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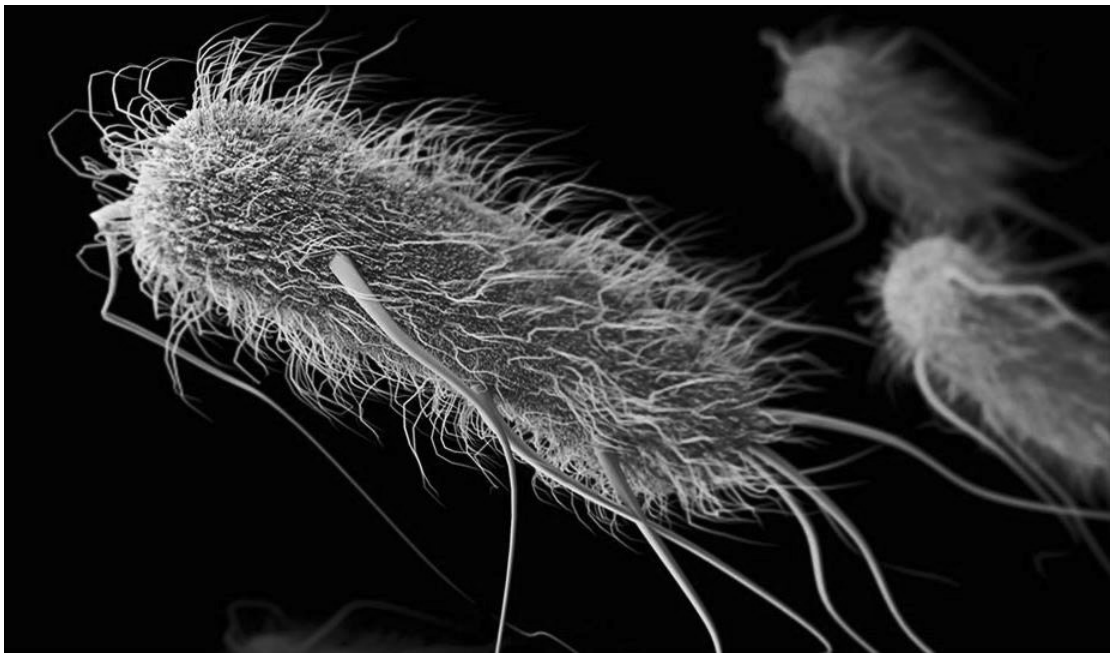
Challenges in perinatal and neonatal infectious diseases



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Abstract book

Technical difficulties in management of neonatal diabetes mellitus in the preterm infant

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To date little data has been published on treatment of neonatal diabetes mellitus (NDM) in premature infants, whether transient neonatal diabetes mellitus (TNDM) or monogenic permanent neonatal diabetes mellitus (PNDM). Initial treatment usually consists of continuous insulin application. If a genetic mutation is detected in genes responsible for potassium channels (e.g. KCNJ11 and ABCC8) treatment may be switched to oral sulfonylurea, overlapping with continuous insulin application. Particularly the technical management of NDM in the preterm infant is heavily underrepresented in current literature.

We present the case of a female preterm infant born at 36 3/7 weeks gestational age with severe symmetrical IUGR and a birth weight of 1600g (P<1). On day six she developed clinical late onset sepsis and was treated with amoxicillin/clavulanate and gentamycin, blood cultures came back positive for staph. epidermidis. Initial presentation of hyperglycemia was assumed to be associated with the sepsis, therefore requiring i.v. insulin. Subsequently we observed persistent hyperglycemia, leading us to suspect NDM. Insulin infusion was therefore reintroduced before switching to continuous subcutaneous insulin infusion (CSII) on day 17. Basal rate was adjusted for blood glucose levels, meal boluses were not administered. Genetic testing for mutations in KCNJ11, ABCC8 and INS genes was carried out at Exeter Molecular Genetics Laboratory, no mutation was found. Insulin requirement was continuously reduced and CSII was discontinued on day of life 33.

When switching from i.v. insulin to CSII we encountered various technical difficulties in administering an accurate dose of Novorapid® preventing hypoglycemia. Firstly, Insulin U100 had to be diluted to U10 in order to maintain appropriate flow rate in the catheter. Secondly, all subcutaneous devices readily available are decidedly oversized when used on an infant weighing under 2000g. Thirdly, localization of sufficient subcutaneous fatty tissue in a severely IUGR infant posed an additional problem, inducing stress for the infant and its parents. Finally, flow rate on the Medtronic Minimed 640G pump could not be switched to U10 concentration, the displayed dose had to be calculated separately and dilution and stability of the insulin was critical.

Conclusions When treating severely IUGR and/or premature infants with CSII modifications according to patient size and weight are required.

Cortical response to sensory stimuli in newborns after birth – the NociCop trial

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Aims and objectives The process of vaginal birth prepares the fetus for the extra-uterine environment and, in comparison to infants delivered by planned caesarean section (PCS), confers respiratory, cardiovascular and homeostatic advantages to the newborn. The effect of delivery mode and birth stress on nociception is largely unknown. The objective of this study was to examine noxious-evoked brain activity a few hours after birth in infants born by vaginal delivery (VD) as compared to PCS.

Materials and Methods A prospective, single-centre study was performed at the University Hospital of Basel after approval by the local CEC (EKNZ 2015-079). Parents of infants who expected to deliver their infants at term age by VD (n=92) or PCS (n=48) were approached. Due to various predefined exclusion criteria such as infections, assisted VD, contractions or rupture of membranes prior to PCD, transfer to the NICU or incomplete data, finally a total of 41 infants were included, VD n=22, PCS n=19. Noxious stimulation was induced 3 to 5 hours after birth by a punctate mechanical stimulus to the right dorsal hand (semiautomatic pinprick device, 32 mN, 50 stimuli repetitions each patient) and evoked potentials were recorded in addition to facial expression of the baby. The vasopressin surrogate marker copeptin was measured in arterial cord blood at birth. Analyses of EEG signals were performed as previously published by our group.

Results The average gestational age at the time of the study was 39 ± 0.91 weeks (mean ± SD). The magnitude of the evoked nociceptive-specific brain activity was significantly higher in infants born by PCS 25 ± 1.3 µV (median ± SD) as compared to VD (18 ± 1.2, p<0.01). The evoked magnitude was positively correlated with arterial cord blood pH (p=0.038) and negatively correlated with copeptin (p=0.015). In a linear regression model with evoked magnitude as dependent variable and delivery mode, sex and parity as independent variables, boys had significantly higher nociceptive sensitivity than girls also after adjustment for gestational age at delivery.

Conclusion Birth experience shapes nociceptive sensitivity in newborn infants in a stress and sex-dependent fashion.

Association of axonal injury and preeclampSIA

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Aims and objectives Preeclampsia (PE) is a main reason of preterm birth and is characterized by maternal hypertension, proteinuria and neurologic symptoms. Neuronal damage is the morphological substrate of acute or persisting neurological disability. Neurofilaments (Nf) are specific scaffolding proteins of neurons and their quantification in serum serves as biomarker for axonal injury e.g. in neurodegenerative diseases. The aim of this study was to determine serum Nf concentrations in pregnant women with and without preeclampsia.

Materials and methods A prospective, single-centre study was performed at the University Hospital of Basel enrolling high risk pregnant women for preeclampsia. Nf light chain (NfL) was measured using a newly established single molecular assay (Simoa) in serum samples collected during serial visits from 25 weeks gestational age (GA) until shortly after birth in addition to the two PE prediction markers soluble VEGF receptor-1 (sFLT1) and placental growth factor (PlGF). Multivariate logistic models were performed with NfL or PE as dependent variable regressed on baseline covariates. Linear mixed effects models with random intercept and slopes were calculated to address the serial visits.

Results In total 250 pregnant women were enrolled of which 17 were excluded due to missing blood samples. 81 out of the remaining 233 developed PE (34.8%). NfL serum concentrations were significantly higher in women with PE (mean [95% CI] 47.0 pg/nl (33.2-60.9) as compared to controls 22.9 pg/nl (20.7-25.3), with 3.4 fold higher levels at 25-28 weeks GA (visit 1), 2.9 at 29-32 (visit 2), 1.6 at 33-36 (visit 3) and 1.5 at 37-40 (visit 4). After adjusting for covariates NfL was an independent predictor for PE at visits 1, 2 and 3, sFLT1 at visit 1 and 4 and PlGF at visit 2 and 3.

Conclusions In pregnant women who develop preeclampsia the axonal injury serum marker NfL is significantly increased. The underlying mechanisms are unknown. A possible explanation is that the preeclampsia underlying endothelial dysfunction causes blood-brain-barrier disruption and concomitant neuronal damage. In summary, NfL may be an early marker to predict the occurrence of preeclampsia.

The impact of maternal grave's disease for the newborn – a case presentation

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Objectives Neonatal Graves' disease (GD) develops in about 1-5% of infants born to mothers with GD. It is caused by transplacentar passage of maternal TSH receptor antibodies (TSHR-Ab) and can lead to prematurity or symptoms of hyperthyroidism in the newborn. We present the case of a premature infant born to a mother with GD.

Background Neonatal GD is caused by the transplacentar passage of maternal stimulatory TSHR-Ab binding to and stimulating the TSH-receptor of the baby leading to hyperthyroidism. On the other hand, blocking TSHR-Ab may cause hypothyroidism, which may also result from the transplacentar transfer of thyreostatic drugs. According to The European Society for Pediatric Endocrinology Consensus Guideline (ESPEC) TSHR-Ab, FT4, T3 and TSH in the umbilical cord should be measured. If TSHR-Ab are positive, the measurement should be repeated on day 4 and within 7-10 days. If the thyroid function is normal and the child is asymptomatic, no further investigation is necessary. Otherwise, an individual treatment needs to be discussed. Generally, prognosis of neonatal GD is good as it often resolves spontaneously within 3-12 weeks when maternal antibodies have decreased.

Case Description A premature boy (33 4/7 weeks GA, bw 2580g) was born to a mother with GD. Previously, the mother was treated with total thyroidectomy at 28 1/7 weeks GA after medical treatment failed. Maternal serum TSHR-Ab were elevated in the 3rd trimester. Following the ESPEC, thyroid function parameters were measured in the umbilical cord blood. TSHR-Ab were elevated with suppressed TSH while the child did not show any symptoms of hyper- or hypothyroidism. Follow-up evaluation at 4 days of age still showed elevated fT4 and suppressed TSH. Over the next weeks the fT4 level decreased gradually below the normal range. Therefore, he was started on Euthyrox on day 41.

Conclusion Maternal GD can lead to hyper- or hypothyroidism in the newborn. If TSHR-Ab are elevated in the 3rd trimester, it is important to check the newborn's thyroid function and the clinical state regularly. The presented boy showed transient subclinical hyperthyroidism during the first days of life, which resolved spontaneously. He consecutively developed hypothyroidism which required levothyroxine substitution. We expect that he can be weaned off such therapy at the age of 6-12 months.

The enlighted chest in an extremely preterm girl

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Asymmetric translucency in chest radiographs of neonates is often assigned to atelectasis, pulmonary infiltration, or pneumothorax; congenital pulmonary malformations are rarely in the forefront of the differential diagnosis. We depict the case of a female infant born at 24 2/7 weeks of gestation with a suspected congenital lobar overinflation (formerly known as congenital lobar emphysema). She was admitted with respiratory support by CPAP and an oxygen requirement below 35%, and needed mechanical ventilation in the second week of life for severe apnoea. Areas of varying opacification in consecutive chest x-rays [pictures] were originally interpreted as atelectasis. However, at the age of 4 weeks, the radiograph showed a well demarcated hypertranslucency in the area of the left upper pulmonary lobe that, retrospectively, had evolved unnoticed over the past few weeks. The picture was best matching to congenital lobar overinflation, assumed to represent a malformation that leads to progressive lobar expansion postnatally. Despite the impressive radiologic findings [picture] with herniation of the left upper lobe and mediastinal shift, the girl continued on moderate levels of supplemental oxygen and with stable circulation. In agreement with the thoracic surgeons, we decided for a conservative management. Here, we show the course of this girl's pulmonary finding until discharge [pictures]; and we discuss this particular condition to raise the awareness of the neonatologist for the class of congenital pulmonary malformations, which might or might not need urgent surgery in the neonatal period.

Genetic susceptibility to neonatal group B streptococcal disease

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Aims and objectives Group B streptococcus (GBS) or Streptococcus agalactiae, a Gram positive β-hemolytic bacterium, is one of the most common pathogens causing neonatal sepsis. The incidence of GBS disease is higher in the neonatal period

compared to other age groups. However, even in the absence of maternal intrapartum prophylaxis, only a small proportion of healthy full-term newborn infants exposed to GBS develops overt disease. This observation suggests that host determinants play a major role in determining individual susceptibility. Monogenic conditions underlying inborn errors of immunity have been shown to contribute to susceptibility to infectious diseases during infancy and childhood. Our aim is to test the hypothesis that rare or novel genetic variants causing single-gene inborn errors of the protective immunity to GBS contribute to individual susceptibility to GBS.

Materials and Methods Infants who suffered from life-threatening, late-onset (after 6 days of life) GBS infection were enrolled in the study. We performed whole-exome sequencing of 42 patients and, if available, their parents. After read alignment and variant calling, we prioritized variants by filtering according to the minor allele frequency (MAF) in the general population (we only kept homozygous variants with a MAF < 0.01 and heterozygous variants with a MAF < 0.0001 in the ExAC database) and according to the genetic and functional annotation (we only kept predicted loss-of-function, LOF, variants, and missense variants predicted to be deleterious by publically available prediction tools).

Results No known variants in primary immunodeficiency genes previously associated with neonatal GBS disease have been identified. We generated a list of candidate pathogenic variants in novel genes not previously associated with primary immunodeficiencies.

Conclusion Further investigations, including additional filtering, prioritization, case-control analyses and pathway analyses are required to identify the best candidate variants for functional follow up. Experimental validation will be necessary to confirm the causative role of the prioritized genetic variants in the susceptibility to GBS.

Amoxicillin dosing regimens in neonates across nine swiss neonatal intensive care units and in four international guidelines

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Objectives To assess the variability in amoxicillin neonatal dosing regimens and the achievement of adequate drug exposure across 9 Swiss NICUs and in 4 international guidelines.

Materials and Methods Dosing regimens for amoxicillin were collected from the 9 Swiss level III NICUs (Zurich, Basel, Bern, St. Gallen, Aarau, Chur, Luzern, Geneva and Lausanne) and 4 international guidelines (Swissmedic®, BNF for children®, Neonatal Formulary®, Frank Shann's Drug Doses®). Demographic factors used for dosing individualization in addition to distribution of dose, daily dose and dosing interval in each guideline were assessed. Model-based simulations were performed to compare the various dosing regimens with respect to their ability to maintain drug levels above predefined minimum inhibitory concentrations (MICs) for 100% of the dosing interval. Simulations used real demographic data from 1119 neonates taken from the ARPEC point-prevalence survey in Europe.

Results Amoxicillin dosing regimens used in the 9 Swiss level III NICUs and recommended in 4 international guidelines showed considerable variability with 12 of the 13 dosing regimens being different with respect to dose, dosing interval, demographic factors (birth weight and current weight, gestational age, postnatal age, postmenstrual age), and the demographic factors cut-off taken into account in selecting individual amoxicillin dosing regimen. Overall dosing regimen ranged from 20 mg/kg q8h to 100 mg/kg q12h, but varied also within neonatal subgroups. None of the Swiss NICUs uses any of the analyzed international guidelines. Simulations suggested that all guidelines maintain drug concentrations above a MIC of 2 mg/l for 100 % of the dosing interval in the neonatal population tested. However, simulations with 6 of the 12 dosing recommendations resulted in drug concentrations not being maintained above a MIC of 8 mg/l for 100% of the dosing interval in 90% of the neonates. Term neonates (≥ 37 weeks of gestation) failed to achieve an effective exposure if a MIC of 8 mg/l was considered.

Conclusions The different amoxicillin neonatal dosing regimens used in Swiss NICUs along with those defined in international guidelines result in variable neonatal drug exposures. There is a clear requirement for amoxicillin dosing regimen harmonization and simplification for neonates across Switzerland, based on quantitative rationale to achieve effective drug exposure in this vulnerable population.

Multiple infantile hemangiomas in a very preterm infant

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Introduction Hemangiomas represent the most common tumors of infancy with a higher incidence in preterm infants. The incidence is increasing with decreasing gestational age, ranging from 1-4% in term infants to 23% in infants with a birth weight <1000 g, with a female and Caucasian predominance. They occur in the first few days to weeks after birth and proliferate in the following weeks and months. The involution phase lasts over several months to years. The aetiology of hemangiomas is not yet fully understood. One hypothesis is that hemangiomas are associated with the expression of vascular endothelial growth factor (VEGF), which also plays a predominant role in the aetiology of retinopathy of prematurity. Multiple hemangiomas are defined by 5 or more hemangiomas; they are usually small in size. Occasionally, they can be associated with visceral hemangiomas, particularly in the liver.

Case report We present a male preterm infant born to a healthy 31-year-old G1/P1 by Cesarean section at 28 4/7 weeks due to preeclampsia. The baby had a birthweight of 1100 g and his postnatal course was unremarkable. At about 3 weeks of age, he presented some small hemangiomas all over the body with the size of a pinhead (pictures). Over the next few days and weeks the number and size of hemangiomas increased. Abdominal ultrasound did not reveal any intestinal or liver hemangiomas. As the cutaneous hemangiomas were small in size and not located close to orifices, no therapeutic measure was mandatory.

Discussion Multiple hemangiomas mainly appear on the skin, but these infants have a risk of internal hemangiomas which are usually located in the liver. Bleeding is the typical complication. For this reason, these infants require clinical and sonographic follow up. There are no clear guidelines for treatment indications. Usually, therapy depends on the size and location of the lesions, as well as on the risk factors for complications. Hemangiomas which are big in size and those located either on the face (eyes, nose) or in the intestinal tract usually require treatment. Therapeutic options include systemic and local treatment with beta blockers, laser coagulation, or corticosteroids. However, overall treatment is rarely required and the long-term outcome is good.

Parechovirus infection: a rare cause of neonatal encephalitis

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Introduction Parechovirus infections show a variety of clinical manifestations. Infections in early childhood are often severe. We present a patient with neonatal encephalitis.

Case report This female term infant was born in a regional hospital by elective caesarean section after a pregnancy marked by gestational diabetes. Good postnatal adaptation with Apgar 8 at 1, 5, and 10 minutes. Respiratory distress due to wet lung and lung immaturity was treated with CPAP for 24h, and then changed to high flow nasal canulae. At day 7, she developed fever of 39.1°C. Two days later, she showed clinical decline with irritability, central apnea and desaturations needing again respiratory support by CPAP and a max FiO2 of 0.3. Emergency transfer to the NICU was necessary. Regarding the cardiovascular system she remained stable. Cerebral function monitoring and EEG showed no seizures. Blood tests were normal, including lumbar puncture without pleiocytosis. However, PCR for parechovirus in the LCR was strongly positive while PCR for enterovirus was negative. Cerebral MRI revealed multiple punctiforme areas with necrosis and edema in the periventricular white matter. At day 10, neurological examination normalized. High flow nasal cannula, introduced at day 10, were stopped at day 20.

Discussion Parechovirus is, like enterovirus, part of the picornaviridae family. Transmission is by fecal-oral, respiratory or placental way. Symptoms include fever, apnea, digestive signs (abdominal distension, diarrhea), rash, sepsis, neurological signs (hypotonia, irritability, drowsiness, and seizures). Blood tests are not contributory. Lumbar puncture typically shows no pleiocytosis. Diagnostic gold standard is PCR. Necrotic lesions in the periventricular and subcortical white matter are described, similar to enterovirus infections, in particular in newborn and young infants. Breastfeeding is a protective factor. Neurodevelopmental outcome may be impaired according to cerebral insults and may present as behavioral disorders, impaired motor skills, deafness, visual disorders, or cerebral palsy. No specific treatment available.

Conclusions 1) Parechovius infection has to be taken into consideration in newborns with sepsis like symptoms, and apnea, in particular when a bacterial cause is not probable or excluded. 2) Normal findings in lumbar puncture do not exclude parechovirus encephalitis. 3) Neurological follow up is essential in children who experienced parechovirus encephalitis.

Psychomotor development in children prenatally exposed to methadone

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Background Methadone maintenance treatment (MMT) has been accepted as therapy for opioid-addicted pregnant women since several decades. Previous studies indicate increased risk of psychomotor difficulties in children prenatally exposed to opioids.

Objectives To determine the effect of MMT in women on infant's neonatal outcome, growth parameters and neurodevelopment until 24 months of age. To study the relationship between maternal methadone dose and child outcome.

Method We performed a retrospective study. Data were collected from 53 children exposed to MMT during pregnancy and born from 2002 to 2014. Mental and motor functioning of the children were assessed at 6 months and 18-24 months with the Bayley Scales of Infant Development (BSID II; MDI and PDI scores respectively). Maternal methadone dosage/day at delivery was then categorized in low dose (<70 mg/d) and high dose (>70 mg/d)

Results At birth, mean gestational age was 37.8 (+/- 2.1) weeks, 43 % of the infants had a birth weight < 10th percentile and 26% of them presented microcephaly. All the children developed a Neonatal Abstinence Syndrome requiring pharmacological treatment. Mean duration of infant's treatment before discharge was 55.3 days and the average length of hospital stay was 76 days. At 6 months, 37children were assessed with the BSID II; MDI mean score was in the lower limits of the normal range (M=88.2, SD=8) and PDI mean score was moderately delayed (M=76.3; SD=15); moreover, the proportion of children having scores below standardized range was of 43% for MDI and 77% for PDI. This trend tends to persist at 18-24 months of age, with PDI mean score raising slightly. With higher maternal methadone dose there was an increase of infants being born smaller (<P10), being treated for Neonatal Abstinence Syndrome longer and spending longer periods in hospital. At 18-24 months, children in the high dose group had lower MDI scores compared to the low dose group ($p < .05$). PDI scores were lower in the high dose group as well, but the difference between groups did not reach significance.

Conclusion During the first two years of life, neurodevelopmental outcome of children born from MMT mothers tended to be lower than normative mean, with motor abilities being more affected than cognitive competences. Our results suggest that higher methadone doses during pregnancy can have a detrimental effect on neonatal characteristics and children psychomotor development.

Evaluation of ROP screening criteria in Switzerland and results on possible new screening criteria

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Aims and Objective Retinopathy of prematurity (ROP) is a severe complication of preterm birth. Criteria for ROP-Screening differ between countries as well as between units in Switzerland and usually include patients of less than 31-32 weeks of gestational age (GA) and/or a birthweight (BW) of less than 1250-1500g. Our aim was to evaluate the incidence of ROP in Switzerland and to assess if it is possible to change screening criteria so that fewer patients are screened without missing patients at risk.

Material and Methods Cohort study of prospectively collected population based data of very preterm infants born alive in Switzerland from 2006 to 2015 (SwissNeoNet, SNN). Missing data on ROP intervention was collected retrospectively.

Incidence of ROP and ROP treatment as well as patient characteristics were analyzed for all patients as well as stratified for year of birth or according to GA. Risk factors known from literature were used to build a logistic regression prediction model for ROP intervention using 5-fold imputed data and a step-wise elimination process while ensuring that variable elimination did not significantly change model. Model was built with data from 2006-2012: Predictive validity was tested with data from 2013-2015

Results Of the 7871 eligible SNN patients, data on ROP-treatment was missing in 1116 patients of which we were able to retrospectively check and complete 942 cases. ROP-treatment was necessary for patients with a GA of 24, 25, 26, 27, 28, 29, 30 and 31 weeks in 14.5%, 7.3%, 2.7%, 1.1%, 0.5%, 0.1%, 0.2% and 0.1%, respectively. Record completeness of all infants according to comparison with Swiss Federal Statistical Office was 96%.

Logistic regression for the outcome ROP intervention was performed with predictors GA, days of supplemental O2, days of CPAP, days of mechanical ventilation, birth weight z-score, surfactant, multiple birth, caesarean section, antenatal steroids, and growth per week. The final model contained the first 7 predictors up to multiple birth and reached a predictive c-statistics value of 0.912.

The model's application on data collected during 2013-2015 predicted a reduction in the number of screened patients to 281/2089 (13.5%) to reach a sensitivity of 94.7% and specificity of 87.3% (one patient not detected). The undetected patient was born at 30+1 weeks with congenital nephroblastoma and therefore probably with a different physiology and additional risk factors. Reducing the screening accordingly would roughly save 100.000 CHF / year. However, all patients would have required screening to reach a sensitivity of 100%.

Conclusions The rate of ROP-treatment in Switzerland during the observation period was very low (1.2% for children born below 32 weeks GA, 0.1% in infants born 28-32 weeks). It may be possible to optimize existing screening criteria based on risk factor analysis and subgroup analysis. We recommend a prospective setup to test the possibility of ROP screening reduction and subgroup definition.

Early neonatal death caused by severe ketoacidosis in a pregnant woman with poorly-regulated type-1 diabetes

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A 27-year old G2/P1 with type-1 diabetes was admitted at 32+3 weeks with premature labour. She had a history of vomiting for two days. Tocolysis with hexaprenaline had been initiated in the transferring hospital. On admission, she was in reduced condition with vomiting, tachycardia and headache. Blood pressure was normal. Urin dipstick revealed protein- and ketonuria. Blood glucose (BG) was 7.5 mmol/l. There was no evidence of preeclampsia other than headache. Transabdominal ultrasound was unremarkable except cardiomegaly. Due to increasing maternal tachycardia and contractions the tocolytic drug was changed to atosiban. Dexamethasone was given for lung maturation. Fetal heart rate (FHR) tracing showed variable decelerations and was recurrently not feasible. Confirmation of FHR with ultrasound was necessary. Urgent caesarean section was performed 6 hours after admission because of fetal bradycardia. Apgar scores were 0, 0 and 0 at 1, 5 and 10 minutes, respectively. We initiated ventilation, chest compressions, intubation and placement of umbilical venous line. Adrenalin was administered repeatedly. Fluid boli were given twice. Transfusion of packed red cells was performed. Diaphanoscopy was not suggestive for pneumothorax, nevertheless, bilateral chest drains were placed. Repeated echocardiography showed asystoly and resuscitation was discontinued in minute 50. Repeated blood gas analyses (BGA) revealed hyperglycemic metabolic acidosis with a pH<6.3 and hyperkalemia. Just before the decision to withdraw resuscitation it became obvious that the mother suffered from severe hyperglycemic (BG 28 mmol/l) metabolic acidosis (pH 6.9) with a potassium of 6.9 mmol/l. Suspected cause of death is the metabolic acidosis which had been pre-existent and aggravated by fetal bradycardia . Cardiomegaly related to diabetic fetopathy (birth weight > P97) may have played an additional role. The parents refused an autopsy. Medical history disclosed that the patient had not injected insuline for 58 hours due to her suspected gastroenteritis. On admission no BGA was performed until after birth, no insuline was given as the patient claimed to be competent to adjust insuline according to her needs. The use of steroids led to metabolic decompensation. In summary, this case report illustrates the significant impact of diabetic ketoacidosis in pregnancy on perinatal outcome. We suggest that BGA to exclude ketoacidosis should be performed in all diabetic women on admission to birth.

Objectives To assess the variability in amoxicillin neonatal dosing regimens and the achievement of adequate drug exposure across 9 Swiss NICUs and in 4 international guidelines.

Materials and Methods Dosing regimens for amoxicillin were collected from the 9 Swiss level III NICUs (Zurich, Basel, Bern, St. Gallen, Aarau, Chur, Luzern, Geneva and Lausanne) and 4 international guidelines (Swissmedic®, BNF for children®, Neonatal Formulary®, Frank Shann's Drug Doses®). Demographic factors used for dosing individualization in addition to distribution of dose, daily dose and dosing interval in each guideline were assessed. Model-based simulations were performed to compare the various dosing regimens with respect to their ability to maintain drug levels above predefined minimum inhibitory concentrations (MICs) for 100% of the dosing interval. Simulations used real demographic data from 1119 neonates taken from the ARPEC point-prevalence survey in Europe.

Results Amoxicillin dosing regimens used in the 9 Swiss level III NICUs and recommended in 4 international guidelines showed considerable variability with 12 of the 13 dosing regimens being different with respect to dose, dosing interval, demographic factors (birth weight and current weight, gestational age, postnatal age, postmenstrual age), and the demographic factors cut-off taken into account in selecting individual amoxicillin dosing regimen. Overall dosing regimen ranged from 20 mg/kg q8h to 100 mg/kg q12h, but varied also within neonatal subgroups. None of the Swiss NICUs uses any of the analyzed international guidelines. Simulations suggested that all guidelines maintain drug concentrations above a MIC of 2 mg/l for 100 % of the dosing interval in the neonatal population tested. However, simulations with 6 of the 12 dosing recommendations resulted in drug concentrations not being maintained above a MIC of 8 mg/l for 100% of the dosing interval in 90% of the neonates. Term neonates (≥ 37 weeks of gestation) failed to achieve an effective exposure if a MIC of 8 mg/l was considered.

Conclusions The different amoxicillin neonatal dosing regimens used in Swiss NICUs along with those defined in international guidelines result in variable neonatal drug exposures. There is a clear requirement for amoxicillin dosing regimen harmonization and simplification for neonates across Switzerland, based on quantitative rationale to achieve effective drug exposure in this vulnerable population.

Distal humeral epiphyseal separation

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Distal humeral epiphyseal separation is a rare orthopedic condition in newborn age. Its diagnosis is challenging as it can be easily misinterpreted as an elbow dislocation, brachial plexus palsy or even overlooked. We report the case of a term newborn boy (3750g, 92. centile) with a distal humeral epiphyseal separation and short-term outcome after surgical correction. Moderate swelling, painful and decreased movements of the right arm were observed since the first day of life (DOL). A traumatic nature of the symptoms was supposed but no delivery complication was reported. After radiographic (DOL 2) and subsequent ultrasound (DOL 4) exams as well as consultation with the pediatric orthopedist (DOL 4) the diagnosis of distal humeral epiphyseal separation was made. Given the displaced and acute nature of the fracture, closed reduction and percutaneous pinning was performed under arthrography. Postoperative clinical and radiographic follow-up examination showed early restoration of function and abundant bony healing, respectively. Despite very poor epidemiological data, distal humeral epiphyseal separation seems to be rare and associated with traumatic delivery with excessive traction and rotation of the forearm. Because of the skeletal immaturity in the newborn, it is mandatory to perform both radiographic and ultrasound assessments of a painful hypokinetic elbow in the newborn. This may allow early diagnosis and consequent treatment. While a consensus on the therapeutic approach is lacking, surgical reposition is indicated as the condition can lead to elbow cubitus varus deformity or elbow dysfunction.

A preterm infant with clostridium perfringens intestinal gangrene

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Aims and Objectives We report about a preterm boy who developed fulminant and fatal necrotising enterocolitis (NEC).

Materials and Methods A single case study was conducted and review of the current literature was performed.

Results The premature baby, born at 25 0/7 weeks of gestation with a birth weight of 840g, was delivered by caesarian section due to chorioamnionitis. Antibiotics were given for the first two days of life (DOL), blood cultures and septical workout were negative. Gut priming was started at the first DOL and enteral feedings with formula milk were increased daily up to DOL 8.

On the 12th DOL, the baby presented with progressing apnoes and distended abdomen. Antibiotics were started and oral feeding was stopped. Abdomen X-rays (picture) showed advanced signs of NEC with portal gas and pneumoperitoneum. Within two hours, peritoneal drainage was inserted. However, the baby deteriorated further and emergency laparotomy, performed 18 hours later, showed complete gangrenous necrosis of the small intestines as well as the major part of the colon, which were partly liquefied. Resection of the whole intestinal tract was no longer an option so palliative care was instaured after discussion with the parents. The baby died less than 24 hours after the first onset of symptoms. Cultures of peritoneal lavage grew for Clostridium perfringens whereas the blood culture remained negative.

Discussion NEC typically affects premature infants and has a multifactorial aetiology. Among the risk factors, imbalance of the microbial colonisation of the immature gut seems to play a key role. In our case, cultures grew for Clostridium perfringens, a gram positive anaerobic bacterium present in the gut of healthy children.

However, it can also be pathogenic, particularly in the presence of an α-toxine responsible for gas gangrene and tissue putrefaction, also known as clostridial myonecrosis. Some authors speculate that clostridial gas gangrene has to be differenciated from the classical NEC observed in premature infants.

Conclusion In the case of a fulminant NEC with rapid evolution toward an intestinal gangrene, C. perfringens needs to be considered as causative agent.

2 cases of failed delivery room resuscitation -> unexpected and why?

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Our patients were both late preterm neonates at 36 0/7 gestational age (GA) and 36 3/7 GA. In the first case the neonate was born by vaginal delivery after premature ruptur of the membrans and in the second case by cesarian section because of a suspicious cardiotocogram.

In the first case we knew about some malformations seen in the fetal ultrasound (US) as club feet, retrognathia, possible malposition of the fingers. Additional polyhydramnion, and sparse fetal movements. A genetic workup showed a normal chromosome set and a normal micro array.

In the second case we didn't have much information. The progress of the pregnancy seemed normal. The mother was transvered to our unit because of decreasing fetal movements confirmed in the US.

In both cases the main problem was the respiratory system. They both failed to start breathing. No chest excursions could be observed. In the first case we were unable to ventilate the lungs by bag-mask. Several attempts of oro-tracheal intubation also with smaller tubuses were unsuccessful. The newborn died 44 minutes after birth.

In the second case we also inubated because of lack of breathing. Ventilation with a bag-mask failed. The intubation was successful but we were not able to ventilate the lungs as well with a tubus regardless of which pressure we used. The right position of the tubus was controlled by inspection with the laryngoscope. This newborn also died 60 minutes after birth.

After both cases a lot of questions were remaining. To find answers is not only important for the parents but also for us clinicians. A diagnostical workup following an unexpected perinatal death including an autopsy is essential to find these answers. When parents don't agree to an autopsy we have the possibility to conduct a postmortem computertomography and a biopsie (stanza) of the skin to cultivate a fibroblast culture for a genetic workup.

Fortunately both parental couples agreed to conduct an autopsy. In both cases a severe lung hypoplasia was responsible for the failed ventilation or/and oro-tracheal intubation. Additional malformations were also found in both patients.

The next question would be the underlying genetic problem.

In the first case we found 2 mutations in the NEB gene responsible for Nemalin-Myopathy. A severe form of this myopathy (10-20 %) causes absent fetal movements and severe lung hypoplasie.

In the second case we found a variation of CHD7 Gene which hypothetically could be responsible for a neuromuscular impairment and resulting lung hypoplasia. The parents refused further investigations.

Volumetric capnography is associated with duration of supplemental oxygen requirement in very preterm infants

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Aims and Objectives Volumetric capnography may reflect sequelae of neonatal lung disease and might discriminate between infants with and without bronchopulmonary dysplasia (BPD). Our aim was to determine indices derived from volumetric capnography in spontaneously breathing preterm infants at 36 weeks post-menstrual age (PMA) and investigate its association with BPD defined as supplemental oxygen requirement at 36 weeks PMA (BPD36) and with the duration of oxygen supplementation.

Material and Methods In this prospective cohort study very preterm infants born before 32 weeks PMA were measured by an ultrasonic flowmeter and a mainstream CO2 sensor in spontaneous sleep at 36 weeks PMA and slopes of phase II (SII) and phase III (SIII) were calculated.

Results Volumetric capnographies were calculated from 99 infants (16 infants with BPD36, 83 without BPD36) (mean gestational age 28.3 ± 2.4 weeks, mean birth weight 1040 ± 370 g). SII was less steep in infants with BPD36 (227 ± 203/L) compared to infants without BPD36 (420 ± 208/L; P = 0.006). SIII was steeper in infants with BPD36 (173 ± 58/L) compared to infants without BPD36 (106 (± 56) /L; P < 0.001). SII and SIII were significantly associated with the duration of supplemental oxygen requirement (coefficient β = -0.003, P = 0.019 and coefficient β = 0.008, P = 0.04 respectively).

Conclusions Indices derived from volumetric capnography at 36 weeks PMA seem to be associated with sequelae of neonatal lung disease. Volumetric capnography appears to be a promising tool in the assessment of respiratory outcome after preterm birth.