). Neonatal cerebral sensors were placed on the patients´ forehead. rcSO2 values were recorded by the INVOS System (Covidien©) in a 5 second interval. Mean values were calculated by using all values obtained over the whole measurement period of each patient. Pulseoximetric peripheral oxygen saturation (SpO2) and heart rate were measured continuously. Records of the ICIP Critical Care Patient Monitoring System (Philips©) with a recording interval of 15 minutes were used for further calculations. Fractional tissue oxygen extraction (FTOE) was calculated using the equation FTOE= (SpO2-rcSO2)/SpO2. Cerebral ultrasound (CUS) including Doppler measurements were performed once daily in all patients and resistive indices (RI) were collected before and after ventricular decompression.
Result: Five preterm infants were included. Their mean gestational age at intervention was 29+1 weeks', their mean birth weight 1228g. NIRS was measured for a mean of 5.3 hours before, and a mean of 19.5 hours after intervention. Before decompression, mean rcSO2 value was 46% (range: 35-54%), and increased to 59% after intervention (range: 51-67%). With increasing ventricular width, the FTOE showed a mean value of 0.5 (range: 0.44- 0.62) and decreased to a mean of 0.36 (range: 0.27- 0.45) after decompression. Before EVD placement RI showed a mean of 0.74 (range: 0.63- 0.82) and remained unchanged after the intervention (mean 0.75, range: 0.74- 0.76).
Conclusions: All five patients showed a compromised rcSO2 before intervention, which improved after EVD-placement. We hypothesize, that due to increased intracranial pressure, cerebral oxygen delivery was impaired. Correspondingly, FTOE was increased before intervention and decreased after decompression. Again, we hypothesize, that increased FTOE values are indicating a compensation for decreased oxygen delivery before intervention. After decompression FTOE values normalized. Thus, NIRS might be of clinical value to detect impaired cerebral oxygenation in patients with increased intracranial pressure with progressive PHVD. It might be a beneficial additional tool to determine the optimal time-point for ventricular decompression in patients with PHVD in the future.

REGIONAL CEREBRAL OXYGENATION VALUES IN THE FIRST 48 HOURS OF LIFE ARE LOWER IN VERY PRETERM INFANTS WITH ADVERSE OUTCOME?

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Background: Preterm infants are at risk of death or brain injury. Near Infrared Spectroscopy (NIRS) is a non-invasive optical technology that can be used to monitor neonatal cerebral oxygenation, and allows assessment of the degree of hypoxia-hyperoxia.?
Objective: To determine in preterm infants less than 32 weeks gestation (1) the relationship between regional cerebral oxygenation rCSO2 measurements and adverse outcome, defined as death or cranial ultrasound abnormality (2) degree of cerebral hypoxia/hyperoxia defined as rCSO2 values less than 55% and greater than 85%.?
Design/Methods: This was a prospective, observational study of preterm infants less than 32 weeks in the first 48 hours of life. rCSO2 values were measured using NIRS INVOS 5100C with a neonatal probe. Cranial ultrasound was performed at enrolment, within the first 3-7 days and at 1 month. The outcome was defined as a composite measure of death and abnormal cranial ultrasound findings. Parental consent was obtained in all cases.
Results: 40 preterm infants were enrolled in the study. Median (range) gestational age was 28 weeks (24 - 31), birth weight 1035g (470-1840). 8 babies had an abnormal outcome, 3 died and 5 had abnormal cranial ultrasound. The mean (sd) rCSO2 was 72.5%(±12.5%) in those with an abnormal outcome compared to 82.9 (±7.5%) who had a normal outcome, p=0.02. There were no significant differences between groups in measures of variability, including range (47% versus 44%, p=0.9) and standard deviation (5.6 vs 5.5%, p=0.88) of rCSO2. For the entire group the mean percentage of time spent < 55% (cerebral hypoxia) was 2.6% compared to 30.2% > 85% (presumed hyperoxia). Patients with a normal outcome spent a greater proportion of the time above 85% (36% versus 9%, p=0.04) and likewise spent a significantly shorter percentage of the recording time less than 55% (0.7% versus 10.1%, p=0.03).?
Conclusions: Preterm infants who die or have cranial ultrasound abnormaiities have lower mean rCSO2 values in the first 48 hours of life. Variability measures were not associated with adverse outcome. In very preterm infants when monitoring cerebral oxygenation with the neonatal probe, rCSO2 values of 55% and 85% do not reflect the degree of cerebral hypoxia or hyperoxia.

BILATERAL CORTICAL N20 MAY PREDICT NORMAL BRAIN MRI IN NEWBORNS WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY TREATED WITH HYPOTHERMIA

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Introduction: Therapeutic hypothermia (TH) is becoming standard neuroprotective strategy for neonatal hypoxic-ischemic encephalopathy (HIE). Brain MRI is highly predictive of neurological outcome and early somatosensory evoked potentials (SEP) have been shown to give extremely high (up to 97-100%) positive predictions of outcomes in infants with HIE. Aim of this study is to compare predictive value of early somatosensory evoked potentials (SEP) in respect to magnetic resonance imaging (MRI).
Methods:A total of 10 newborns with HIE underwent TH. After rewarming, newborns performed: a) SEP (within 6 hours from rewarming) and b) brain MRI (performed 9.09±5 days after birth). SEP and MRI data were scored as follows: N/N (N20 cortical component bilaterally recorded), A/A (N20 cortical component bilaterally absence), N/A (asymmetrical response) and n.e. (not evaluable); n-MRI and j-MRI (respectively normal MRI and MRI injury).
Results: Cortical SEP were: N/N in 6/10 newborns (5 with n-MRI and 1 with j-MRI); A/A in 1 newborn with j-MRI; N/A in 1 newborn with j-MRI. One newborn presented A/n.e. SEP with j-MRI and one newborn presented N/n.e. SEP with n-MRI.
Conclusions: In our case series 85% of newborns with N20 cortical component bilaterally recorded, presented normal brain MRI. SEP may represent a reliable early predictor of MRI findings providing relevant information already at the bedside. These data need to be evaluated in large prospective study.

CONDUCTING REPETITIVE MRI AND VOLUMETRIC MEASUREMENTS OF THE PRETERM PIGLET BRAIN

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Background/introduction: The term piglet is often used as a model for the hypoxic ischaemic encephalopathy in the term newborn infant. Animal models for the preterm brain are also needed. Optimally, the animal model should allow the evaluation of both brain structure and brain function with methods that are comparable to those used for premature infants, e.g. cerebral ultrasound, MRI, neurologic examinations, and later on developmental/intelligence tests. Repeated MRI scans, volumetric measurements and cognitive testing have previously been performed in term piglets, but not in preterm piglets. In this pilot-study we evaluated repetitive MRI scans in premature piglets. We assessed the reproducibility of the volumetric measurements and compared the results to newborn term piglets.
Patients and Method: Eight premature piglets delivered by caesarean 10 days before term (91% gestation) were included in the study at age 0-1 day. Four one-day-old term pigs served as controls. We planned three subsequent brain MRIs during the first 24 days of life in the premature piglets whereas the term piglets were scanned at day 1, only. The piglets were sedated with a single intramuscular injection of a mixture of tiletamin, zolazepam, ketamine, xylacine and butorphanol, placed in ventral recumbency on heating pads (CURAPAX® CARE CONCEPT) and covered with towels. The head was stabilised with foam rubber in the MR-coil to prevent movements. They were quiet and needed no respiratory support during the procedure. After the MRI the piglets returned to the preterm care unit. We used a 3 Tesla SIEMENS MAGNETOM trio with an 8 channel head coil (LMC®, Neonatal head array coil for 1.5/3.0T). Brain volume was measured on 3D T1 weighted images with the script RIP for MATLAB. All images were measured twice by the same investigator. Repeatability and correlation coefficients was determined according to Bland (1987) and Altman (1999).
Results: Due to various developmental immaturities, only three of the eight premature piglets survived to have all three MRIs whereas the rest were scanned once or twice. Hence a total of 21 MRIs was conducted. The overall repeatability was 0.633ml and inter class correlation coefficient was 0.997. Mean brain volume (±SD) for the preterm and term piglets at day 0-1 was 29.2ml±0.49 and 35.8ml±0.98 ($p<0.0001$) respectively. At term equivalent age (10-11 days) the preterm piglet brain was still significantly smaller than the controls; 32.7ml±2.0 ($p=<0.05$). The premature piglets at term equivalent age also showed weight deficit; 1191g±205 vs. 1430g±11 ($p=0.06$). In the preterm piglets brain volume increased by 26% (28.9ml to 36.6ml) from day 1 to 18 ($n=3$). Overall correlation between body weight and brain volume in the premature piglets was 0.90. The procedure did not seem to stress the animals. We found no MRI evidence of brain injury in any of the piglets.
Conclusions: It is possible to conduct repetitive MRI in preterm piglets. It appears to be possible to monitor brain growth with little error. Brain growth after preterm delivery is short of intrauterine growth, but the premature piglets also showed weight deficit. Volumetric measurements may be useful in a preterm piglet brain model.

TEMPORARY THERAPEUTIC WINDOW OF CANNABIDIOL FOR NEUROPROTECTION AFTER BRAIN HYPOXIA-ISCHEMIA IN NEWBORN MICE.

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Background: cannabidiol (CBD) administered to newborn rodents 15 min after a hypoxic-ischemic (HI) insult leads to significant and long-term sustained neuroprotection. Aim: to determine the temporary therapeutic window of CBD, that is how long CBD administration can be delayed after HI without loosing its neuroprotective effect.
Methods: 9-day old C57BL6 mice underwent a HI insult by being exposed to 10% oxygen for 90 min after electrocoagulation under anaesthesia of the left carotid artery. Then, 0.1 mL of vehicle (ethanol:solutol:saline 2:1:17) or CBD (1 mg/kg) was administered s.c. 15 min, or 1, 3, 6 or 12 h after the end of the HI insult HI with VEH(HV) n=25-, HI with CBD immediately after the insult (HC0) n=15, HI with CBD 1 hr (HC1), HI with CBD after 3 hrs (HC3),HI with CBD after 6hrs (HC6) and HI with CBD after 12 hrs (HC12) n=6-9 for each group). Seven days later pups were killed, transcardially perfused with formaline 10% and their brains removed and stored in formaline. Then, the ipsilateral hemisphere volume (IHV) loss was calculated from T2W sequences of brain MRI scan. Non-HI mice served as controls (n=15).
Result: HI led to the loss of 12.5±1% ipsilatral hemisphere volume (IHV). This was reduced by CBD administered 15 min after HI (5±1% IHV loss, $p<0.05$). The effect of CBD was still significant when treatment started 6 (6.4±1% IHV loss, $p<0.05$) or even 12 hrs after HI (7.5±1% IHV loss, $p<0.05$.
Conclusions: CBD treatment offer 60% neuroprotection when administered 15 min after HI and even 40% when treatment started up to 12 h after a HI insult Supported by FIS PS09/01900, Health Trust South East Norway and GWCRI091190-2

ENDOGENOUS CDP-CHOLINE AS A PROMISING CANDIDATE BIOMARKER FOR HYPOXIA-DERIVED BRAIN DAMAGE IN A NEWBORN PIGLET MODEL

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Introduction/Background: Clinical grading, therapeutic intervention strategies, and prognosis of newborns suffering from brain injury secondary to birth asphyxia could be substantially improved by the availability of reliable biomarkers. Hence, the primary objective of this study was to assess metabolic changes that reflect the intensity of hypoxia in retina samples from a newly born piglet model in order to guide further research for the discovery of highly reliable non-invasive biomarkers of brain injury secondary to birth asphyxia.
Animals and Methods: A total of 10 piglets underwent the experimental procedure. Out of these, 5 were randomly assigned to hypoxia and the remaining 5 to room air. Hypoxemia was achieved by ventilation with a gas mixture of 8% O2 in N2 until either the mean arterial blood pressure decreased to 20 mmHg or the base excess (BE) reached -20 mmol/L. CO2 was added during hypoxemia aiming at a PaCO2 of 8-9.5 kPa to imitate perinatal asphyxia. At the end of hypoxia, or at the corresponding time point for the control group, the eyes were extracted (from the full anesthetized piglets), placed on an ice-cold glass plate and excised to quickly remove the retina of each eye. Once the retinas were obtained, they were frozen on liquid N2 and stored at -80°C. Retina samples were homogenized and analyzed employing an ultra performance liquid chromatography - quadrupole time of flight mass spectrometry (UPLC-QTOFMS) untargeted metabolomic approach and multivariate data analysis including Partial Least Squares - Discriminant Analysis (PLSDA). Due to the limited number of available samples, a statistic validation approach was employed for assessing the significance of the obtained discriminant model.
Results: The untargeted metabolomic analysis of retina samples obtained from asphyxiated and control newborn piglets allowed the selection of eight differentiating metabolites by means of PLSDA. Validation of the results was conducted by targeted UPLC-MS/MS for the quantification of one of the identified differentiating metabolites (CDP-choline) confirming the obtained results.
Conclusions:CDP-choline was classified as a promising biomarker for hypoxia in retinal (neuronal-like) tissue. Obtained results are of great value in basic research in the hypothesis generation phase to guide further investigations eventually leading to a biomarker qualification. However, validity of CDP-choline has yet to be confirmed upon resuscitation with further experiments in hypoxic animals resuscitated with different oxygen concentrations. Moreover, applicability of CDP-choline in the clinical setting and especially in the newborn period would request confirmation of its reliability in non-invasively attainable biofluids such as urine. Future studies in larger populations and additional matrices are going to be carried out in order to test the performance of CDP-choline as a biomarker for hypoxia in retina and its reliability upon resuscitation. Acknowledgements We acknowledge the support from the Servicio de Soporte a la Investigación Experimental (University of Valencia). JK and JE acknowledge their personal Sara Borrell grants (CD12/00667 and CD11/00154) from the Instituto Carlos III (Spanish Ministry of Economy and Competitiveness). MV acknowledges the FISPI11/0313 grant from the Instituto Carlos III and EC11-244 from the Spanish Ministry of Health, Social Services and Equality and GQ the Spanish Ministry of Economy and Competitiveness (SAF2012-39948).

IMAGING PH CHANGES IN PIGLET BRAIN AFTER ACUTE HYPOXIA-ISCHEMIA USING AMIDE PROTON TRANSFER (APT)

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Background: Hypoxia-ischemia (HI) in the new born infant is an important cause of death with 4 in 1000 neonates suffering asphyxiation before or at birth resulting in neonatal encephalopathy (NE) with a survival rate of 40% of which at least 25% suffer long term neurodevelopmental sequelae. Following HI, brain undergoes dramatic metabolic disturbances which lead to alterations in the pH of the tissues. Change in tissue pH is a good biomarker of the severeness of the condition; therefore it is important to develop techniques that track brain pH changes [1,2,3]. P-31 NMR spectroscopy, a well-established MR technique, allows quantitative pH measurements using the Henderson-Hasselbalch equation (Petroff et al., 1985a). However, the main limitation of this technique is that it offers no spatial resolution. Amide proton transfer (APT) has the ability to indirectly detect protein concentrations in soluble form, through chemical exchange of the amide groups with the free water surrounding them. Transfer rate between amide protons and water is pH dependent which follows a base-catalyzed amide proton exchange relationship (Zhou et al., 2003)[4]. Aim Non-invasive mapping of regional pH changes in piglet brain undergoing neonatal Hypoxic-Ischemic insult using APT-MRI.
Methods: Piglets (n=6) were surgically prepared within 24 hours of birth and both common carotid arteries were isolated and encircled by remotely controlled vascular occluders. Piglets were then placed into the MRI scanner were anesthesia was maintained by the combination of 2% isoflurane, nitrous oxide and continuous infusion of morphine (0.05mg/kg/hr) [1]. APT scans and global 31P MRS were acquired pre- and 60 minutes post- induced HI [5]. The APT sequence consisted of a saturation train of 80 Gaussian pulses (pulse length=50ms, FA=400o, 91% duty cycle), followed by a turbo-flash readout (TR=4.14ms, TE=2.09ms, FA=10, FOV=100x100mm2, matrix=128x128, slice thickness=4mm). Saturation was applied at ±6ppm for 77 frequency offsets. Pixel by pixel Z-spectra were analysed at 3.5ppm from water (APT peak) and the percentage change in APT was calculated.
Results: and discussion A clear disappearance of the amide peak is observed in all subjects following HI, consistent with a reduction in amide exchange rate due to acidification of the tissue. The global acidification of the brain was confirmed by 31P NMR spectroscopy. The advantage of APT over 31p NMR is that it provides a regional pH change information which hugely improves the diagnosis of insult severity and extent. In conclusion, this study shows that the APT technique is suited for mapping the pH changes in the brain of piglet undergoing HI. However the current stage of the technique only informs in pH changes, for absolute pH quantification further work is required to establish a reliable measure.
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GENE EXPRESSION CHANGES IN THE BRAIN OF OGG1/MUTYH KNOCKOUT MICE FOLLOWING A HYPOXIA-REOXYGENATION INSULT

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Background: Hypoxia-reoxygenation (HR) can cause considerable damage to the newborn brain. DNA-glycosylases, e.g. Ogg1 (8-oxoguanine DNA-glycosylase 1) and Mutyh (MutY homolog), are important in the repair of oxidative DNA damage. We have studied the gene expression changes of 44 a priori selected genes in the brain of Ogg1-/-/Mutyh-/- knockout mice (KO) and compared with changes in wild type mice (WT).
Materials and Methods: Forty-four KO and 63 WT mice postnatal day 7 were randomized to 120 min of hypoxia (FiO2 0.08, KO n = 33, WT n = 47) or 180 min in air (control, KO n = 11, WT, n = 16). The hypoxia group was further randomized to 30 min reoxygenation in air (H21) or FiO2 0.60 (H60). The mice were sacrificed either immediately after reoxygenation (R0) or after 3 days observation (R3d). mRNA extracted from homogenate of hippocampus and striatum was analyzed with real-time RT-PCR. For analyses, the comparative ?CT method, ANOVA with posthoc Tukey correction and t-tests were used.
Result: At R0, there was significant ($p < 0.05$) upregulation in KO compared to controls of Edn1, Lcn2, Mt1, Slc2a1 and Vegfa and downregulation of Ccnd1 and Cxcl10 in both the H21 and H60 group. Nfkb1 was downregulated in the H21 group only and Neil3 in the H60 group. At R3d no significant changes were observed between KO and controls. Further there were no significant changes in the comparison between H21 and H60 at either time point. At R0 there was significant higher expression in WT than KO of Ccnd1, Ccl12, Cxcl10, Mt1, Nfkb1 and Slc2a1 in both the H21 and H60 group. Ccl5 and Il6 had higher expression in WT in the H21 group and Bnip3, Hmox1, Tgfb1 and Tlr4 in the H60 group only. At R3d the situation was different with higher expression in KO than WT of Bcl2l1 in both the H21 and H60 group, while Atm, Ccl12, Stat3, Tlr4 and Tnf were higher in the H21 group and Il6 and Jun in the H60 group only. WT had higher expression than KO of Ccnb1, Chek1 and Tgfb1.
Interpretation: KO had a weak immediate inflammatory and oxidative stress response after HR, by means of suppression of Cxcl10 compared to controls, and sole induction of Mt1 and Lcn2. At R0, KO had a lower expression than WT of inflammatory genes (Ccl12, Cxcl10, Ccl5, Il6, Tgfb1 and Tlr4), oxidative stress responsive genes (Hmox1 and Mt1) and anti-apoptotic genes (Nfkb1 and Bnip3). Lower expression of Ccnd1 in the KO suggests increased cell-cycle arrest. After three days the expression pattern had changed with some inflammatory genes higher in KO and others higher in WT. KO also had higher expression of genes of transcription regulation (Stat3 and Jun) and apoptosis (Bcl2l1 and Tnf).
Conclusions: These results imply that Ogg1 and Mutyh are important in the immediate stress response and to prevent apoptosis and cell-cycle arrest, however not after 3 days.

MPGES-1 AND COX-2 EXPRESSION IN BRAINSTEM BEFORE AND AFTER RESUSCITATION IN PRETERM LAMB.

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Background: Prostaglandin E2 (PGE2) depresses respiration and is present in the fetus, subjected to the relative hypoxia in utero. Hypoxia and inflammation induces Prostaglandin E2 release via the metabolism of arachnidonic acid via cyclooxygenase-2 (COX-2) and microsomal PGE synthase-1 (mPGES-1). We hypothesize that resuscitation in the newborn sheep gives the re-oxygenation needed to supress PGE2 and COX-2 expression leading to survival.
Methods: Lambs delivered at 129 days (term = 150 days), were subjected to either 1) direct sacrifice (n = 6) or 2) ventilated resuscitation for a total of 1,5 hours (n = 6). Brainstems were collected and paraffin embedded. Sectioning was performed and slides were selected for areas containing respiratory related regions and the blood brain barrier. Sections were used for immunohistochemistry using mPGES-1 and COX-2 antibodies.
Result: Preliminary results show a reduced expression of mPGES-1 and COX-2 in the nucleus of tractus solitarius (NTS), and the rostral ventrolateral medulla (RVLM) as well as area postrema and in the blood vessels considered to be the blood brain barrier (BBB) after 1,5 hours of ventilation.
Conclusions: Re-oxygenation of 1,5 hours gives a decrease in mPGES-1 and COX-2 expression in respiratory related areas in the brainstem leading to spontaneous breathing. This further concludes that Prostaglandin E2 is induced by inflammation and hypoxia and correlates to respiratory depression.

REMIFENTANIL EXERTS AN ANTI-APOPTOTIC EFFECT ON IMMATURE MICE BRAIN: ACTION MECHANISMS

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Introduction: The morphinic remifentanil can be used during cesarean delivery and in neonatal intensive care. Its use in a context of potential prematurity strongly leads to explore it during development. In hyperalgesia models, opioids can modulate NMDA receptor (NMDA-R) activity by phosphorylation of the GluN2B subunit. NMDA-R was previously shown to exert necrotic and anti-apoptotic effects on immature mice brain.
Methods: Our study, using cerebral slices from postnatal day 2 mice, evaluates the necrotic and apoptotic potentialities of remifentanil, alone or associated with glycine (contained in the clinical form Ultiva).
Result: Ultiva had no impact on necrotic death. In contrast, it significantly reduced caspase-3 activity, Bax and cleaved caspase-3 contents and targeted the superficial layers of neocortex. Naloxone and ifenprodil (preferentially μ and GluN2B antagonists, respectively) reversed its action. Association of remifentanil and glycine exerted a synergic inhibitory effect on apoptotic death whereas it was devoid of necrotic action. Furthermore, remifentanil (without glycine) significantly reduced apoptosis. Ultiva stimulated the phosphorylation of cortical GluN2B (position 1472) and inhibitors of PKC (chelerythrine) and Src-family tyrosine kinases (PP2) abolished the anti-apoptotic effect of Ultiva.
Conclusions: The present data provide evidence that remifentanil is devoid of necrotic effect in developing mice brain but exerts an anti-apoptotic action which probably involves phosphorylation of GluN2B. Supported by the University of Rouen, INSERM, IRIB, FEDER, Région Haute-Normandie and the LARC Neuroscience network.

NEURO-INFLAMMTION AND MESIAL TEMPORAL LOBE EPILEPSY IN THE DEVELOPING BRAIN: FROM TOLL-LIKE RECEPTOR 4 TO INFLAMMATION RELATED MICRORNAS

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Background: Increasing evidence indicates that neuro-in?ammation plays a critical role in the pathogenesis of mesial temporal lobe epilepsy (MTLE). We aimed to investigate the dynamic expressions of Toll-like receptor 4 (TLR-4), nuclear factor kappaB (NF-kB), interleukin-1ß (IL-1ß), tumor necrosis factor alpha (TNF-a), miR-146a, and miR-155 in the hippocampi of an immature rat model and children with MTLE.
Method: To study the expressions of TLR-4, NF-kB, IL-1ß, TNF-a, miR-146a, and miR-155, we performed a reverse transcription PCR, Western blot, EMSA, and real-time quantitative PCR on the hippocampi of immature rats at 25 days of age. Expressions were monitored in the acute, latent, and chronic stages of disease (2 h and 3 and 8 weeks after induction of lithium-pilocarpine status epilepticus, respectively), and in control hippocampal tissues corresponding to the same timeframes. Similar expression methods were applied to hippocampi obtained from children with MTLE and normal controls.
Result: The expression of TLR-4, NF-kB, IL-1ß, TNF-a and miR-155 showed upregulation in the acute and chronic stages, while in the latent stage the expressions were nearly equal to the control group. MiR-146a was upregulated in the latent and chronic stage while in the acute stage it was nearly equal to the control. All markers were upregulated in children with MTLE.
Conclusions: MicroRNAs start to emerge as promising novel players in MTLE pathogenesis in the developing brains. Modulation of the signaling pathway starting from TLR-4 level to inflammation-related microRNAs may be a novel therapeutic target in MTLE treatment.

DECREASED PROLIFERATION OF THE CEREBELLAR EXTERNAL GRANULAR LAYER FOLLOWING PRETERM BIRTH IN RABBIT PUPS

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Background: In very preterm human infants the cerebellum is smaller at term age as compared to term infants and the observed reduction in cerebellar volume has been associated with neurodevelopmental impairment. The causal mechanisms for decreased cerebellar growth following very preterm birth are unknown. Preterm birth is followed by a decline in circulating levels of insulin-like growth 1 (IGF-1) which in turn is associated with decreased cerebellar volume at term age. The IGF system is a necessary component of external granular layer (EGL) proliferation, the EGL forming a layer of neuronal progenitors essential for continued cerebellar development. Animal models, incorporating premature loss of placental trophic support and with a brain maturity corresponding to that of the very preterm infant have been difficult to establish.
Aim: To evaluate the effect of preterm birth on circulating levels of IGF-I and cerebellar EGL development in a rabbit pup model. Study design: Preterm (PT) rabbit pups were delivered by cesarean section at day 29 (E 29) of gestation (term =32 days), cared for in closed incubators with humidified air (60 % humidity at 36 C) and gavage-fed with increasing amounts of kitten milk replacement formula (70-200 ml/kg/day). Control term (T) pups delivered by spontaneous vaginal delivery at 32 days were housed and fed with/by their lactating doe. Pups were weighed daily. Blood sampling for IGF-I analysis and in vivo perfusion-fixation for cerebellar histology were performed at E29 (N=8), P0 (N=8) and P2 (N=5) in PT pups and at P0 (N=10) and P2 (N=10) in T pups. Serum levels of IGF-I were quantified by ELISA. Cerebellar sections were stained with hematoxylin-eosin and proliferating cells were stained with antibody against nuclear antigen Ki-67. Width of the total EGL (outer proliferative zone + inner differentiating zone) was measured and cell numbers/area were counted in the outer EGL zone and the inner EGL zone in each pup.
Result: Total cerebellar EGL width was lower in PT pups at P2 as compared to that in T pups, mean (SD) 55 (3) µm vs. 60 (4) µm, p=0.03. Number of differentiated neuronal cells in the EGL did not differ between the PT and T group at any of the studied time points. Width of the proliferative zone (Ki67-positive) of the EGL decreased from P0 to P2 in the PT group ($p<0.05$) and was reduced at P2 as compared to that of the T group at P2, mean (SD) 35 (3) µm vs. 44 (4) µm, p=0.01. Mean values of body weight and serum IGF-I were lower in the PT group as compared to those of the T group at P0 and P2 (all $p<0.05$).
Conclusions: Preterm birth in rabbit pups is associated with decreased proliferation of the cerebellar EGL, lower body weight and decreased circulating levels of IGF-I. This preterm rabbit pup model thus mimics important aspects of preterm human birth. Ongoing study will evaluate if decreased cerebellar EGL proliferation is primarily due to increased apoptosis or to decreased trophic input from Purkinje cells.

A NEW METHOD FOR THE STUDY OF CSF IN IMMATURE RATS.

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Background: Biomarkers of brain damage in cerebrospinal fluid (CSF) (protein S-100B, neuro-specific enolase) in infants with hypoxic ischemic encephalopathy (HIE) are useful to assess the severity of brain injury and to predict the outcome. Despite its importance in clinical practice, they are not used in small animal models of neonatal hypoxic-ischemic injury because of technical difficulty to obtaining CSF in immature rats. Therefore, in the rat animal model of hypoxic-ischemic injury most studies analyze only brain damage extension through histological extension but never biomarkers. We present a new method to obtain CSF in immature rats and we questioned if CSF-S100B could assess brain injury in HIE rat pups.
Methods: Wistar rat pups were anesthetized with 4% isofluorane. Their head was placed at 45 degree position showing the cistern magna orifice. Once the space was identified by palpation, it was punctured with a 24 G needle. CSF was recollected with a pipette. After the procedure, rats were immediately sacrificed and their brains removed. Samples of CSF were also extracted using the same methodology in animals with brain damage (Rice-Vanucci model). CSF samples were immediately frozen at - 80°C for further analysis. S100B was determined by means of a PS100 ELISA.
Results: 82 Wistar rat pups (54% females) aged between 7 and 12 days (28% 10 days) were used. Mean anesthesia time was 120.72 seconds (+/- 19. 82). Animals weight was 18.15 grams (+/- 3.3) and brain weight 0.80 grams (+/- 0.13). CSF was successfully obtained in 96.2% of the rat pups, with a CSF mean amount of 21.28 µl (5-40 µl) average. The biggest volume of CSF was obtained in animals with more weight (p=0.042). CSF amount did not correlate with days age or brain weight (p>0. 05). PS100 values in normal animals were between 5-10 ng/ml. Animals with damage (Rice-Vannucci models) showed values S100B levels significantly higher than those without brain injury (12.84 ± 10 vs 40 ±28.3; p<0.01). All animals with brain injury had CSF-S100B levels upper 20 ng/ml.
Conclusions:A new method to obtain CSF from immature rats has been successful developed, obtaining enough amount of CSF to perform biochemical determinations. Normal levels of Protein S100B obtained in a cohort of rats between 7 to 12 days has permitted establisher a normality curve of this biomarker. The standardization of this technique will make it applicable in animal studies in order to have new strategies to evaluate new neuroprotective strategies in HIE or other neurological disorders during the neonatal period.

EFFECTS OF NEONATAL OXYGEN TOXICITY ON MYELIN ULTRASTRUCTURE IN MICE

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Objective: Preterm birth often causes diffuse white matter damage (WMD) in association with impaired neurodevelopmental outcome. Oxygen toxicity is one of the potential factors of WMD. However, myelin deficits are often subtle and may not be detected through the use of conventional techniques like MRI and ultrasound. We used a hyperoxia mouse model to investigate oxygen-induced effects on distinct myelin compounds that are expressed during brain development, and to determine myelin ultrastructural changes using electron microscopy in young adult mice.
Methods: Newborn mice were exposed to 48 h of hyperoxia (80% O2) from P6 to P8, and synthesis of myelin proteins MAG, MOG, PLP, and CNPase was determined by Western blot analysis during recovery in room air at ages P12, P15, and P30 in comparison to litters always kept in room air. Immunohistochemistry for MAG was performed in the white matter to determine mature and myelinating oligodendrocytes. At P15 and P30, axon diameters, myelin thickness, and myelin ultrastructure were determined using a Leo 906 Zeiss electron microscope.
Result: Mice after neonatal hyperoxia showed decreased expression of MAG and PLP and ages P12, P15, and P30. MOG was decreased at P12 but not at later ages, and CNPase was unaffected at all ages. Cell numbers in the white matter positive for MAG immuno-histochemistry were lower after hyperoxia during recovery from P8 to P30. Electron microscopy at P15 and P30 revealed decreased axon diameters and reduced thickness of the myelin sheath in the corpus callosum fibers of hyperoxia-experienced mice. Moreover, extra myelin loops were found in mice after hyperoxia at P30, indicating persistent structural myelin defects caused by neonatal hyperoxia.
Interpretation: Exposure to hyperoxia at newborn ages may diminish various myelin compounds and cause aberrations of myelin ultrastructure. This work has been supported by: DFG grant SCHM 3007/2; Förderverein für Frühgeborene an der Charité e.V.

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION (NIPPV) VERSUS NASAL CPAP (NCPAP) POST-EXTUBATION IN PRETERM INFANTS: AN UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction/Background: Previous systematic reviews report less extubation failures in preterm infants randomized to NIPPV compared with nCPAP after extubation. However, limited data on longer term outcomes like bronchopulmonary dysplasia (BPD) or death are available. The objective of this study was to update an existing Cochrane systematic review (Davis et al 2004), including data from the NIPPV international randomized controlled trial (RCT) to compare the effect of NIPPV versus nCPAP, on BPD, death and extubation failure. Patients and
Methods: We searched MEDLINE (MeSH terms: Infant, Newborn (exp) and intermittent positive-pressure ventilation (1966- March 2013), Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL. Additional information was obtained from trial authors. Inclusion criteria were RCTs enrolling ventilated preterm infants being extubated. Interventions compared were NIPPV and nCPAP - both delivered by short nasal prongs, nasopharyngeal tube or nasal mask. Outcomes assessed were BPD (oxygen requirement at 36 weeks post-menstrual age), death prior to discharge, and extubation failure within 48h to 7 days, gastrointestinal complications and air leaks.
Result: 8 trials enrolling 1280 infants met inclusion criteria. No advantage of NIPPV over nCPAP was seen for either BPD [RR 0.97 (95%CI 0.83-1.14)] or death [RR 0.82 (95%CI 0.54-1.22)]. Infants randomized to NIPPV had less extubation failures needing reintubation [RR 0.76 (95%CI 0.65-0.88)]. No increased risk of NEC [RR 0.90 (95%CI 0.66-1.24)] or GI perforation [RR 0.97 (95%CI 0.61-1.54)] were observed. Less air leaks were observed in infants treated with NIPPV [RR 0.50 (95%CI 0.28-0.89)].
Conclusions: For premature infants who receive non-invasive respiratory support after extubation, current devices providing NIPPV do not confer additional long-term benefit when compared to nCPAP. However less extubation failures within the first week of life are observed. Infants managed with NIPPV have less air leaks and similar rates of gastrointestinal side effects.

RESPIRATORY BEHAVIOR OF VERY PRETERM INFANTS RECEIVING NASAL CPAP OR NON-SYNCHRONIZED NIPPV DURING THE POST-EXTUBATION PERIOD

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Introduction: Very preterm infants require endotracheal tube mechanical ventilation (ETT-MV) during their first few days of life. These infants are quickly weaned from ETT-MV and extubated to some type of noninvasive ventilatory support; usually Nasal Continuous Positive Airway Pressure (CPAP) or non-synchronized Nasal Intermittent Positive Pressure Ventilation (NIPPV). At present, there is no evidence to select one mode over another. The aim of this study was to compare nasal CPAP and NIPPV by evaluating the respiratory behavior of infants during the immediate post-extubation period, using novel automated techniques.
Patients & Methods: An observational study was conducted in two Neonatal Intensive Care Units of the McGill University Health Centre after approval from the research ethics board. Written informed consent was obtained from parents. Inclusion criteria: very preterm infants with gestational age (GA) <= 32 weeks and birth weight (BW) <= 1250g, under ETT-MV undergoing their first extubation attempt. Exclusion criteria: major congenital anomalies or neuromuscular disease. Guidelines for extubation readiness and re-intubation were provided, but the decision to extubate and the choice of post-extubation support was made by the attending physician. In all infants, data were collected during each of the 3 phases (Ph): PhI = 30-45min post-extubation; PhII = 12-24hr post-extubation; and PhIII = 48-72hr post-extubation. For each phase, the 3 modes of non-invasive support were applied in a random order for 45 minutes each: CPAP, NIPPV at a rate of 20 (NIPPV20) and 40 (NIPPV40) breaths/minute. Respiratory movements of the ribcage and abdomen were measured with Respiratory Inductance Plethysmography (sampled at 1kHz) and recorded using PowerLab software on a computer for subsequent analysis. The respiratory signals were analyzed with an Automated Unsupervised Respiratory Event Analysis system (AUREA), which extracts metrics that provide sample-by-sample measures of frequency, amplitude, and thoraco-abdominal asynchrony. These metrics are then used to classify the respiratory state into pause, movement artifact, synchronous and asynchronous breathing. The probability distributions of the metrics were characterized using their skewness, median, mode and kurtosis. The state features were the duration, frequency, and density of each state. The Wilcoxon rank sum test was used to evaluate significant differences between modalities ($p<0.05$). Linear logistic regression and nonlinear AdaBoost classifiers were used to distinguish between the modalities.
Results: A total of 15 patients were included in the study, with baseline characteristics: BW 842.7±197.9 grams, GA 26.5±1.6 weeks. Data were collected from 15 patients in PhI, 10 in PhII and 5 in PhIII. There were no significant differences in any of the features defined by the metrics or in the state features between CPAP and NIPPV20, NIPPV40. Furthermore, classification attempts using logistic regression and AdaBoost were no better than chance.
Conclusions: There were no significant differences in the respiratory behavior of very preterm infants under CPAP, NIPPV20 or NIPPV40 during the post-extubation period. Based on the computed features, there was no advantage in selecting one non-invasive support over another. Thus, the choice of which mode to use remains to be clarified in future clinical studies.

CONTINUOUS POSITIVE AIRWAY PRESSURE AS THE FIRST TREATMENT CHOICE FOR RESPIRATORY DISTRESS IN PRETERM INFANTS - A POPULATION BASED STUDY.

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Introduction: Continuous positive airway pressure (CPAP) in one of the first treatment choices for respiratory distress in preterm infants. However, CPAP in not always successful and some infants with respiratory distress syndrome (RDS), managed with CPAP without surfactant therapy, develop pneumothorax. Objectives. To (1) evaluate the development in respiratory assistance for preterm infants in Iceland for the past 20 years and to (2) find predictors for failure of CPAP therapy and the development of pneumothorax during CPAP therapy.
Methods: This was a retrospective study including all preterm infants admitted to the NICU at Children's Hospital Iceland (the only level II-III NICU in the country) from 1993-2012 diagnosed with respiratory distress syndrome or wet lungs. Of those, two groups of infants were selected: 1) 40 preterm infants who were initially managed with CPAP but subsequently required mechanical ventilation. 2) All infants who developed pneumothorax during CPAP therapy during the study period (n=17). For each infant in the first group, one infant was selected as a control and two in the second group. The controls received treatment with CPAP solely and did not develop pneumothorax. Cases and controls were matched on gestational age, birth weight and year of birth. Pre-, peri- and postnatal clinical data were selected on cases and controls.
Results: Administration of CPAP increased significantly during the study period with a corresponding decrease in mechanical ventilation and surfactant therapy. RDS proved to be the only independent risk factor for both CPAP failure and pneumothorax. Both case groups were found to have a significantly higher oxygen requirement in the first hours post partum than controls, but pCO2 was similar between cases and controls.
Conclusions: CPAP therapy is associated with decreased need for mechanical ventilation and surfactant therapy. Nevertheless, most extremely low birth weight infants require mechanical ventilation. RDS appears to be the primary risk factor for both CPAP failure and the development of pneumothorax in this population of infants. Infants who fail CPAP therapy and therefore require mechanical ventilation do so primarily due to type I, but not type II, respiratory failure.

EARLY (PROPHYLACTIC) SURFACTANT AT DELIVERY DOES NOT IMPROVE OUTCOME IN VERY LOW BIRTH WEIGHT INFANTS

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Introduction: The effect of early and prophylactic surfactant treatment is still uncertain. Invasive instillation of surfactant in very premature infants could destabilize the infant during the fragile period immediately after birth. Patients and
Methods: The effect of surfactant treatment on short time pulmonary outcome was studied retrospectively in infants with birth weight < 1500 grams treated at St. Olavs University Hospital during the period 1.1.2001 to 31.12.2010. Infants with major malformations were excluded from the study. Data on timing of surfactant treatment and FiO2 levels before and after treatment were obtained from patient records. Poractant alfa (Curosurf) in a dose of 100 mg/kg was standard treatment during the whole study period.
Results: Of total of 472 infants included in the study, 235 infants (49.8%) with a birth weight of 912 ± 271 grams and gestational age 26.5 ± 2.1 weeks were treated with surfactant. The treatment frequency remained stable during the study period. Thirty of the treated infants later died. The incidence of prenatal steroid treatment to the mother was as high as 97.4%, this parameter was therefore not included in the data analysis. Of treated infants, 67.4% were given prophylactic surfactant in the delivery room shortly after delivery, and at an increasing frequency with lower gestational age. Of infants with a gestational age = 26 weeks 87.2% of the infants were given surfactant in the delivery room. Infants were given on average 1.5 ± 0.7 treatments. Only 38.7% of infants received two treatments and 8,5% received three treatments or more . Between 5-15% of infants did not respond to surfactant treatment defined as a need of FiO2 > 0.6 at twelve hours after treatment. The effect of early, prophylactic treatment compared to later rescue treatment in the NICU was studied in a subsets of infants with gestational age = 27 weeks. Of these, fifty-seven infants with gestational age 27.8 ± 1,0 weeks and birth weight 1 047 ± 239 grams given prophylactic surfactant were compared with 62 infants with gestational age 28.7 ± 1,2 weeks and birth weight 1 119 ± 199 grams given rescue treatment only. These infants had comparable birth weights (p=0.78), but the small difference in gestational age was still significant (p < 0,001). No significant differences in FiO2 before treatment or 30 minutes and 12 hours after treatment could be seen between the groups neither after the first nor the second treatment course. Furthermore, the incidence of a second treatment was similar between the groups (33,3% versus 35.4%), and no difference in time latency between the first and a second dose (17 ±14 hours versus 23 ± 17 hours) was seen. Furthermore, days on ventilator or CPAP and days with oxygen supplementation or mortality did not differ between the groups.
Conclusions: The study shows that approximately 50% of infants with a birth weight < 1 500 grams need treatment with surfactant. Furthermore, prophylactic treatment in the delivery room does not result in better pulmonary function or less need for follow-up treatment than later rescue treatment.

SURFACTANT INADVERTENT LOSS USING FEEDING CATHETERS OR ENDOTRACHEAL TUBES

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Background: Surfactant has been administered through various types of endotracheal tubes and also under spontaneous breathing using feeding catheters. Recently, this has been advocated to be a less invasive technique as compared to the classical endotracheal intubation and a specific RCT showed promising results using this method. [1] Ideal surfactant administration technique has not been clearly defined. We asked if different tube diameters and temperature may affect the amount of surfactant effectively delivered to the lungs, taking into account also at least one insufflation after the surfactant bolus. Methods. We designed a bench study using high accuracy, legal balance and tube/catheters of different diameters. 200 mg poractant-alfa were injected into the tubes followed by 2.5 mL air boluses. Experiments were performed in triplicate, both at room temperature and in a incubator chamber at 37°C. Phospholipid concentration remaining in the tube was calculated.
Results: Surfactant lost into thin catheters (11+-0.4%) is more than that in endotracheal tubes (diameter 2.0: 3.6+-1.4%; diameter 2.5: 3.7+-0.2%; diameter 3:5: 2+-0.4%; $p<0.001$ at Dunnet post-hoc test in each comparison against the thin catheter). Similar findings were found at 37°C (tube 2: 3.4+-0.4%; tube 2.5: 3.8+-0.2%; tube 3: 3.6+-0.4%; feeding tube: 11.5+-0.6%; $p<0.001$ same test as above). In terms of lost phospholipids, 23+-0.8 mg were lost in the feeding tubes; 7.2+-2.9 mg were lost in tubes of 2.0 diameter, 7.4+-0.4 mg in tubes of 2.5 diameter and 10.3+-0.9 mg in diameter 3 tubes ($p<0.001$ in each post-hoc comparison against the feeding tube at the Dunnet test).
Conclusions: Surfactant loss using thin catheters is around 2-3 times higher than using common endotracheal tubes: on average 20 mg phospholipids (11% of the administered dose) are lost. This loss may be even increased since endotracheal tubes may be used to provide ventilation for some minutes after the surfactant bolus, while feeding tubes must be removed. These data may be useful to refine surfactant dosing and are preliminary to further lab and animal studies in order to find the best way to administer surfactant bolus in premies.

PROPHYLACTIC INTUBATION AND SURFACTANT VS PROPHYLACTIC BUBBLE-NCPAP AND SELECTIVE SURFACTANT AT 2-4 HOURS OF AGE IN PRETERM INFANTS OF 23+0-29+6 WEEKS GESTATION (GA)

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Background: NCPAP started soon after birth appears to reduce BPD/death and is an alternative to the prophylactic or early surfactant approach. Trials of early surfactant in addition to the early CPAP strategy show mixed results. Studies that explore when to best give surfactant in patients on NCPAP are lacking. Aim: To compare prophylactic intubation and surfactant with brief ventilation vs. prophylactic Bubble-NCPAP and early selective surfactant at 2-4 hours of age.
Methods: Retrospective matched-pair cohort analysis of surviving preterm infants 23+0 - 29+6 GA born in a single tertiary centre between 2006 and 2012. Patients with congenital anomalies were excluded. Patients included were grouped according to whether they were intubated at birth (<1 hour) and received surfactant (100 mg/kg/dose) (IN+SURF) or received prophylactic Bubble-NCPAP (8 cmH2O) followed by early selective surfactant (200 mg/kg/dose) between 2-4 hours of life (CPAP±SURF), if FiO2 >0.4, pCO2 >8.5kPa, pH <7.2 or frequent apnoeas and/or bradycardias present. Groups were matched for premature prolonged ruptured membranes (PPROM), antenatal steroids (AS), GA, birth weight (BW), male gender (MALE) and plurality (SINGLETON). Outcome measures were: Surfactant doses (SURF), length of ventilation (MV), length of non-invasive respiratory support (NIRSup), pneumothoraces (PNEU), and oxygen at 36 weeks corrected gestational age (BPD). Qualitative data were analyzed using Chi-Square- and quantitative data using Mann-Whitney-test. P<0.05 was considered significant. Data are displayed as median and 25th-75th quartile range (IQR) or ratio (n/N) and percentage (%).
Result: 222 patients were included. There was no significant difference in the baseline characteristics between the two groups (CPAP±SURF N=106 vs. IN+SURF N=116): PPROM, 33/106 (31%) vs. 33/116 (28%), p=0.77; AS 100/106 (94%) vs. 102/116 (88%), p=0.11; GA 28 (27-29) vs. 27 (26-28), p=0.1; BW 1105 (930-1279) vs. 1113 (936-1270), p=0.84; MALE 66/106 (62%) vs. 65/116 (56%), p=0.41; SINGLETON 69/106 (65%) vs. 80/116 (69%), p=0.57. With regard to outcome measures a significant difference in the number of surfactant doses, length of invasive and non-invasive respiratory support and BPD was noted. Patients receiving prophylactic NCPAP and early selective surfactant had less surfactant doses (37/106 [35%] vs. 116/116 [100%], p<0.001), were ventilated for a shorter period (1 [0-5] vs. 3 [1-9] days, p<0.001), spent less time on non-invasive respiratory support (8 [5-23] vs. 20 [5-49] days, p=0.01) and had a lower BPD rate (22/106 [23%] vs. 41/116 [38%], p=0.03). No significant difference was found with regard to pneumothoraces (6/106 [6%] vs. 8/116 [7%], p=0.79).
Conclusions: In infants born between 23-29 weeks gestation prophylactic Bubble-NCPAP and early selective Surfactant between 2-4 hours of life seems to reduce the need for intubation & surfactant (35%), length of mechanical ventilation (1 day), non-invasive respiratory support (8 days) and risk of BPD (23%). These results are comparable to the CURPAP- or COIN-trial, where the median age for surfactant administration in the NCPAP group was 4.0 vs. 6.6 hours, the rate of surfactant administration was 49% vs. 38%, the length of mechanical ventilation was 5 vs. 3 days and the BPD rate was 22% vs. 29%.

CAN OPTIFLOW DELIVER HIGH FLOW NASAL CANNULAE OXYGEN FLOW EFFECTIVELY?

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Introduction: The use of Humidified High Flow Nasal Cannulae Oxygen (HHFNO) as a form of respiratory support has gained widespread acceptance by Neonatal Units. At present in the UK two delivery systems have the majority of use, Optiflow (Fischer and Paykel, NZ) and Pricision flow (Vapotherm, US). Previous reports by Lampland et al 1 suggest the Optiflow system is unable to deliver flow rates in excess of 2L/min via neonatal cannulae, thus limiting its effectiveness. As our experience with the Optiflow device is contrary to this suggestion, we tested the flow rate delivered by Optiflow.
Method: The basis of our study was to use the flow of two gases to create a flow calibration curve by using an incubator as the reservoir for the two gases. We used air at a constant flow rate (4 L/min) and oxygen via a standard flowmeter at variable rate from 1 to 8 L/min and created a reference curve. Steady state was achieved at 15 minutes. We then used the Optiflow circuit and recreated the calibration curve with flow ranging from 1 to 6 L/min. Three readings were obtained at each flow rate of oxygen and their means were plotted.
Results: The oxygen concentration rose linearly with the increase in flow rate. This relationship was still true when the Optiflow circuit was used. The two graphs superimposed with close agreement. This suggests that Optiflow is able to deliver the set flow of humidified oxygen to the recommended limits of the smallest neonatal cannulae. Discussion - The study by Lampland et al measured flow directly at the end of the nasal catheter by attaching a flowmeter. We question whether application of a tightly fitted flowmeter significantly increases resistance, thus raising circuit pressure beyond the safety blow-off valve limits. With our study we have showed conclusively that Optiflow can effectively deliver flow rate of upto 6 L/min as per the manufacturer's instructions.
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PATIENT COMFORT DURING TREATMENT WITH HIGH FLOW NASAL CANNULA VERSUS NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE: A RANDOMISED CROSSOVER TRIAL

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Introduction/Background: The use of high flow nasal cannula (HFNC) for respiratory support of preterm neonates has rapidly expanded. The presumed benefit of HFNC versus nasal continuous positive airway pressure (NCPAP) is increased patient comfort, but evidence for this is limited. Our objective was to compare patient comfort in preterm infants treated with HFNC versus NCPAP.
Patients and Methods: Preterm infants, < 34 weeks postmenstrual age, deemed respiratory stable on NCPAP were eligible for inclusion in a randomised crossover trial. After parental consent, 2 x 24 h of treatment with NCPAP or HFNC was initiated in random order. The primary outcome was patient comfort, assessed by a validated neonatal pain and comfort scale (EDIN-score). Secondary outcomes were salivary cortisol, surrounding noise level, parental satisfaction and respiratory parameters (respiratory rate, FiO2, SpO2, TcPCO2).
Result: Twenty-four infants were included. Four were later excluded; 3 due to missing data and 1 due to parents refusing to put the baby back on NCPAP after 24 h HFNC. Mean (SD) birth weight was 1236 (278) g, gestational age was 29.3 (1.7) weeks and postnatal age at trial entry was 10 (12) days. Mean (SD) cumulative 24 h-EDIN score was 10.4 (3.0) in the HFNC-arm and 10.9 (3.2) in the CPAP-arm (p 0.61). Mean (SD) surrounding noise was 74 (7) dB during NCPAP and 70 (10) dB during HFNC (p 0.18). During HFNC, parents reported that their child was more satisfied (p 0.002) and that they had improved contact with their child (p< 0.001). There were no significant differences in salivary cortisol or respiratory parameters during the 2 x 24 h study period.Conclusion(s): Using EDIN-score, we could not document improved patient comfort with HFNC versus NCPAP. However, parents clearly preferred HFNC. Respiratory parameters were similar in NCPAP and HFNC.

NEW MODES OF RESPIRATORY SUPPORT FOR PRETERM INFANTS: HAVE ASSOCIATED OUTCOMES IMPROVED?

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Background: In common with many neonatal units, St George's NICU has recently seen the introduction of new modes of non invasive respiratory support for preterm infants: biphasic infant flow nasal continous airway pressure (Biphasic) and humidified high flow nasal oxygen therapy (Vapotherm). Their introduction has occurred despite the lack of large scale trials defining their short and long term benefits over CPAP. We recently observed a concerning increase in ROP requiring lazer therapy (12 cases in 2012 compared to a previous maximum of 7 cases in 2006). A recent change in NICU practice included the introduction of Biphasic and Vapotherm respiratory support post extubation. We reviewed associated outcomes as we were concerned that hyperoxia may be a result of increased partial pressures and/or flow.
Methods: Outcomes for 992 infants born at or below 30 weeks gestation over the previous 9 years were reviewed. St George's NICU is a tertiary unit caring for medical & surgical infants from a multi ethnic London population. Three epochs of post extubation respiratory support were compared: (1) CPAP (2004-2009); (2) Biphasic (2009-2010); (3) Biphasic/ Vapotherm (2011-2012). Biphasic became the predominant mode of post extubation support in 2009. Vapotherm and Biphasic were used post extubation from 2011.
Result: The number of admissions at or below 30 weeks GA during each epoch were: CPAP: 512, Biphasic: 255, Biphasic/ Vapotherm: 225. Admissions <25 w/ [30 w or below]: (15%, 18%, 22%). CLD at 36 w cGA remained unchanged (33%, 29%, 33%). IVH > grade 2/3 decreased over time (12%, 9%, 4% p=0.002). There was a significant decrease in medical treatment of PDA's over time (18%, 8%, 1%, p <0.0001) with PDA ligation rates decreasing (4%, 3%, 1%, p=0.08). Pneumothoraces decreased in the Biphasic/ Vapotherm epoch (5%, 5%, 3%, p 0.008). Mortality increased during the Vapotherm/ Biphasic epoch (8%, 8%, 12% p=0.3), as did ROP >/= grade 2 (5%, 3%, 12%, p=0.003) and ROP requiring lazer (3%, 1%, 6%, p=0.03). Surgical NEC was unchanged (2%, 3%, 2%). Discussion: The introduction of Biphasic and Vapotherm saw an associated decrease in the rates of severe IVH's and PDA treatment. CLD and surgical NEC remained unchanged. An increase in mortality and ROP was observed over one year during the biphasic/ vapotherm epoch. This may be partially explained by the increase in proportion of infants admitted < 25 w GA. This increase iin mortality was within the London network average (1). The only reported RCT comparing Biphasic and CPAP (stopped early due to recruitment shortages) reported a significant increase in ROP with Biphasic support (2). We observed an increase in ROP during the Biphasic/ Vapotherm epoch but not during the Biphasic epoch. ROP and other adverse events have not been evalauted for Vapotherm (3) or Biphasic support.
Conclusions: The short and long term benefits and safety of Biphasic and Vapotherm respiratory support in preterm infants need to be established in large scale clinical trials.
References: 1. London Perinatal Networks Annual Report 2010-11. 2. O'Brien et al. BMC Pediatrics 2012, 12. 3. Manley et al. Neonatology 2012; 102.

A RANDOMISED CROSS-OVER TRIAL OF ALGORITHM-GUIDED VERSUS ROUTINE NURSE OXYGEN THERAPY MANAGEMENT FOR PRETERM INFANTS

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Background: Oxygen therapy management for preterm infants involve utilising a strategy of maintaining oxygen saturation levels (SpO2) within a defined range, so-called oxygen saturation targetting. The NICU nurse is the main personnel involved in the control of oxygen therapy for these infants. Nurse training often emphasise the avoidance of hyperoxia, to reduce ROP risk, for example in the Vermont-Oxford's 'Breathsavers' guidelines for oxygen management. We developed an algorithm based on those guidelines (which also mirrors the nursing practise in our Level III NICU). Our aim was to compare the proportion of time spent within SpO2 target range during algorithm-based management of oxygen delivery versus routine nursing care.
Method: SpO2 during routine nursing care was compared with algorithm-based care (administered by a dedicated research nurse) for 2-4hrs period in a randomised crossover trial. The SpO2 target(88-92%) and pulse oximeter alarm limits(86-94%) were identical in both arms. Infants <32 weeks gestation were eligible if having >8 desaturations episodes(<85%) per 4 hrs while receiving CPAP or SIMV via the Draeger Babylog 8000+ ventolator. Data was recorded via Powerlab system from Masimo oximeters and Babylog 8000+ ventilators. Desaturation severity index (DSI) was calculated using the AUC method.
Result: 16 infants; mean (±SD) gestation 26.7(±1.3) weeks and birthweight 901.2(±192.9) grams were studied at mean postmenstrual age (PMA) of 30.5(±2.4) weeks. Time within target range was 34.6(±28.5)% during routine nursing care versus 38.3(±29.3) during algorithm-based care; p=0.23. Compliance with alarm limits was 58.4(±21.8)% during routine care versus 64.7(±22.1)% during algorithm-based care, p=0.091. The algorithm control protocol did not significantly alter median (range) desaturation frequency (<86%: 23.1 (12.8-25.8) vs. 17.1 (7.7-27.1), p=0.6) and episode severity (DSI<86%: 0.73 (0.13-1.13) vs. 0.57 (0.16-1.01), p=0.98) or number of FIO2 adjustment; 1.0 (0.0-4.1) vs. 1.7 (0.7-3.6) p=0.95.
Conclusions: In our NICU, the time spent within SpO2 target and alarm limits was not significantly different between routine nurse and algorithm-guided oxygen management. Infants experiencing frequent desaturations may require a faster response time than advocated by the 'Breathsavers' guidelines to prevent prolonged hypoxia or hyperoxia.

THE PROSEAL LARYNGEAL MASK AIRWAY IN PEDIATRIC PATIENTS UNDERGOING ELECTIVE GENITOURINARY SURGERY

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Introduction: The ProSeal Laryngeal Mask Airway (PLMA) is an airway device that differs from the standard LMA in a gastric drainage lumen and absent aperture bars. In pediatrics it is reported to provide a more effective seal with the ability to evacuate the stomach, thus it has been used for patients in whom intermittent positive pressure ventilation is desired(1). It has also been reported to be more difficult to insert than the traditional LMA. We report our experience with 250 patients aged 2 months to 8 years undergoing genitourinary surgery.
Methods: Data were collected prospectively with IRB approval. At the time of insertion, the following data were noted: induction agent, number of attempts, placement success or failure, PLMA size, ventilatory pattern, gastric suction tube placement success or failure. Cuffs were inflated to the maximum volume recommended by the manufacturer or to an intracuff pressure of 60 cm H2O.
Result: Patients were induced with sevoflurane in a mixture of air/O2 or IV propofol; none received muscle relaxant. Intravenous fenatnyl 1-2 mcg/kg was administered All patients had the PLMA successfully placed by the primary investigator as judged by endtidal CO2, bilateral chest movement, and ability to successfully pass a gastric suction catheter via the drainage lumen. 22 patients required 2 attempts to achieve successful placement (91.2 % success rate on first attempt). 5 patient required removal of the device prior to the completion of the procedure. Procedures included herniorrhaphy, orchidopexy, cystoscopy, vaginal and/or rectal exam. Patients were positioned in supine or lateral position; all positions were well tolerated. IPPV was used in all children. Each PLMA was removed with the patient awake. 2 patiens had laryngospasm, 12 patients evidence of traumatic placement (blood on PLMA)
Conclusions: We found that the PLMA is easily placed with a higher 1st attempt success rate in children. Although used with IPPV, the PLMA's higher leak pressure suggests that it may be a useful alternative to endotracheal intubation for procedures in which IPPV is desired in pediatric patients
References: 1. Zhang X et al. The ProSeal Laryngeal Mask Airway is more effective than the LMA-Classic in pediatric anesthesia: a meta-analysis. J Clin Anesth. 2012 Dec;24(8):639-46

DURATION OF WEANING PREMATURE INFANTS FROM CPAP - SINGLE INSTITUTIONAL DATA

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Background: The practice of weaning premature infants from continuous positive airway pressure (CPAP) varies considerably between neonatal units, as the best approach is still a matter of research and debate. Generally, it seems beneficial to stop CPAP as early as possible. Using fixed stability and failure criteria, discontinuing CPAP with a clear intention to stay OFF appears superior to cycling CPAP ON/OFF. Though, there is a lack of information on the duration of weaning outside of clinical trials. We therefore retrospectively analysed the duration of weaning from CPAP in our institution. Patients and
Methods: We performed a retrospective chart review of all premature infants, who had CPAP as primary or secondary treatment within the year 2010. Infants with major malformations or severe limiting diseases were excluded. During the study period our unit did not have a written weaning protocol. However, there was a general approach that consisted of gradually reducing CPAP to 3-4 cm H2O followed by cycling CPAP ON/OFF. Irrespective of the need of supplemental oxygen, a nasal cannula with a flow rate of 1-(2) l/min was employed in times OFF CPAP. Decision making was at the individual nurses' and or physician's discretion. Infants were considered as successfully weaned from CPAP, once they were 72 hours without CPAP.
Results: During the 12 month review period 65 premature infants had CPAP primarily or following mechanical ventilation. In 36 infants <32 weeks gestational age (GA) (1) duration of CPAP was 23.9±25.6 days, (2) postmenstrual age (PMA) OFF CPAP was 32.4±2.1 weeks and (3) PMA OFF any respiratory support (CPAP and nasal cannula) was 33.3±2.8 weeks. In 29 premature infants =32 weeks GA (1) duration of CPAP was 1.7±1.5 days, (2) PMA OFF CPAP was 34.5±1.1 weeks and (3) PMA OFF any respiratory support was also 34.5±1.1 weeks. All results are expressed as mean±SD.
Conclusion: We present information on the duration of weaning premature infants from CPAP in clinical routine outside of trials. These data also reveal the time of weaning when a non-standardised approach is used, that is primarily based on individual decisions of the caregivers. PMA OFF CPAP observed in our institution appears higher when compared to the lowest PMA OFF CPAP achievable as published in randomised controlled trials. Currently, we are implementing a standardised weaning protocol in our institution. The data obtained in the present study will serve as baseline values. Because of the small sample size and the retrospective nature of our results, they need to be interpreted with caution.

NEONATAL OUTCOME AND PROGNOSTIC EVALUATION OF CEREBRAL ULTRASOUND IN PRETERM INFANTS.

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Background: Cerebral ultrasonography (CUS) performed by trained neonatologists is an excellent tool for the early detection of major brain lesions in preterm neonates. Limitations exist in the evaluation and significance of minor CUS abnormalities such as isolated cerebral hyper echogenicities (CHE). Aim: To evaluate significance and prognostic value of CUS minor abnormalities in a cohort of preterm infants. Materials and
Methods: 129 newborns of gestational age <= 32 weeks and birth weight <= 1500 gr, admitted in the Neonatal Intensive Care Unit of Siena between January 2008 and May 2010, were consecutively enrolled in our follow up study. Newborns with major congenital malformations and/or genetic syndromes or lost to follow-up and newborns with severe motor handicap were excluded from the study. 71 children completed the follow-up period. CUS protocol included the evaluation at 1, 3, 7, 10, 14, 21 30 days. Neurodevelopmental follow-up was performed at 30 months of postmenstrual-age using the Bayley Scales of Infant and Toddler Development-III (BSID-IIIed), consisting of five specific patterns: Cognitive (CS), Language (LS), Motor (MS), Social-Emotional (SES) and Adaptive Behavior (ABS) Scales. Statistical analysis was performed using univariate ANOVA and the Mann-Whitney test.
Result: No babies showed severe disability at 30 months. Bayley Scales patterns: LS (96.15 ± 9.05), MS (102.02±6.2), CS (99.88 ±7,03), SES (100.56 ±6.4) and ABS (100.74±6.52), were in the normal range. ANOVA univariate analysis revealed that severe abnormal CUS, (periventricular leucomalacia, intraventricular hemorrhage, post-hemorrhagic ventricular dilatation) significantly reduced LS (p=0.001, p=0.009, p=0.027, respectively), MS (p=0.000, p=0.001, p=0.038, respectively), CS (p=0.000, p=0.000, p=0.008, respectively), SES (p=0.000, p=0.000, p=0.014, respectively), ABS (p=0.000, p=0.000, p=0.014, respectively) scores. Isolated CHE did not influence LS, MS, CS, SES, ABS scores, but parietal localizations were significantly associated with a poor CS (p=0.047) and MS (p=0.012) scores. Babies with periventricular hyperechogenicities showed a lower CS score (p=0.034) than those without.
Conclusions: Parietal and periventricular CHE are significantly associated with a poor outcome at 30 months of age. CUS monitoring of these lesions for at least 4 weeks seems to be mandatory to evaluate their prognostic significance. Larger studies are needed to confirm these results.

CRANIAL ULTRASOUND FINDINGS IN VERY LOW BIRTH WEIGHT NEWBORNS: EXPERIENCE FROM ARMENIA

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Background and aims:: to evaluate the usefulness and feasibility of performing cranial ultrasound scans (cUS) on very low birth weight (VLBW) infants in resource limited neonatal units.
Methods: VLBW newborns of <32 weeks gestation or BW <1500 g admitted between February-December 2012 to the two neonatal intensive care units (NICU) in Yerevan, were studied prospectively with serial cUS. The scans were performed according a protocol (soon after admission, at 2-3 weeks, at discharge and term age) using a hand portable machine and stored in digital format.The scans were assessed for normal anatomy, ventricular size, haemorrhage, intraparenchymal lesions, focal or diffuse increased white matter echogenicity, subependymal cysts , independent of germinal matrix-intraventricular haemorrhage, lenticulostriate vasculopathy, cerebellar and any other abnormalities.
Result: Data from 320 scan series from 100 infants were analyzed by 2 authors (PM and FC) independently. Scan quality was good. The commonest findings were subependymal cysts in caudothalamic notch (SECs) (14%), bilateral (generally mild) periventricular white matter echodensity (PVE) persisting at term age (13%), grade III germinal matrix-intraventricular haemorrhage (GMH-IVH) 11%, haemorrhagic parenchymal infarction (8%), lenticulostriate vasculopathy (4%), no congenital abnormality was found.
Conclusions: our findings suggest that VLBW newborns in NICUs in our resource limited setting had more abnormalities detected with cUS than reported in other VLBW populations. The relatively high incidence of persistent PVE and also SECs may relate to the high incidence of infections in our population. Grade III GMH-IVH may be due to the high prevalence of neonatal respiratory disorders and the low rate of antenatal corticosteroids and postnatal vitamin K administration. Monitoring of cUS abnormalities may provide a useful measure of improvements in the quality of perinatal care.
Author Keywords: VLBW newborns, cranial ultrasound, supependymal cysts, periventricular white matter echodensity, germinal matrix-intraventricular haemorrhage.

LOW-GRADE INTRACRANIAL HEMORRHAGES OF PREMATURITY: IS ULTRASOUND GOOD ENOUGH?

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Background: Previous studies on effects of grade I-II germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) on neurodevelopmental outcomes of premature infants showed conflicting results. However, all these studies were based on ultrasound assessment of GMH-IVH. Despite cranial ultrasound (CUS) has become the primary modality to identify all degrees of GMH-IVH, small lesions may be missed when assessed with CUS. Similarly, cerebellar microhemorrhages (microCBH) may remain undetected by CUS. Since large studies focusing on cerebellar hemorrhage in preterm infants are based on CUS, incidence and prognosis of microCBH are still unknown. Magnetic resonance susceptibility-weighted imaging (SWI), a recently developed MRI sequence, is very sensitive in detecting small-sized cerebral hemorrhages.
Objective: To assess diagnostic accuracy of cranial ultrasonography (CUS) in detecting low-grade GMH-IVH (i.e. grade I and grade II according to Papile classification) and microCBH in consecutively admitted very low birth weight (VLBW) infants.
Methods: VLBW infants admitted at Gaslini Children's Hospital NICU between January and November 2012 underwent both serial CUS and SWI at term-equivalent age. CUS was performed at day 1, 2, 3 and 7 after birth and subsequently weekly until term-equivalent age. All CUS examinations were performed through the anterior and postero-lateral fontanel using a 8 Mhz convex probe (Aloka Prosound Alpha 7). Diagnostic accuracy of CUS in detecting low-grade GMH-IVH and microCBH was assessed in terms of sensitivity and specificity by comparing it to SWI, used as the gold-standard technique.
Results: Sixty VLBW infants were included in the study. Incidence of grade I-II GMH-IVH diagnosed by CUS was comparable to that reported in large multicenter studies. Sensitivity of CUS in detecting low-grade GMH-IVH was low (60%), whilst specificity was 100% when compared to SWI. None of the cerebellar microhemorrhages diagnosed by SWI (18.3 % of the population) was identified by CUS.
Conclusions: In the present study, CUS sensitivity proved to be surprisingly low, in contrast with specificity, in detecting grade I-II GMH-IVH. In other words, low-grade GMH-IVH may be underdiagnosed in VLBW infants when assessed exclusively with CUS. Furthermore, microCBH were not detectable by CUS. Therefore, we suggest that studies assessing the impact of both low-grade GMH-IVH and microCBH on neurodevelopmental outcome of VLBW should be based on MRI rather than CUS.

SERIAL LUMBAR PUNCTURE IN PRETERM INFANTS WITH POST-HAEMORRHAGIC VENTRICULAR DILATATION: EXPERIENCE IN AN OUTBORNE CENTRE.

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Background: Intraventricular haemorrhage (IVH) is a major complication of prematurity potentially leading to neonatal post-haemorrhagic ventricular dilatation (PHVD). PHVD may evolve, acutely or subacutely, to hydrocephalus requiring surgical treatment. Only in a minority of cases PHVD worsening may stop spontaneously, although increased risk of delayed PHVD at 3-6 months of life may persists. PHVD diagnosis is based on both clinical and sonographic signs. Among the sonographic diagnostic criteria, Levene's Ventricular Index (VI) represents a valid diagnostic tool to asses PHVD severity. Since surgical treatment of PHVD might be potentially associated with neurodevelopmental sequelae secondary to shunt placement procedures, alternative therapeutic strategies, such as serial lumbar punctures (LP) to drain cerebrospinal fluid in excess, have been suggested as conservative therapies. In the present case series we performed repeated LP in preterm neonates with PHVD with in the attempt to prevent surgical shunt placement.
Methods: Cerebral ultrasound was performed in all neonates at the admission. In case of VI <97° centile, ultrasound monitoring was performed every 48-72 hours. In the presence of VI >97° centile, serial LP were performed daily or further apart in time. Each lumbar puncture was always followed immediately after by ultrasound evaluation. If the VI was =97°centile +4 mm, external ventricular drainage was placed. Surgical treatment was also performed in the presence of 'rapidly progressing' PHVD, diagnosed according to either clinical signs (head circumeference increase >1.5-2 cm/week, bulging anterior fontanelle, splitting of sutures, signs of endocranial hypertension) or ultrasound findings (increased resistive index, 'ballooning' ventricular shape).
Result: Serial LP were performed in 11 neonates with PHVD. Mean gestational age and birth weight were 28 ± 5 weeks (25-33+1 weeks) and 1197 grams (570-1260 grams), respectively. The number of LP performed in each patient depended on both PHVD severity and worsening rapidity and ranged from 1 to 7. Shunt positioning was not necessary.in 6/11 (54,5 %) cases. Surgical shunt placement was required in 2 cases (18,2 %) due to ventricular rapid enlargement and in 3 cases (27,3 %) due to no response to repeated LP.
Conclusions: According to our experience, serial LP decreased the need for surgical shunt placement and had no side effects. We suggest that a conservative therapeutic approach to neonatal PHVD with serial LP might be considered to decrease the risk of neurodevelopmental sequelae linked to shunt placement procedures.

LONG-TERM NEURODEVELOPMENTAL OUTCOMES OF PRETERM INFANTS WITH POST HEMORRHAGIC HYDROCEPHALUS REQUIRING SURGERY

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Introduction: Post hemorrhagic hydrocephalus (PHH) is a major complication of severe intraventricular hemorrhage (IVH grade 3 and 4). PHH has significant effects on long term neurodevelopment outcomes. Previous studies have evaluated long term neurodevelopmental outcomes in small series or in a non-systematic manner in non-multidisciplinary clinic at =18 -24 months of age. However, long term neurodevelopmental outcome at 3 years of age in preterm infants with progressive PHH are still lacking. Objective: To study the long term growth and neurodevelopmental outcomes at 3 years of age in VLBW infants with severe intraventricular haemorrhage (IVH grade =3) and progressive post hemorrhagic hydrocephalus (PHH) who required surgical interventions.
Methods: In a retrospective cohort study, all surviving babies =1250 g birth weight admitted to NICU from 1990-2007 were eligible for follow-up assessment at 3 yrs corrected age (CA). Demographic and follow-up data were collected on all infants who required surgery (IVHS) and no surgery (IVHNS) groups. Neurodevelopmental impairment (NDI) was considered present if child had any of moderate to severe cerebral palsy (CP), cognitive delay (>2SD below the mean), blindness, or deafness. Baseline characteristics and outcomes were compared between the two groups by using chi-square tests for categorical variables and t-test for continuous variables. Logistic regression was used to determine the effect of significant variables and possible confounders.
Result: Of 2105 live born babies, 90/1759 who survived to discharge had IVH = III. IVHS (n=28) and IVHNS (n=48) groups had mean birth weight of 874 g (±191) and 823 g (±236) and mean gestational age of 26.1 (±1.5) and 25.7 (±1.7) weeks respectively. All maternal characteristics were similar between the groups. Infants in IVHS group had more grade IV IVH than IVHNS (p=0.049). Three years outcome data was available for 76 (86%) babies. IVHS group had higher rates of cerebral palsy (64%) vs. IVHNS (29%), (p=0.003) with no statistically significant difference in other disabilities and growth delay. In the regression model, for infants requiring surgery, the odds of moderate to severe CP were almost 4 times higher than those not requiring surgery (OR 3.82, 95% CI 1.32-11.08), after controlling for IVH grade and ROP.
Conclusions: Preterm infants with progressive post-hemorrhagic hydrocephalus who required surgery had more moderate to severe cerebral palsy but no difference in growth delay at three years of CA compared to preterm infant with severe intraventricular hemorrhage. The odds of moderate to severe CP was 3.82 (95% CI 1.32-11.08) higher for progressive PHH requiring surgery than for severe IVH not requiring surgery, after controlling for IVH grade and ROP

POST-HAEMORRHAGIC VENTRICULAR DILATATION IN PRETERM INFANTS: INTERVENTIONS AND OUTCOMES IN A UK NEUROSURGICAL CENTRE

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Background: Post-haemorrhagic ventricular dilatation (PHVD) in preterm infants is associated with significant subsequent morbidity and mortality. There is no current consensus regarding the optimal treatment approach for these babies, particularly with respect to the timing of neurosurgical intervention. Aims: To review our current management of PHVD, identifying factors associated with increased likelihood of neurosurgical intervention.
Methods: We reviewed the cranial ultrasound scans of all babies with PHVD with ventricular index (VI) above 97th centile in a regional neonatal/neurosurgical unit over a 3-yr period (January 2009-December 2012). We excluded infants with other causes of hydrocephalus (eg congenital abnormalities) or other causes of intracranial haemorrhage, or with VI below the 97th centile . We then divided infants into 1) those who required surveillance only, 2) those who required intervention, subdividing them into lumbar puncture (LP) only, LP and ventricular reservoir (VR) and LP, VR and ventriculo-peritoneal shunt (VPS).
Result: 62 infants (58% male) were identified over the 3-yr period with a median gestational age of 25+5 weeks (range 24+2-34+6weeks) and birth weight 790grams (range 500-2600grams). Of the 62 infants, 17 (27%) died before discharge, with intensive support withdrawn in most cases due to multiple severe complications of prematurity. The infants who died had a significantly lower birth weight centile (means of 25% vs 50% respectively, $p<0.001$). 31 infants (50%) were monitored with weekly VI measurement and twice-weekly head circumferences, until these parameters stabilised or improved. All infants needing intervention had VI>4mm above the 97th centile, compared to 19% on the observation group (of which 50% were had unilaterally dilated ventricle). The remaining 14 infants (22%) received intervention, with 5 requiring just LP (performed between 2 and 7 times/week) and 9 having repeated LP followed by VR insertion. Of the 9 infants who had a reservoir, 4 eventually had VPS inserted. The median age of reservoir insertion was 56 days (range 26-214 days) and median of shunt insertion was 92 days (64-112 days).
Conclusions: Our results support the current evidence that intraventricular haemorrhage with ventricular dilatation is associated with high mortality. Of the survivors with PHVD, 69% required no intervention. A significant number of infants who had an LP went on to have a VR inserted, however less than one third in whom intervention was carried out eventually had a VPS inserted. As well as for benchmarking practice, this data is useful for counselling parents with infants with PHVD on the likelihood of intervention and whether this will be temporary or long-term.

PRETERM INFANTS ARE AT RISK FOR IMPAIRED CEREBELLAR GROWTH: A PROSPECTIVE ULTRASOUND STUDY

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Introduction: Recent studies realized with magnetic resonance (MRI) showed impaired cerebellar growth in follow-up of preterm infants. Cerebellar injury may contribute to impaired motor, cognitive, language and behavioral dysfunction seen among this group. This study was designed to evaluate cerebellar growth in premature babies by ultrasound, a bedside imaging method.
Patients and Methods: Postnatal cerebellar growth, measured by transverse cerebellar diameter (TCD), was prospectively assessed in 88 consecutive preterm infants born = 32 weeks gestation. TCD was obtained via mastoid fontanelle (MF) ultrasound in a weekly basis, since the first week of life until 40 weeks post menstrual age (p.m.a.). Variables that could influence cerebellar growth, such as gestational age (GA), periventricular leukomalacia (PVL), peri-intraventricular hemorrhage (IVH), posterior fossa hemorrhage and intrauterine growth restriction (IUGR) were also evaluated.
Result: TCD could be measured by MF ultrasound in all patients. Cerebellar growth occurred linearly with postnatal age. At 40th p.m.a. week, TCD was smaller in IUGR group compared with no IUGR infants but their weekly cerebellar growth was similar. At term-equivalent age, cerebellar size was statistically influenced by PVL and IVH severity, and fossa posterior hemorrhage.
Conclusions: TCD measured by MF ultrasound has demonstrated to be a bedside reproducible method for measuring the cerebellum in preterm babies. Impaired cerebellar growth seems to be influenced by other variables as suggested by MRI studies. IUGR infant's cerebellum was smaller than no IUGR infant's cerebellum maybe due to their smaller global size. We suggest that preterm cerebellum should be studied at-term equivalent age using MF ultrasound.

PERSISTENT PERIVENTRICULAR FLARES ARE NOT RELATED TO SMALLER BRAINS AT TERM-EQUIVALENT AGE IN VERY PRETERM INFANTS

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Introduction: Periventricular white matter is particularly vulnerable to injury in very preterm infants. Nowadays cystic periventricular leukomalacia (cPVL) is a relatively rare entity, and non-cystic white matter injury or non-cystic PVL (ncPVL) is by far the commonest "lesion" affecting the preterm brain. Some authors argue that ncPVL can be identified from cUS when there is a persistence of periventricular flares, but there is no clear consensus about the intensity or duration of periventricular flares that should be considered significant or whether there is any reliable correlate of ncPVL on cUS at TEA.
Methods:A cohort of preterm infants of <32 weeks gestational age (GA) was prospectively and serially assessed with cUS. ncPVL was defined as periventricular white matter echogenicity comparable to the adjacent choroid plexus persisting for at least 3 weeks after birth and seen on two scans at least two weeks apart after the first post-natal week. Infants who developed major cerebral lesions were excluded. The infants were also scanned at TEA for the estimation of brain size using a previously described three-dimensional model (Graca AM et al. Early Hum Dev 2013 2013; 89(9):643-8) and for measurements of ventricular dimensions, corpus callosum (CC) length/thickness, central grey matter width and head circumference (HC). The dimensions were compared between those with/without ncPVL. We also evaluated the reliability of intra/inter-observer agreement for detection of ncPVL using kappa statistic.
Results: 63 consecutive and serially scanned very preterm infants were without major lesions, 28% of whom had persistent periventricular flare (ncPVL). No significant differences were found between those with/without ncPVL for birthweight, birth HC, GA, gender, SGA status, inotropes, PDA, culture-proven sepsis and NEC. Infants with ncPVL had significantly higher CRIB, lower 5-minute Apgar, more invasive ventilation and chronic lung disease. At TEA no significant differences were found for estimated brain volume, ventricular size, CC length/thickness or central grey matter width; infants with ncPVL had lower HC and estimated cranial volume at TEA (Table). Intra-observer reliability was moderate (kappa=0.51-0.56) and inter-observer reliability was poor (kappa=0.20-0.32) on repeated assessment of cUS diagnosis of significant flares blinded to the original data. Repeated assessments of dependent variables for each observer had similar results to the ones shown on the table.

Table – Comparison at TEA of head circumference, measured ventricular and cerebral structure dimensions and estimated cranial and cerebral volumes between very preterm infants with and without a diagnosis of ncPVL.

	ncPVL	Normal	p
Number	18	45	
PMA at scan	39.8 (1.3)	40.7 (1.4)	<0.04
Head circumference at TEA (cm) §,†	34.5 (2.2)	35.9 (1.7)	<0.02*
Cranial volume (cm^3) §§,†	384 (57)	428 (62)	<0.02#
Cerebral volume (cm^3) §§,†	327 (51)	351 (45)	NS
Lateral ventricle coronal area (cm^2) §,‡	0.34 (0.22)	0.31 (0.18)	NS
Thalamo-occipital distance (cm) §,†	2.1 (0.4)	2.0 (0.3)	NS
Corpus callosum length (cm) §,‡	4.7 (0.3)	4.9 (0.3)	NS
Corpus callosum thickness (mm) §,†	2.3 (0.4)	2.3 (0.3)	NS
Basal ganglia width (cm) §,†	4.2 (0.3)	4.3 (0.2)	NS

Values described as mean (SD); § Measured values; §§ Estimated values; † *t* test for independent samples; ‡ Mann-Whitney test; * Significant after correcting for PMA at scan; # Non-significant after correcting for PMA at scan

Conclusions: This study indicates that the cUS diagnosis of ncPVL using strict criteria should not be used as a predictor of lower brain growth detectable at TEA, given that infants with this diagnosis showed identical estimated cerebral size at TEA when compared to babies without ncPVL. Additionally, there was an unsatisfactory intra and inter-observer reliability, suggesting a degree of subjectivity in this cUS diagnosis despite the application of well-defined criteria.

CEREBELLAR VOLUMES AND COGNITIVE FUNCTION AT EARLY SCHOOL AGE AFTER INTRAUTERINE GROWTH RESTRICTION AND VERY PRETERM BIRTH

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Background: We have previously shown that children born very preterm after IUGR have an increased risk for cognitive impairment at early school age compared with children delivered very preterm for other reasons. Reduction in cerebellar volume has been associated with neuro-developmental impairment and cerebellar development may be particularly vulnerable to the consequences of restricted fetal growth. Objective: To evaluate the effects of intrauterine growth restriction (IUGR) with absent or reversed end-diastolic blood flow in the umbilical artery and very preterm birth on cerebellar volumes and cognitive function at 5 to 8 years of age.
Methods: We studied 24 children with IUGR born at a median of 26.9 gestational weeks (GWs) (range: 24-29 GWs) (PT-IUGR), 24 matched preterm appropriate-for-gestational age (PT-AGA) children, and 24 term AGA children (T-AGA) by measuring cerebellar volume using magnetic resonance imaging. Cognitive function was assessed by using the Wechsler Preschool and Primary Scale of Intelligence and the Wechsler Intelligence Scale for Children.
Result: The PT-IUGR group had a mean (SD) cerebellar white matter volume and cerebellar cortical volume of 24.4 (5.2) and 101.3 (10.2) cm3 respectively, compared with the PT-AGA group, which had cerebellar volumes of 26.0 (6.6) and 101.5 (13.9) cm3 (both NS), and the T-AGA group, which had volumes of 31.7 (9.1) and 105.1 (13.9) cm3 (P = .003 and NS), respectively. Boys in the PT-IUGR and the PT-AGA group respectively, had larger cerebellar cortical volumes than girls ($p<0.05$). There was no significant relationship between measured cerebellar volumes and either Verbal IQ, Performance IQ or Full Scale IQ.
Conclusions: Cerebellar volume is decreased at early school age following very preterm birth with no clear additional effect of IUGR. This effect is dependent on cerebellar white matter reduction with no differences observed in cerebellar cortical matter. Cognitive impairment following IUGR and very preterm birth is not related to persisting changes in cerebellar volume at early school age.

NEUROLOGICAL LONG TERM OUTCOME OF FETAL ISOLATED MILD VENTRICULOMEGALY.

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Introduction: Ventriculomegaly (VM) is a relatively common finding (0.3-1.5â€°) during fetal life. It may be either a sign of an underlying disorder or an isolated finding. Isolated VM is usually mild and often resolves spontaneously during fetal or postnatal life although, the pathophysiological mechanisms and potential detrimental effects on the developing brain, including long neurodevelopmental outcome, remain unclear and underinvesitgated. For these reasons, parental counseling is often not univocal. Aim: To evaluate the long term neurological outcome of babies diagnosed with mild isolated VM in utero, using two parent-completed questionnaires.
Methods: Sixteen fetuses with mild isolated VM at fetal ultrasound (US) (defined as ventricular atria 10-15 mm), confirmed by fetal brain Magnetic Resonance Imaging, were enrolled. At birth, all babies underwent cerebral US scan, brain MRI was performed in case of further suspected abnormality at US. Neonates with normal US or mild VM at US confirmed by MRI were enrolled (G1). Long term neurological outcome was evaluated with ASQ-3 (Ages & Stages Questionnaires Third Edition) at 36-48-54-60 months and CBCL (Child Beahviour Cecklist for Ages 1½ -5 years) questionnaires, filled out by families. G1 babies were compared with age-matched control children (G2). Specialist evaluation was offered to children with low ASQ score.
Result: Mild VM was confirmed postnatally in 5 out of 16 children; 3/16 showed mild asymmetry in lateral ventricles size without dilatation, 8 had normal cranial US. Two of 5 babies who underwent neonatal cerebral MRI were excluded for diagnosis of aqueductal stenosis. Fourteen babies in G1 group were compared with 33 controls in G2. The distribution of babies according to postnatal age at ASQ assessment was: 6 babies (G1/G2=2/4) at 36 months; 14 (4/10) at 48 months; 8 (2/6) at 54 months; 19 (6/13) at 60 months.The rate of babies with ASQ score below normal values was comparable in the two groups (G1: 2/14; G2: 4/33). Low ASQ scoring was mostly related to educational problems or bilingualism. A slight gross motor delay was reported at 48 months in one child belonging to G1: fetal VM was the only abnormal finding in the clinical history of this child. Internalizing problems were reported thanks to CBCL filled by the mother of a single child with normal ASQ score belonging to G1.
Discussion: Our study supports the use of parent completed questionnaires for cost-effective monitoring of this low-risk population. Preliminary results suggest a favorable outcome at 3-5 years in children with mild isolated VM. These findings, if confirmed in a larger population, could have a significant impact on prenatal counseling.

FETAL GROWTH RESTRICTION PREDISPOSES PRETERM CHILDREN TO SPECIFIC NEUROCOGNITIVE DEFICITS

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Introduction: Preterm birth may predispose children to neurocognitive deficits later in life. Perinatal factors may affect the outcome. Aims: Our aim was to investigate the role of pre- and postnatal risk factors on neurocognitive outcomes in very low gestational age (VLGA, born < 32 wks of gestation) children assessed at the age of 9 years and to find out differences in neurocognitive outcomes between VLGA children and their controls.
Methods: We evaluated a longitudinal cohort of children (n=163) born VLGA in Oulu University Hospital (Kallankari et al. Ann Med 2010;42:416-25). Altogether 87 (53%) of them were studied at the age of 9 years. We included 27 term born children as a control group with an age and gender distribution similar to that of the cases. All these children participated in neuropsychological assessments (6 subtests from the WISC-III and 14 subtests from the NEPSY-2). Mean scores (range 1-19) were calculated and analysed for each of the five domains; Language, Memory/Learning, Sensorimotor /Visuospatial Processing, Executive Functioning and Social Perception.
Result: After excluding children with cerebral palsy (n=7) or mild intellectual impairment (n=2) or both (n=1), the final study group comprised of 77 VLGA children. After adjustment for sex and maternal education, VLGA predicted 1.5 points (95% CI 0.6-2.3; P=0.001) reduction in mean score of Visuospatial/Sensorimotor Processing and 1.3 points (95% CI 0.6-2.1; P=0.001) reduction in mean score of Executive Functions compared to term controls. None of the neurocognitive test results associated with gestational age at birth. Fetal growth restriction (FGR) proved to be the only perinatal risk factor associating with the neurocognitive outcome in VLGA children. After adjustment for gestational age, sex and maternal education, mean score of Language was reduced by 1.6 points (95% CI 0.40-2.8; P=0.011) and mean score of Memory/Learning by 1.6 points (95% CI 0.4-2.8; P=0.01) in VLGA children with FGR compared to VLGA children without FGR.
Conclusions: Children born VLGA without major neurologic or developmental impairments had poorer performance in visuospatial and sensorimotor skills as well as in executive functioning compared to controls and FGR seems to comprise a special subgroup with the neurocognitive difficulties at the age of nine years. Time before birth and fetal growth may lay a fundamental base on neurocognitive development later in life. Prophylactic treatment of FGR or prospective intervention of this high-risk population after birth is required to prevent or ameliorate neurocognitive disorders.

GESTATIONAL AGE AND IN-UTERINE GROWTH RESTRICTION PREDICT ATTENTION PROBLEMS AT SCHOOL AGE

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Background: Attention skills have been found to be impaired in very preterm children and adolescents (gestational age at birth<32 weeks), while inconsistent findings have been reported for preterm children born moderate or late preterm (gestational age at birth =32 weeks). Some preterm births are difficult to prevent due to spontaneous start of labour, and other are medically induced. Compared to vaginal birth, elective delivery has been associated with adverse outcomes in the neonatal period, and beyond. Intrauterine fetal growth restriction (IUGR), a common final outcome of a range of pregnancy complications is amongst the most common reasons for elective delivery. However, some newborns are constitutionally small which might foretell negative outcomes later in life if early brain growth indicated by reduced head circumference is affected.
Aims: We investigated, firstly, whether gestational age at birth has a linear or non-linear relation with child attention at 6 and 8 years. We hypothesized a non-linear relation due to strong associations found in very preterm samples with attention difficulties compared to successively weaker associations in those born at increasing gestation. Secondly, we examined whether mode of delivery, and SGA types additionally predict attention outcomes. We hypothesized that elective delivery and SGA due to IUGR would have independent effects on attention whereas the effect of being constitutionally small would be only found if head growth in infancy was impaired.
Method: This was a prospective cohort study of 1435 children who were followed from birth to 8 years old. The outcome was attention problems assessed by parents and attention skills assessed by examiners at 6 and 8 years. The effects of gestational age, mode of delivery, and SGA types were examined in hierarchical regression analyses.
Results:. Gestational age at birth ranged from 25 weeks to 41 weeks. We found a quadratic effect of gestational age on attention problems (B6years=.023 95%CI=.011;.034 B8years= .022 95%CI=.012;.032) and skills (B6years=-.014 95%CI= -.020;-.008 B8years=-.008 95%CI=-.014;-.003). Of the 355 SGA children, 65 were identified as constitutionally small. Constitutional smallness was defined by having a mother whose height was below the 10th percentile of the mothers' height distribution according to study norms. In adjusted models, SGA due to risk factors, but not constitutional smallness, was an additional risk factor for attention problems ((B6years=.702 95%CI=.286;1.119 B8years= .599 95%CI=.231;.967) and skills (B6years=-.545 95%CI= -.772;-.318 B8years=-.370 95%CI=-.563;-.117).
Conclusion: Our study suggests that attention problems are not limited to the children born very early in terms of gestation; timing of delivery matters for all preterm children. Smallness in fetal size is amongst the most common reasons for elective caesarean section and one reason for shortened gestation. Distinguishing between constitutionally small fetuses from IUGR fetuses due to pregnancy complications may be one way of identifying small fetuses with reduced need of obstetric intervention, which may reduce later attention problems at school age.