Amsterdam Kindersymposium 2021: The virtual edition

Abstract book

AKS2021_054	**Diaphragm activity pre- and post-extubation in ventilated critically ill paediatric patients, measured with transcutaneous electromyography**	55
AKS2021_055	**Configuring SCD care through talk**	56
AKS2021_056	**Faecal volatile metabolomics to predict late-onset sepsis in preterm infants: a multi-centre case control study**	57
AKS2021_057	**Gut organoids, a promising model to study enterovirus infection and disease pathogenesis**	58
AKS2021_058	**Predicting neurodevelopment from intraoperative vital functions: a machine learning approach**	59
AKS2021_059	**The Pyridoxine-Dependent Epilepsy Registry: a digital tool to answer rare disease questions**	60
AKS2021_060	**Efficacy and safety of enteral recombinant human insulin in preterm infants: A randomized, double-blind, placebo-controlled trial**	61
AKS2021_061	**Improving hospital to home transition for Children with Medical Complexity and their families**	62
AKS2021_062	**Lipoprotein(a) levels in effectively treated perinatally HIV-infected children and adolescents over time.**	63
AKS2021_063	**High plasma oxalate values not necessarily suggestive for PH**	64
AKS2021_064	**Parental distress and PTSD in parents of patients with congenital gastrointestinal malformations**	65
AKS2021_065	**Faecal free amino acids as potential early biomarkers for severe necrotizing enterocolitis in preterm infants: a case-control study**	66
AKS2021_066	**Mortality and causes of death from sickle cell disease in the Netherlands, 1985-2017**	67
AKS2021_067	**The efficacy of Gut-Directed Hypnotherapy compared to Standard Medical Treatment in paediatric patients with Functional Nausea: a Multicentre, Randomized Clinical Trial**	68
AKS2021_068	**The Effects of Preterm Birth on Static Balance Function and its Relationship to Motor Development at Five Years of Age**	69
AKS2021_069	**Linking the proteome to the bleeding phenotype in Mild Haemophilia A**	70
AKS2021_070	**Modeling HIV-1 neuropathogenesis using iPSC-derived Brain Organoids and iPSC-derived microglia**	71

AKS2021_004

The Effect of Single-Room Care versus Open-Bay Care on the Incidence of Bacterial Nosocomial Infections in Pre-term Neonates: A Retrospective Cohort Study

Jansen, S.J. (1), Lopriore, E (1), Berkhout, R.J.M. (1), van der Hoeven, A (2) , Saccoccia, B (1), de Boer, J.M. (1), Veldkamp, K.E. (2), van der Beek, M.T. (2), Bekker, V (1)

Affiliations: (1) Division of Neonatology, Dept. of Paediatrics, Willem Alexander Children's Hospital - Leiden UMC (LUMC), Leiden, The Netherlands; (2) Dept. of Medical Microbiology, Leiden UMC (LUMC), Leiden, The Netherlands

Corresponding author: Sophie Jansen, MD (s.j.jansen@lumc.nl)

Rationale: Nosocomial infections (NIs) are a major source of iatrogenic harm in neonatal intensive care units (NICUs). The influence of the infrastructure of NICUs on NIs is not well-documented. This study aims to examine the effect of single-room units (SRU) versus open-bay units (OBU) on the incidence of NIs, including central-line associated bloodstream infections (CLABSI), in preterm neonates.

Methods: All preterm neonates (<32 weeks gestational age) admitted to our NICU were included. Two study-periods were compared: one prior to (May 2015 – May 2017) and one following (May 2017 – May 2019) transition from OBU to SRU. Incidence density (number of infections per 1,000 patient-days) and cumulative incidence (number of infections per 100 neonates) for NI were calculated. CLABSIs were calculated per 1,000 central-line days. U chart analysis was performed to determine special-cause variation in quarterly CLABSI and NI rates. Multivariate competing risk regression was performed to identify independent NI risk factors.

Results: Of the 712 included infants, 164 (23%) infants acquired ≥ 1 NIs. No difference was found in incidence density (13.68 vs. 12.62, p=0.62) and cumulative incidence of NI (23.97 vs. 22.02, p=0.59) between OBU and SRU. CLABSIs showed a similar non-significant reduction after the move (14.00 vs. 10.59, p=0.51). U chart analysis did not identify unit transition as a potential source of special-cause variation for CLABSI and NI (see supplementary materials S1 and S2, p73). Competing risks regression analysis revealed longer duration of invasive mechanical ventilation as a significant risk factor for NI (subhazards ratio: 1.03 per day on ventilation, p=0.01).

Discussion: Single-rooms are not associated with a significant reduction in NIs in the NICU. This study therefore does not add evidence that could support the transition to SRUs if based only on a large multimodal infection control strategy. Recommendations to build SRUs require a wider justification considering other SRU benefits as well.

AKS2021_005

Choice of local anesthetic in reducing needle-induced pain during minor procedures in children: A clinical practice guideline

Stavleu, D.C. (1,2), Kruimer, D.M. (1), Mulder, R.L. (1), Mensink, M.O. (1), Kremer, L.C.M. (1), Loeffen, E.A.H. (1,2), Tissing, W.J.E. (1,2)

Affiliations: (1) Princess Máxima Center for Paediatric Oncology, Utrecht, the Netherlands; (2) University of Groningen, Dept. of Paediatric Oncology/haematology, Groningen, the Netherlands

Corresponding author: Debbie Stavleu, MD (d.c.stavleu@prinsesmaximacentrum.nl)

Rationale: Children often undergo needle-related minor procedures (i.e. venapunctures, venous cannulation or puncture of central venous access ports). The use of local anaesthetics before these procedures reduces pain in children. There is, however, uncertainty about the type of local anaesthetic (i.e. EMLA® or tetracaine-containing creams such as Rapydan®) that should be used. Therefore, a clinical practice guideline (CPG) was developed to establish a comprehensive, evidence-based overview and provide recommendations for clinical practice.

Methods: The GRADE methodology was used to assess, extract and summarize the evidence. All Paediatric populations were included to make this guideline applicable to all children. A multidisciplinary panel was assembled, comprising 15 professionals from different childcare backgrounds, e.g. Paediatric oncology, general Paediatrics, anaesthesiology, pharmacology, psychology and patient representative. In November 2019 an in-person meeting was held in Utrecht (the Netherlands) to complete an evidence-to-decision framework and formulate recommendations. Final recommendations were unanimously supported by all members.

Results: The comprehensive literature search resulted in the inclusion of 11 randomized controlled trials. We recommend the use of EMLA in children who need to undergo a minor needle-related procedure (strong recommendation, very low quality evidence). Moreover, we suggest the use of tetracaine-containing creams only when rapid cannulation/puncture (i.e. within 30-60 minutes) is required (weak recommendation, very low quality evidence).

Discussion: In this CPG, an evidence-based approach was used to provide recommendations regarding the choice of local anaesthetic for needle-induced pain during minor procedures in children. With these recommendations we aim to contribute to reducing procedural pain.

AKS2021_006

Synovial signal intensity on static contrast-enhanced MRI for evaluation of disease activity in juvenile idiopathic arthritis – A look at the bright side of the knee

Verkuil, F. (1, 2), van den Berg, M.J. (1), van Gulik, C.E. (1, 2), Barendregt, A.M. (1, 2), Nassar-Sheikh Rashid, A. (1), Schonenberg-Meinema, D. (1), Dolman, K.M. (3, 4, 5), Kuijpers, T.W. (1), Maas, M. (2), Hemke, R. (2)

Affiliations: (1) Emma Children's Hospital, Amsterdam University Medical Centres, UvA, Paediatric Immunology, Rheumatology and Infectious Diseases, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands; (2) Radiology and Nuclear Medicine, Amsterdam University Medical Centres, UvA, Amsterdam Movement Sciences, Meibergdreef 9, 1105 AZ, Amsterdam, The Netherlands; (3) OLVG, Dept. of Paediatrics; location OLVG Oost, Oosterpark 9, 1091 AC, Amsterdam, The Netherlands; (4) OLVG, Dept. of Paediatrics; location OLVG West, Jan Tooropstraat 164, 1061 AE, Amsterdam, The Netherlands; (5) Reade, Paediatric Rheumatology, Dr. Jan van Breemenstraat 2, 1056 AB, Amsterdam, The Netherlands.

Corresponding author: Floris Verkluil, MD (f.verkuil@amsterdamumc.nl)

Rationale: In children with juvenile idiopathic arthritis (JIA), contrast-enhanced (CE) MRI is the best imaging tool for evaluation of synovitis, which is the hallmark of JIA disease activity (DA). Although, the knee is the most involved joint in JIA, quantitative CE-MRI methods that assess the synovium in the knee are sparse. More objective tools are desirable, since they will increase the sensitivity of knee CE-MRI by allowing aggregation of multiple measurements. A potential quantitative CE-MRI variable for evaluation of JIA DA in the knee could be synovial signal intensity (SI). This is based on the concept that disease state related alterations in synovial microvascularization could lead to changes in synovial SI. We assessed, for the first time, the value of synovial SI on static CE-MRI of the knee for evaluation of JIA DA.

Methods: Clinically inactive and active JIA patients (pts) who underwent static CE-MRI of the knee were included. Synovial SI was assessed on post-contrast T1 images using a 0.02cm2 region of interest drawn in the area of the synovium that contained visually the highest SI. To control for time-dependent post-contrast enhancement variability, a ratio between the SI of the synovium to the m. gastrocnemius was calculated.

Results: We included 427 JIA pts (inactive JIA: 150 [35,1%]; active JIA: 277 [64.9%]) with a mean age of 13.3 ±3.2 yrs. Mean SI synovium-to-muscle ratio was 2.1 ±0.7 in inactive JIA pts versus 2.2 ±0.8 in active JIA pts. No significant difference was found between subgroups (p-value 0.22).

Discussion: Synovial SI grading on static CE-MRI of the knee has no additional value for evaluation of JIA DA. Synovial SI on static CE-MRI is not just a reflection of synovial vascularization, but also the product of an unknown number of different components (e.g. MRI hardware,JIA subtype). Although, the impact of other factors might be small, their presence could have significant effect on the accuracy of synovial SI as measurement tool

AKS2021_007

No association between glucocorticoid receptor polymorphisms and long-term respiratory outcome after very preterm birth

Baas, E.M.* (1), Romijn, M.* (1), Van der Pal, S.M. (2), Vrijlandt, E.J.L.E. (3), Rotteveel, J. (1), Finken, M.J.J. (1), Dutch POPS-19 Collaborative Study Group
* Authors contributed equally

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Pediatric Endocrinology, Amsterdam, The Netherlands; (2) TNO, Child Health, Leiden, The Netherlands; (3) Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Dept. of Pediatric Pulmonology and Pediatric Allergy, Groningen, The Netherlands

Corresponding author: Emma Baas, BSc (e.m.baas@amsterdamumc.nl)

Rationale: In preterm infants in their first weeks of life the hypothalamic-pituitary-adrenal axis is unable to produce sufficient amounts of cortisol for the degree of illness. This may predispose to lung inflammation and, consequently, increased risks of short- and long-term respiratory morbidity. It is unknown whether glucocorticoid sensitivity, which is partly determined by the glucocorticoid receptor (GR), could contribute to respiratory morbidity among adults born preterm. The aim of this study was to investigate whether R23K and N363S single-nucleotide polymorphisms (SNPs) in the GR gene are associated with respiratory outcome 19 years after very preterm birth.

Methods: Subjects born preterm (n = 294) were recruited from the Dutch Project On Preterm and Small-for-gestational-age infants (POPS) cohort, which included 94% of all liveborn infants with a gestational age <32 weeks and/or with a birth weight <1,500 g throughout the Netherlands in 1983, for a survey at age 19 years. Respiratory outcomes were based on the European Community Respiratory Health Survey. Associations between GR polymorphisms and respiratory outcomes at age 19 were assessed with logistic regression.

Results: No differences in scores of asthma, chest wheezing or shortness of breath were found between R23K-carriers and non-carriers, or between N363S-carriers and non-carriers. Eczema was positively associated with R23K carriage (p = 0.045). Neonatal respiratory outcomes, such as BPD, did not differ between GR SNPs.

Discussion: This study showed that the GR polymorphisms R23K and N363S were not associated with the majority of respiratory outcomes in young adults born very preterm.

AKS2021_008

Estimated impact of maternal vaccination on global influenza Paediatric-related mortality: a retrospective case series

Löwensteyn, Y.N. (1), Nair, H. (2), Nunes, M. (3), Tempia, S. (4), van Roessel, I. (1), Vernooij, F. (1), Willemsen, J. (1), Bont, L..J. (1), Mazur, N.I. (1), on behalf of the FLU GOLD study group

Affiliations: (1) Division of Infectious Diseases, Dept. of Paediatrics, University Medical Centre Utrecht, Utrecht, Netherlands; (2) Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK; (3) Respiratory and Meningeal Pathogens Research Unit, University of Witwatersrand, Chris Hani Baragwanath Academic Hospital, Soweto South Africa; (4) Influenza Division, Centres for Disease Control and Prevention, Atlanta, Georgia, USA and Influenza Programme, Centres for Disease Control and Prevention - South Africa, Pretoria, South Africa

Corresponding author: Yvette Löwensteyn, MD (y.n.loewensteyn@umcutrecht.nl)

Rationale: Globally, influenza virus infection is an important cause of under-five mortality. In this age group, influenza virus was associated with 13,200-97,200 deaths due to acute respiratory infection in 2018. Maternal vaccination protects infants against influenza up to 3 months of age. It is unknown to what extent maternal influenza vaccination will prevent Paediatric influenza-related mortality since global age-stratified data at time of death are lacking.

Methods: We invited clinicians and researchers from leading child pneumonia research groups identified through a comprehensive literature search and existing research networks to share data from children younger than 5 years who died with influenza infection between January 1, 1995 and March 31, 2020. We collected clinical and demographic characteristics. To evaluate the potential impact of a maternal vaccine, we estimated the number of in-hospital deaths younger than 3 months using global mortality estimates.

Results: We included 324 children with in-hospital influenza-related death from 31 countries across the world with equal distribution among different income regions. Comorbidities were present in 170 (53%) children. Median age at influenza-related death was 8.9 (IQR 4.5-16.3), 11.7 (IQR 4.5-24.0), and 15.5 (IQR 7.8-27.0) months for children from low- and lower-middle-income countries (LMICs), upper-middle-income countries (UMICs), and high-income countries (HICs), respectively. The proportion of children younger than 3 months at time of death was highest in LMICs (18%), compared to 12% in UMICs or 7% in HICs. We estimated that 3339 annual influenza-related ARTI in-hospital deaths occur in the first 3 months of life.

Discussion: Only a fraction of children dying with influenza was younger than 3 months at time of death. Although maternal vaccination will impact maternal and infant influenza disease burden, additional strategies are needed to prevent influenza-related childhood mortality.

AKS2021_009

Human Parechovirus 1 infection in the intestinal epithelium

García-Rodríguez, I. (1,2), Sridhar, A. (1,2), Wolthers, K.C. (1), Pajkrt, D. (2)

Affiliations: (1) OrganoVIR Lab, Dept. of Medical Microbiology, Amsterdam UMC, location Academic Medical Center, UvA, Amsterdam, The Netherlands**;** (2)Dept. of Paediatrics Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, location Academic Medical Center, UvA, Amsterdam, The Netherlands

Corresponding author: Ines Garcia Rodriguez, MSc (i.garciarodriguez@amsterdamumc.nl)

Rationale: Human parechoviruses (PeV-As) are understudied viruses within the Picornaviridae family. Human Parechovirus 1 (PeV-A1) is the most often detected virus and its infection can range from asymptomatic to severe disease, affecting infants mainly. The primary site of infection is believed to be the respiratory or the gastrointestinal tract, in order to further characterize this virus studies using organoid models were used.

Methods: Human intestinal epithelium (HIE) models derived from foetal intestine were used to study PeV-A1 infection. This model consists of a Transwell insert were cells are grown and differentiated into the cell types that can be found in the gut. After infection of this system with PeV-A1 analysis of the replication kinetics, polarity of infection and cell target were performed.

Results: The HIE model was susceptible for PeV-A1 infection, this virus infected preferentially from the basolateral side and virions were mainly released on the apical side. Using confocal microscopy the cell target was identified as chromogranin positive cells, a marker for enteroendocrine cells.

Discussion: These results suggest that PeV-A1 can infect the gut from the basolateral side of the tissue. In the human situation the virus could reach that side via transcytosis from the apical compartment or after replication in other sites of the body. Further studies to characterize this entry should be done in order to better understand the entry mechanism in the body.

AKS2021_010

The Modified Bristol Stool Form Scale: a reliable and valid tool to score stool consistency in Dutch (non) toilet trained toddlers

Wegh, C.A.M. (1,4) , Hermes, G. (1), Schoterman, M.H.C. (2), Vaughan, E.E. (3), Smidt, H. (1), Belzer, C. (1), Benninga, M.A. (4)

Affiliations: (1) Laboratory of Microbiology, Wageningen University and Research, Wageningen, The Netherlands; (2) FrieslandCampina, Amersfoort, The Netherlands; (3) Sensus BV (Royal Cosun), Roosendaal, The Netherlands; (4) Dept. of Paediatric Gastroenterology and Nutrition, Emma's Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands.

Corresponding author: Carrie A.M. Wegh, MSc (c.a.wegh@amsterdamumc.nl)

Rationale: To assess whether the modified Bristol Stool Form Scale (m-BSFS) is reliable and valid to use by parents, grandparents and day-care employees to evaluate stool consistency in both toilet and non-toilet trained toddlers in the Netherlands.

Methods: The translation to Dutch and validity of the m-BSFS was evaluated for parents, grandparents and child day-care employees of 1-3 year old toddlers (n=89) in the Netherlands with the originally published 32 pictures of stools [1]. To further validate the m-BSFS for toddlers wearing diapers, an additional 7 pictures of stools in diapers were subsequently scored by a subgroup of the same child carers (n=16). For interrater reliability a two-way intraclass correlation coefficient (ICC)agreement was used. Intrarater reliability was measured by Cohen's kappa (κ) by rating the same pictures in random order twice, with at least one week in between.

Results: Interrater and intrarater reliability of the m-BSFS when applied by Dutch child carers were high for the original 32 stool pictures as well for the additional 7 pictures of stools in diapers; ICCagreement for the 32 stool pictures of the first and second ratings were 0.71 (n=89) and 0.79 (n=77), respectively, with a κ of 0.71 (n=77), both with p<.001. ICCagreement for the 7 diaper stool pictures of the first and second ratings were 0.93 (n=16) and 0.93 (n=15), respectively, with a κ of 0.75 (n=15), all p<.001.

Discussion: The modified m-BSFS is reliable and valid to use for Dutch parents, grandparents and day-care employees to evaluate stool consistency in both toilet and non-toilet trained toddlers.

1. Chumpitazi, B.P., et al., Creation and initial evaluation of a Stool Form Scale for children. The Journal of Paediatrics, 2010. 157(4): p. 594-597.

AKS2021_011

Smartphone-based experience sampling and personalized treatment advice (PROfeel) in fatigued children with chronic conditions: a feasibility study

Nap-van der Vlist, M.M. (1); Houtveen, J. (1); Dalmeijer, G.W. (2); Grootenhuis, M.A. (3); van der Ent, C.K. (4); van Grotel, M. (3); Swart, J.F. (5); van Montfrans, J.M. (5); van de Putte, E.M. (1) & Nijhof, S.L. (1)

Affiliations: (1) Dept. of Paediatrics, Wilhelmina Children's Hospital, UMC Utrecht, Utrecht University, Utrecht, the Netherlands; (2) Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht University, Utrecht, the Netherlands; (3) Princess Máxima Center for Paediatric Oncology, Utrecht, the Netherlands; (4) Dept. of Paediatric Pulmonology, Wilhelmina Children's Hospital, UMC Utrecht, Utrecht University, Utrecht, the Netherlands; (5) Dept. of Paediatric Rheumatology/Immunology and Infectious Diseases, Wilhelmina Children's Hospital, UMC Utrecht, Utrecht University, Utrecht, The Netherlands

Corresponding author: Merel Marlena Nap-van der Vlist, MD (m.m.vandervlist-3@umcutrecht.nl)

Rationale: Growing up with a chronic disease brings along extra challenges, such as coping with fatigue. Twenty-one percent of children with a chronic disease is severely fatigued. Factors associated with fatigue can differ per person and over time. We assessed whether PROfeel, a combination of smartphone-based ecological momentary assessment (EMA) followed by personalized treatment advice based on intensive longitudinal data analyses, is feasible and usable.

Methods: Feasibility study, assessing fatigued adolescents 12-18 years of age with an autoimmune disease, cystic fibrosis, post-cancer treatment, or with medically unexplained symptoms, visiting the outpatient clinics. Participants were assessed at baseline to personalize the EMA questions. EMA was conducted via smartphone notifications 5x/day for approximately six weeks. The measurements were translated into a personalized report, which was discussed with the participant by the researcher and a healthcare professional, leading to personalized treatment advice. Afterwards, semi-structured interviews on feasibility and usability were held.

Results: 57 adolescents were assessed (59% participation rate, mean age 16.2y±1.6, 16% male). Adolescents deemed the smartphone-based EMA feasible, with the app being used for an average duration of 49 days. Forty-two percent of the notifications were answered. EMA was found usable, and 85% of the participants would recommend the app to other adolescents. The personalized report was deemed feasible, since 95% recognized themselves in the personalized report, and usable with 64% reporting improved insight in their symptoms and subsequent steps towards treatment as good or very good.

Discussion: PROfeel, the combination of EMA and a personalized report, is feasible and usable for fatigued adolescents with a chronic condition. This innovative method seems to have clinical relevance and can be used to build a bridge between the person's daily life and the consultation room.

AKS2021_012

The diagnostic performance of a trained physician vs. a Paediatric radiologist in performing an intestinal ultrasound in children with Inflammatory Bowel Disease

van Wassenaer, E.A. (1), de Voogd, F.A.E. (2), Deurloo, E.E. (3), Gecse, K.B. (2), D'Haens, G.R. (2), Benninga, M.A. (1), van Rijn, R.R. (3), Koot, B.G.P. (1)

Affiliations: (1) Dept. of Paediatric Gastroenterology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Gastroenterology and Hepatology, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3) Dept. of Radiology, Amsterdam UMC, UvA, Amsterdam, The Netherlands

Corresponding author: Elsa van Wassenaer, MD (e.a.vanwassenaer@amsterdamumc.nl)

Rationale: To assess whether a physician can be trained to perform an Intestinal Ultrasound (IUS), with an accuracy that is non-inferior to an experienced radiologist in children with Inflammatory Bowel Disease.

Methods: In this ongoing cross-sectional study, consecutive children with (suspicion of) IBD, who needed to undergo an ileo-colonoscopy for regular care underwent an IUS. IUS was performed by the physician and radiologist on the same day. The physician was trained by an international training curriculum for IUS (IBUS). Operators were blinded for each other's IUS results and for clinical details. Disease activity per bowel segment (terminal ileum (TI), ascending colon (AC) and transverse colon (TC)) was defined as a SPAUSS score >7 for IUS, and an endoscopic score (SES-CD or Mayo) ≥1 for ileo-colonoscopy. Inter-observer variability for bowel wall thickness (BWT) was assessed with Bland-Altman plots. Accuracy of the trained physician and Paediatric radiologist was compared with the McNemar test.

Results: We included 34 patients (14 males, mean age 15 years (range 8-17)). A total of 14/30 had active disease in TI (in 3 TI was not intubated), 10/33 in AC and 11/32 in TC according to the reference standard. The mean (SD) difference in BWT between the operators for TI, AC and TC respectively was -0.04 (1.58, 95% CI: -3.06 – 3.13), 0.18 (1.21, 95% CI -2.02– 2.37), and 0.04 (1.11, 95% CI:-2.12 – 2.21) mm. There was no systematic difference. For AC and TC, a trend towards a higher sensitivity was noted when IUS was performed by the trained physician although not significantly (Supplementary material S3, p75) (p=1.0 and 0.13 respectively). For TI, the trend was reversed (p=0.22).

Discussion: Our preliminary results suggest that a trained physician can perform IUS with accuracy that is non-inferior to an experienced radiologist in children with IBD, although sensitivity was low for both operators. More research on the most optimal cut-off for IUS is needed.

AKS2021_013

Dismal Outcome of Paediatric Acute Myeloid Leukaemia in a Large Referral Center in Western Kenya: Experiences of a Lower-Middle-Income Country

van Weelderen, R.E. (1, 2), Klein, K. (2, 3), Olbara, G. (4), Vik, T. (5), Njuguna, F. (4) & Kaspers, G.J.L. (1, 2)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, Vu Amsterdam, Paediatric Oncology, Amsterdam, the Netherlands; (2) Princess Máxima Center for Paediatric Oncology, Utrecht, the Netherlands; (3) Wilhelmina Children's Hospital/UMC Utrecht, Utrecht, The Netherlands; (4) Moi Teaching and Referral Hospital, Eldoret, Kenya; (5) Indiana University, Indianapolis, Indiana.

Corresponding author: Romy van Weelderen, MD (r.vanweelderen@amsterdamumc.nl)

Rationale: Survival of Paediatric acute myeloid leukaemia (AML) in low- and middle-income countries (LMICs) is poor. Moi Teaching and Referral Hospital (MTRH) in Eldoret is the only academic hospital in Western Kenya treating childhood cancer. Aim: To evaluate recent outcome of Paediatric AML patients at MTRH.

Methods: Medical records of 71 children (0-18 years) diagnosed between January 2010 and December 2018 with de novo AML were studied using the childhood cancer registry at MTRH, available since 2010. AML diagnosis was mainly based on morphology, cytogenetic studies were unavailable. Treatment comprised two induction courses (7+3; cytarabine, doxorubicin), two consolidation courses (5+3; cytarabine, etoposide), and triple intrathecal therapy at each course (methotrexate, hydrocortisone, cytarabine). Stem cell transplantation was unavailable. Baseline characteristics were studied and Kaplan-Meier methods were used to estimate probabilities of event-free survival (pEFS) and overall survival (pOS).

Results: Forty-one patients were male (57.7%). Median age at diagnosis was 8.7 years (range, 1.2-15). Of 71 patients, 5 refused treatment, 4 died prior to the onset of treatment and 11 opted for palliative care. Of the 51 patients who started treatment, 17 patients achieved complete remission (CR) (33.3%). Reasons for not achieving CR were death <42 days (n=24), refractory disease (n=1), death >42 days, but before CR could be assessed (n=7), and abandonment (n=2). Of the 17 patients who achieved CR, 8 relapsed (47.1%), 3 died in CR, and 6 are assumed to be in continuous CR with a median follow-up duration of 5.2 months (range, 0.3-79.8), but 5 of them are lost to follow-up. Two-year pEFS and pOS were 3.8% ±2.6% and 7.3% ±3.8%, respectively.

Discussion: Survival of Paediatric AML in Western Kenya is poor, due to high ED, TRM and relapse rates. Priority in improving survival should be improvement of supportive care. Furthermore, reasons of abandonment should be studied.

AKS2021_014

The power of 1: N-of-1 studies in rare genetic neurodevelopmental disorders

Müller, A.R. (1,2), Brands, M.M.M.G. (2), Van de Ven, P.M. (3), Roes, K.C.B. (4), Cornel, M.C. (5), Van Karnebeek, C.D.M. (2,6), Wijburg, F.A. (2), Daams, J.G. (7), Boot, E. (1,8,9) & Van Eeghen, A.M. (1,10,11)

Affiliations: (1) 's Heeren Loo, Amersfoort, The Netherlands; (2) Paediatric Metabolic Diseases, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3) Dept. of Epidemiology and Biostatistics, Amsterdam UMC, Amsterdam, The Netherlands; (4) Dept. of Health Evidence, Biostatistics, Radboud UMC, Radboud University, Nijmegen, The Netherlands; (5) Dept. of Clinical Genetics, Amsterdam UMC, Vu Amsterdam, The Netherlands; (6) Dept. of Paediatrics, Radboud Centre for Mitochondrial Medicine, Radboud UMC, Nijmegen, The Netherlands; (7) Medical Library, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (8) Dept. of Psychiatry & Neuropsychology, Maastricht University, Maastricht, The Netherlands; (9) The Dalglish Family 22q Clinic, University Health Network, Toronto, Ontario, Canada; (10) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (11) ENCORE, Erasmus Medical Center, Rotterdam, The Netherlands

Corresponding author: Annelieke Müller, MSc (a.r.muller@amsterdamumc.nl)

Rationale: Millions of children worldwide are affected by one of the nearly 6000 rare genetic disorders, often associated with neurodevelopmental impairments. As treatment targets are increasingly identified, there is a great need for generating evidence for interventions. However, interventional research is challenging due to vulnerable, small and heterogeneous patient populations. N-of-1 studies are randomized, controlled, multiple crossover trials within a single patient and may provide a useful study design (see supplementary material S4, p75). To improve the use of N-of-1 studies in rare genetic neurodevelopmental disorders, we systematically reviewed the literature and formulated recommendations for future studies.

Methods: The systematic review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42020154720). EMBASE and MEDLINE were searched for N-of-1 studies in rare genetic neurodevelopmental disorders. Information was recorded on types of interventions, outcome measures, validity, strengths and limitations using standard reporting guidelines and critical appraisal tools. Qualitative and descriptive analyses were performed.

Results: Twelve studies met N-of-1 inclusion criteria, including both single trials and series. Interventions were mainly directed to neuropsychiatric manifestations. Main strengths were the use of personalized and clinically relevant outcomes. Limitations included lack of power analyses and the use of ancillary statistical analyses. Generalizability was compromised due to limited use of validated and generalizable outcome measures.

Discussion: N-of-1 studies are sporadically reported in rare genetic neurodevelopmental disorders. Properly executed N-of-1 studies may provide a powerful alternative to larger randomized controlled trials in rare disorders and a much needed bridge between practice and science. We provide recommendations for future N-of-1 studies, ultimately optimizing evidence-based and personalized care.

AKS2021_015

Thiopurine therapy in paediatric inflammatory bowel disease: adverse drug reactions and thiopurine metabolites

Jagt, J.Z. (1), Pothof, C.D. (1), Buiter, H.J.C. (2), van Limbergen, J.E. (3), van Wijk, M.P. (1,3), Benninga, M.A. (3), de Boer, N.K.H (4) & de Meij, T.G.J. (1,3)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, Vu Amsterdam, Amsterdam, The Netherlands; (2) Dept. of Clinical Pharmacology and Pharmacy, Amsterdam UMC, Vu Amsterdam, Amsterdam, The Netherlands; (3) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (4) Dept. of Gastroenterology and Hepatology, Amsterdam UMC, Vu Amsterdam, Amsterdam, The Netherlands

Corresponding author: Jasmijn Jagt, MD (j.jagt1@amsterdamumc.nl)

Rationale: In the recent era of growing availability of biological agents, the role of thiopurines needs to be reassessed with the focus on toxicity. We assessed the incidence and predictive factors of thiopurine-induced adverse drug reactions (ADR) resulting in therapy cessation in paediatric inflammatory bowel disease (IBD), related to thiopurine metabolites and biochemical abnormalities, and determined overall drug survival.

Methods: We performed a retrospective, single-centre study of children diagnosed with IBD between 2000 – 2019 and treated with thiopurine therapy. The incidence of ADR and overall drug survival of thiopurines were evaluated using the Kaplan-Meier method. Correlations between thiopurine metabolites and biochemical tests were computed using Spearman's correlation coefficient.

Results: Of 391 paediatric IBD patients, 233 patients (162 Crohn's disease, 62 ulcerative colitis, 9 IBD-unclassified) were prescribed thiopurines (230 azathioprine, 3 mercaptopurine), of whom 50 patients (22%) discontinued treatment, at least temporary, due to thiopurine-induced ADR (median follow-up 20.7 months). Twenty-six patients (52%) were rechallenged and 18 of them (70%) could continue with the same drug. Fifteen patients (6%) switched to mercaptopurine after azathioprine intolerance and 9 of these patients (60%) tolerated this. No predictive factors for development of ADR were identified. Levels of 6-thioguanine nucleotides (6-TGN) were significantly correlated with white blood cell and neutrophil count, 6-methylmercaptopurine (6-MMP) levels with alanine aminotransferase and gamma-glutamyltranspeptidase.

Discussion: Approximately 20% of paediatric IBD patients discontinued thiopurine treatment due to ADR. A rechallenge or switch to mercaptopurine is an effective strategy after development of ADR. Levels of 6-TGN and 6-MMP are associated with biochemical abnormalities.

AKS2021_016

Patient and Healthcare Professional Views on a Personal Health Record in Haemophilia care: a Qualitative Study

Brands, M.R. (1), Driessens, M. (2), van der Meer, F.J.M. (3), Goedhart, G. (3), Meijer, S. (2), van der Bom, J.G. (3), Haverman, L. (1), Cnossen, M.H. (4), Fijnvandraat, C.J. (1), Gouw, S.C. (1), on behalf of the SYMPHONY consortium

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Netherlands Haemophilia Patient Society (NVHP), Nijkerk, the Netherlands; (3) Leiden UMC, Leiden University, Leiden, the Netherlands; (4) Sophia Children's Hospital, Erasmus UMC, Erasmus University Rotterdam, Rotterdam, the Netherlands

Corresponding author: Martijn Brands, MD (m.r.brands@amsterdamumc.nl)

Rationale: Information on health outcomes of people with haemophilia (PWH) is needed for personalized treatment and shared decision making. These data are currently collected from a range of digital sources, which results in fragmented information hampering integrated care and patient empowerment. As a potential solution we set out to develop a nationwide digital personal health record (PHR), in which all relevant medical and personal information is collected, managed and shared by the patient. However, perspectives of PWH and their healthcare professionals regarding a PHR are unknown. We aim to assess the wishes, needs and requirements of PWH and healthcare professionals regarding a PHR for haemophilia care in the Netherlands, and how they expect to use it.

Methods: This qualitative, in-depth interview study is set in the Netherlands among adult and Paediatric PWH (both haemophilia A and B), their caregivers and healthcare professionals of different backgrounds (e.g. (Paediatric) haematologists, nurses, psychologists and physiotherapists). Through semi-structured interviews, circa 40 participants are asked about their views.

Results: Currently, 21 participants have been interviewed. Most patients with severe haemophilia and healthcare professionals have a positive attitude regarding a PHR. Patients with mild or moderate haemophilia consider it less useful. Features deemed most useful are tools to share personal medical information with healthcare professionals and the integration of several apps into a single interface. Other requested features are to enhance patient-professional communication, make appointments and proxy access for caregivers. Concerns are expressed about privacy, interoperability and ownership of data.

Discussion: Our preliminary analysis suggests that PWH, their caregivers and healthcare professionals have a positive attitude regarding a PHR for haemophilia care. Concerns about privacy and practical implementation need to be taken into account.

AKS2021_017

The influence of timing of Maternal administration of Antibiotics during caesarean section on the intestinal Microbial colonization in Infants (MAMI-trial): a randomized controlled trial

Dierikx, T.H. (1,2), Berkhout D.J.C. (1,2), van Limbergen van J. (2,3), Visser D.H. (4), de Boer M. (5), de Boer N.K.H. (6), Touw D.J. (7,8), Benninga M.A. (2), Schierbeek N.L. (1), Visser L. (5), Eck A. (9), Tims S. (9), Roeselers G. (9), de Vries J.I.P. (5), de Meij T.G.J. (1,2)

Affiliations: (1) Dept. of Paediatric Gastroenterology, Emma Children's Hospital, Amsterdam UMC, VU University medical centre, Amsterdam, The Netherlands; (2) Dept. of Paediatric Gastroenterology, Emma Children's Hospital, Amsterdam UMC, Academic Medical Center, Amsterdam, The Netherlands; (3) Dept. of Paediatrics, Dalhousie University, Halifax, Canada; (4) Dept. of Neonatology, Emma Children's Hospital, Amsterdam UMC, Academic Medical Center, Amsterdam, The Netherlands; (5) Dept. of Obstetrics and Gynaecology, Amsterdam UMC, VU University medical centre, Amsterdam, The Netherlands; (6) Dept. of Gastroenterology and Hepatology, Amsterdam UMC, VU University medical centre, AG&M research institute, Amsterdam, The Netherlands; (7) Dept. of Pharmaceutical Analysis, University of Groningen, Groningen Research Institute of Pharmacy, Groningen, The Netherlands; (8) Dept. of Clinical Pharmacy and Pharmacology, UMC Groningen, Groningen, The Netherlands; (9) Danone Nutricia Research, 3584 CT Utrecht, the Netherlands.

Corresponding author: Thomas Dierikx, MD (t.dierikx@amsterdamumc.nl)

Rationale: Revised guidelines for caesarean sections (CS) advise to administer prophylactic antibiotics to the mother prior to skin incision instead of after clamping of the umbilical cord, to reduce the risk of maternal infectious complications. This results in exposure to antibiotics in all CS born infants. Consequences of this exposure on gut colonization and long-term health are unknown. Aim of this study was to investigate the effect of timing of maternally administered antibiotics during CS on the infant microbiome.

Methods: In this randomized controlled trial, 40 women scheduled for an elective CS randomly received antibiotics (1500 mg cefuroxime) prior to skin incision (intrauterine antibiotic exposed infants) or after clamping of the umbilical cord (unexposed infants). A group of 23 women and their vaginally born infants were included as controls. Microbiome analyses was performed on faecal samples collected at day one, seven and 28 and after three years.

Results: At 28 days, CS born infants intrauterine exposed to antibiotics showed a lower abundance of Bifidobacteria compared to non-exposed CS born infants ($p<0.001$) (see supplementary material S5, p76). Compared to vaginally born infants, microbiota of both CS groups was characterized by a decreased diversity ($p<0.001$), a decrease in Bacteroidetes ($p<0.001$) and an increase in Proteobacteria ($p=0.002$) in the first month of life. At three years of age, no differences in microbiome were observed between the three subgroups.

Discussion: We observed that the administration of antibiotics before skin incision in CS, according to the revised NICE guideline, leads to disturbance of early colonization with Bifidobacteria, which has previously been associated with disturbed priming of the immune system, even when these microbial disturbances are restored later in infancy. Our results therefore challenge the statement in the current NICE guidelines that maternal prescription of antibiotics prior to CS does not influence infant health.

AKS2021_018

Health related quality of life and distress of mothers and fathers of children with avoidant restrictive food intake disorder

Krom, H. (1), van Oers, H.A. (2), van der Sluijs Veer, L. (2), van Zundert, S.M.C. (3), Otten, M.A.G.M. (4), Haverman, L. (2), Benninga, M.A. (1), Kindermann, A. (1)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Dept. of Paediatric Gastroenterology, Hepatology and Nutrition, Amsterdam, The Netherlands; (2) Emma Children's Hospital, Amsterdam UMC, UvA, Child and Adolescent Psychiatry & Psychosocial Care, Reproduction and Development, Amsterdam Public Health, Amsterdam, The Netherlands; (3) Emma Children's Hospital, Amsterdam UMC, UvA, Dept. of Dietetics, Amsterdam, The Netherlands; (4) Emma Children's Hospital, Amsterdam UMC, UvA, Dept. of Rehabilitation, Amsterdam, The Netherlands

Corresponding author: Hilde Krom, MD (h.krom@amsterdamumc.nl)

Rationale: Avoidant restrictive food intake disorder (ARFID) is a feeding disorder characterized by an inadequate intake of energy/nutrients, which originates from fear of aversive consequences, lack of interest and/or problems with the sensory characteristics of food. The health-related quality of life (HRQOL) of children with ARFID is impaired. Aim: To measure HRQOL and distress of parents of children with ARFID.

Methods: In this cross-sectional cohort study, mothers and fathers of children with ARFID completed questionnaires on the online KLIK portal (Sept 2014-May 2019); the TNO-AZL QOL (TAAQOL) to assess parental HRQOL and the Distress Thermometer for Parents (DT-P). Dutch reference groups of parents of healthy (HC) and chronically ill children (CIC) were used as comparison.

Results: In total, 85 mothers and 62 fathers of 89 children with ARFID (58% female, median age 1.9y) were included (response rate 68%). No differences were found regarding HRQOL in 11/12 domains. Mothers of children with ARFID reported a significantly higher HRQOL in the domain pain and fathers a lower HRQOL in the domain depressive emotions compared to mothers and fathers of HC. No differences were found in median overall and clinical distress scores. Mothers of children with ARFID reported significantly higher distress scores in the domains parenting problems in children <2y compared to mothers of HC and CIC and cognitive problems compared to mothers of HC. Fathers reported significantly higher distress scores for the domain parenting problems in children <2y compared to fathers of HC and CIC.

Discussion: Total HRQOL and distress scores of parents of children with ARFID were comparable to reference groups. However, lower HRQOL in the domain depressive emotions and higher distress in the domains cognitive problems and parenting problems in children <2y in parents of children with ARFID, emphasize the importance to screen and manage parental psychosocial problems in clinical practice.

AKS2021_019

The clinical phenotype of patients with non-severe haemophilia A and B

Kloosterman, F.R. (1), Zwagemaker, A. (1), Gouw, S.C. (1)(2), Bagot, C.N. (3), Beckers, E.A.M. (4), Boyce, S. (5), Brons, P. (6) Cnossen, M.H. (7), J. Eikenboom, J. (8) Leebeek, F.W.G. (9) Male, C. (10) , Meijer, K. (11) Nieuwenhuizen, L. (12) Coppens, M. (13), Van der Bom, J.G. (2)(14) Castaman, G. (15) Fijnvandraat, K. (1)(16)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Paediatric Hematology, Amsterdam, The Netherlands; (2) Dept. of Clinical Epidemiology, Leiden UMC, Leiden, the Netherlands; (3) Dept. of Haematology, Glasgow Royal Infirmary, Glasgow, UK; (4) Dept. of Hematology, Maastricht University Medical Centre, Maastricht, the Netherlands; (5) Dept. of Haematology, University Hospital Southampton, Southampton, United Kingdom; (6) Dept. of Paediatric Hemato-Oncology, Radboud UMC, Nijmegen, The Netherlands; (7) Dept. of Paediatric Hematology, Erasmus UMC – Sophia Children's Hospital, Rotterdam, the Netherlands; (8) Dept. of Internal Medicine, Division of Thrombosis and Hemostasis, Leiden UMC, Leiden; (9) Dept. of Hematology, Erasmus UMC, Rotterdam, the Netherlands; (10) Dept. of Paediatrics, Medical University of Vienna, Vienna, Austria; (11) Dept. of Hematology, UMC Groningen, Groningen, the Netherlands; (12) Dept. of Hematology, Maxima Medical Center Eindhoven, Eindhoven, The Netherlands; (13) Dept. of Vascular Medicine, Amsterdam University Medical Centres, Amsterdam, the Netherlands; (14) Center for Clinical Transfusion Research, Sanquin-Leiden UMC, Leiden; (15) Dept. of Oncology, Center for Bleeding Disorders, Careggi University Hospital, Florence, Italy; (16) Dept. of Molecular Cellular Hemostasis, Sanquin Research and Landsteiner Laboratory, Amsterdam, the Netherlands

Corresponding author: Fabienne Kloosterman, MD (f.r.kloosterman@amsterdamumc.nl)

Rationale: Haemophilia A and B are inherited coagulation disorders with disease severity based on residual factor VIII (FVIII) and factor IX (FIX) levels, respectively. A hallmark of haemophilia is the occurrence of joint bleeds that could lead to irreversible joint damage. In severe haemophilia the majority experiences their first joint bleed in the first 2 years of life. In patients with non-severe haemophilia we lack detailed knowledge on the onset of bleeding. With this study we aim to provide insight into the occurrence of joint bleeds in patients with non-severe haemophilia A and B.

Methods: The DYNAMO study is a cohort study including moderate (FVIII/FIX 2-5%) and mild (FVIII/FIX 6-35%) haemophilia A and B patients aged 12-55 years. Informed consent was obtained during annual clinic visits. Data on the occurrence of lifetime joint bleeds were collected from medical files.

Results: A total of 133 patients were included in this analysis. Our population consisted of 40 patients with moderate haemophilia and 93 patients with mild haemophilia. The median age was 35 years (IQR 25-48) and the median factor level was 11 IU/dL (IQR 4-17). In this cohort, 44% of the 133 patients had experienced at least one joint bleed requiring treatment with factor concentrates. The age at first joint bleed occurred at a median age of 9 years (IQR 4-18). Patients with moderate haemophilia experienced their first joint bleed earlier than patients with mild haemophilia, namely 7 years (IQR 3-9) vs. 13 years (IQR 5-21).

Discussion: Nearly half of the non-severe haemophilia patients has suffered from a joint bleeding during their lifetime. Onset of joint bleeding mainly occurs during childhood and adolescence. Even though children with non-severe haemophilia have a milder bleeding phenotype, physicians should be vigilant for the occurrence of joint bleeds in this population.

AKS2021_020

Evaluation of the ISTH-BAT and PBQ bleeding assessment tools in children with a suspected hereditary coagulation disorder

Zwagemaker A. (1), Kloosterman F.R. (1), Peters B. (1), Stokhuijzen E. (1), Cnossen M.H. (2), Biss T.T. (3), Peters M. (1), Suijker M.H. (1,4), Blanchette V.S. (5), James P. (6), Rand M.L. (7,8), Fijnvandraat K. (1,9)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Paediatric haematology, Amsterdam, The Netherlands; (2) Dept. of Paediatric haematology, Erasmus UMC – Sophia Children's Hospital, Rotterdam, the Netherlands; (3) Dept. of Haematology, The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom; (4) Dept. of Paediatric haematology, UMC Utrecht, University Utrecht, The Netherlands; (5) Division of Haematology/Oncology, Dept. of Paediatrics, Hospital for Sick Children, University of Toronto, Toronto, Canada; (6) Dept. of Medicine, Division of haematology, Queens University, Kingston General Hospital, Kingston, Canada (7) Division of Haematology/Oncology and Translational Medicine Program, Hospital for Sick Children, Toronto, Canada; (8) Dept.s of Laboratory Medicine & Pathobiology, Biochemistry, and Paediatrics, University of Toronto, Canada; (9) Dept. of Molecular Cellular Haemostasis, Sanquin Research and Landsteiner Laboratory, Amsterdam, the Netherlands.

Corresponding author: Anne-Fleur Zwagemaker (a.zwagemaker@amsterdamumc.nl)

Rationale: The evaluation of bleeding symptoms in children is challenging as symptoms may be subtle and children face less haemostatic challenges compared to adults. There are several bleeding assessment tools (BATs) currently available that are used for screening and to quantify bleeding symptoms. We aimed to evaluate the diagnostic accuracy of the existing ISTH-BAT and PBQ (Paediatric Bleeding Questionnaire) BATs in identifying children with a suspected hereditary coagulation disorder.

Methods: The iCHEC study is a prospective cohort study that includes children who presented with symptoms of bleeding and/or a positive family history of a bleeding disorder. The iCHEC questionnaire (including the ISTH-BAT and PBQ) was completed by subjects before their first clinic appointment with the Paediatric haematologist. Bleeding scores were compared between children with and without a confirmed hereditary coagulation disorder after diagnostic work-up. A total bleeding score of ≥3 for the ISTH-BAT and ≥2 for the PBQ were considered positive test outcomes.

Results: A total of 207 children were enrolled. Their median age was 7 years (IQR 3-13), and 114/207 (55%) were female. Based on laboratory testing, 46 children (22%) were diagnosed with a hereditary bleeding disorder. Their median total ISTH-BAT and PBQ scores were 4 (IQR 2-6) and 4 (IQR 2-5), respectively. These were similar to the group of unaffected children who had median total ISTH-BAT and PBQ scores of 4 (IQR 2-5) and 3 (IQR 2-6), respectively. Both the ISTH-BAT and PBQ showed a very low positive predictive value (22% and 23%) and a moderate negative predictive value (75% and 78%). Sensitivity (ISTH-BAT 63%, PBQ 80%) and specificity (ISTH-BAT 33%, PBQ 20%) were moderate to low.

Discussion: The existing BATs seem to lack discriminative power to identify children with a hereditary coagulation disorder. These findings support the construction of a more refined Paediatric BAT with a higher diagnostic accuracy.

AKS2021_021

Plasma oxalate values in patients with end stage kidney disease

Metry, E.L. (1), Garrelfs, S.F. (1), Oosterveld, M.J.S. (1), Neradova, A. (2), Bijlsma, J. (2), Vaz, F.M. (3) & Groothoff, J.W. (1)

Affiliations: (1) Dept. of Paediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Nephrology, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3) Laboratory Genetic Metabolic Diseases, Amsterdam UMC, UvA, Amsterdam, The Netherlands

Corresponding author: Ella Metry, MD (e.l.metry@amsterdamumc.nl)

Rationale: Patients with end-stage kidney disease (ESKD) are known to have higher plasma concentrations of metabolic waste products than healthy individuals. Patients with Primary Hyperoxaluria (PH), a rare congenital cause of ESKD, suffer from hepatic overproduction of the metabolic end product oxalate. Plasma oxalate (POx) levels are determined in the diagnostic and therapeutic work-up for PH. Remarkably, correct interpretation of these values is hampered by the absence of knowledge concerning POx levels in patients with ESKD due to common causes.

Methods: In this observational study, we obtained POx values in patients with ESKD due to another cause than PH, to establish reference values in this patient group. We collected blood samples from 120 adults with eGFR < 15 mL/min/1.73 m2 who required maintenance haemodialysis or peritoneal dialysis at the Amsterdam UMC.

Results: While there was a wide variation in POx levels in patients with ESKD, the median was 50 umol/L and lowest values were twice the upper reference limit that applies to healthy individuals (6.7 umol/L).

Discussion: This study shows that POx levels of 50 umol/L are not necessarily suggestive for PH which contradicts the current literature. This study could lead to a paradigm shift in the diagnostic and therapeutic work-up for patients with ESKD.

AKS2021_022

Mental and social health of children and adolescents with and without existing mental or somatic problems during the COVID-19 pandemic lockdown

Teela, L. (1), Zijlmans, J. (2), DREAMS consortium (2), Luijten, M.A.J.(1), Muilekom, M.M. (1), Oostrom, K.J. (1), Popma, A. (1,2), van Oers, H.A. (1), Haverman, L. (1), Polderman, T.J.C. (2)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam Reproduction and Development, Amsterdam Public Health, Meibergdreef 9, Amsterdam, Netherlands; (2) Amsterdam UMC, Vu Amsterdam, Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam Public Health, The Netherlands.

Corresponding author: Lorynn Teela, MSc (l.teela@amsterdamumc.nl)

Rationale: Several studies in general population samples show that COVID-19 pandemic restrictions during a country's lockdown affect children's mental health by e.g., increasing feelings of anxiety. We aim to extend this research by examining mental and social health in children and adolescents with and without existing mental or somatic problems, and test for moderating (COVID-19 related) factors.

Method: We included participants (8-18 years) from a general population (N=844), a psychiatric (N=249), and a Paediatric (N=90) sample. Self-reported outcome measures were Patient-Reported Outcomes Measurement Information System (PROMIS) domains: Global Health, Peer Relationships, Anxiety, Depressive Symptoms, Anger, and Sleep-Related Impairment. Also, two items on atmosphere at home before and during the COVID-19 lockdown and an open question on the impact of the lockdown on daily life were evaluated. Measures were assessed during the first Dutch lockdown (April-May 2020).

Results: The three samples scored significantly different on Depressive Symptoms, Anger, and Sleep-Related Impairment, with the Paediatric population reporting the least problems and the psychiatric population reporting the most problems. In addition, the Paediatric population scored significantly better on Anxiety and Peer Relationships compared to the other two populations. Most prominent factors that moderated the outcomes were age, a single parent household, having a COVID-19 affected friend/relative, and a COVID-19 related change in work situation of parents.

Discussion: We observed significant differences in mental and social health between three child and adolescent samples during the COVID-19 pandemic lockdown and identified COVID-19-related factors influencing mental and social health. Our findings are informative for current and future policies in pandemic related restrictive periods regarding mental and social health care for healthy, but also vulnerable populations of children and adolescents.

AKS2021_023

Children and adolescents perinatally infected with HIV experience few symptoms of fatigue

ter Haar, A.M. (1), Nap-van der Vlist, M.M. (2), Van den Hof, M. (1), Nijhof, S.L. (2), van Litsenburg, R.R.L. (3), Oostrom, K.J. (4), Pajkrt, D. (1)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMCs, Location Academic Medical Center, UvA, Paediatric Infectious Diseases, the Netherlands; (2) Dept. of Paediatrics, Wilhelmina Children's Hospital, UMC Utrecht, Utrecht, The Netherlands; (3) Dept. of Paediatric Oncology, Princess Máxima Center for Paediatric Oncology, Utrecht, The Netherlands; (4) Emma Children's Hospital, Amsterdam UMCs, Location Academic Medical Center, UvA, Dept. of Child & Adolescent Psychiatry, Paediatric Psychology and Psychosocial Care.

Corresponding author: Anne Marleen ter Haar, MSc (a.m.terhaar@amsterdamumc.nl)

Rationale: Fatigue is common among adults living with hiv and children with chronic diseases (CCD). It can have disastrous effects on health status, including health related quality of life (HRQOL), yet is underexplored in children perinatally infected with hiv (PHIV) in the Netherlands. This study investigates fatigue in PHIV and its impact on their HRQOL.

Methods: HRQOL and fatigue were measured using the Paediatric Quality of Life Inventory™ (PedsQL 4.0) and the PedsQL Multidimensional Fatigue Scale (MFS). The PedsQL MFS encompasses three subscales: general fatigue, sleep/rest fatigue and cognitive fatigue. Outcomes of PHIV were compared to HIV-uninfected healthy peers (HIV-), matched for age, sex, ethnicity, socioeconomic status (SES) and adoption status. We used regression analysis adjusted for age and gender to assess differences between scores of PHIV and three comparison groups: HIV-, a sample representing the general Dutch population and CCD. The association between fatigue and HRQOL was identified with linear regression analysis.

Results: We enrolled 14 PHIV children (median age 10.2 years [IQR 9.2-11.4]) and fourteen HIV-. Results of the regression analyses are summarized in supplementary material S6 (p77): lower scores indicate more fatigue. PHIV fatigue scores were similar to those of HIV- on general fatigue and sleep/rest fatigue, with the largest negative mean difference on cognitive fatigue. PHIV reported less symptoms of fatigue than CCD, yet again scored lower on the cognitive fatigue scale. PHIV scores were similar to the general Dutch population on all scales, except for a lower score on cognitive fatigue. Among PHIV, a lower score on the total fatigue scale and the cognitive fatigue scale was associated with a lower HRQoL score.

Discussion: These exploratoy findings suggest that PHIV do not necessarily experience more symptoms of fatigue than their healthy peers. However, PHIV seem more likely to experience cognitive fatigue, which significantly predicts their HRQOL.

AKS2021_024

Use of dornase alfa in the paediatric intensive care unit: current literature and a national cross-sectional survey

den Hollander, B.* (1), Linssen, R.S.N.* (1), Cortjens, B. (1), van Etten-Jamaludin, F.S. (2), van Woensel, J.B.M. (1), Bem, R.A. (1)
* Authors contributed equally

Affiliations: (1) Paediatric Intensive Care Unit, Emma Children's Hospital, Amsterdam UMC, location AMC, Amsterdam, The Netherlands; (2) Research Support, Medical Library, Amsterdam UMC Location AMC, Amsterdam, North Holland, The Netherlands.

Corresponding author: Bibiche den Hollander, MSc (b.denhollander@amsterdamumc.nl)

Rationale: Airway mucus obstruction is a major challenge in children admitted to the paediatric intensive care unit (PICU). We aimed to evaluate the evidence and contemporary use of the mucolytic medication dornase alfa for non-cystic fibrosis conditions in the PICU.

Methods: (1) We performed a systematic review with searches in PubMed, EMBASE, and the Cochrane Library. Study selection: for quality assessment and data synthesis, we included only randomised controlled trials (RCTs) that compared dornase alfa to standard care or placebo in critically-ill paediatric patients (<18 years of age) in the PICU. However, non-randomised controlled studies and case series are also discussed. Data extraction: data were extracted independently by multiple reviewers using data extraction forms. The primary outcome was duration of mechanical ventilation. Data synthesis: The GRADE approach was used for quality assessment. No meta-analysis could be performed. (2) A national cross-sectional survey among all seven PICUs in the Netherlands was also performed.

Results: The systematic review yielded only one RCT, comparing dornase alfa with normal saline in children after cardiac surgery. In this study, dornase alfa led to a reduction in duration of mechanical ventilation by approximately 1 day (36% reduction). In addition, we found nine retrospective observational and case studies. The survey revealed high current use of dornase alfa in Dutch PICUs: 42% of the respondents reported prescribing dornase alfa at least once every week. Only 4% of the respondents reported having access to a local PICU dornase alfa protocol.

Discussion: The off-label use of dornase alfa in the PICU is frequent without strong evidence or local protocols, highlighting the need for further research on the effectiveness of this mucolytic agent.

AKS2021_025

The impact of lockdown during the COVID-19 pandemic on mental and social health of children and adolescents

van Muilekom, M.M. (1), Luijten, M.A.J. (1), Teela, L. (1), van Oers, H.A. (1), Terwee, C.B. (2), Zijlmans, J. (3), Klaufus, L. (4), Popma, A. (1), Oostrom, K.J. (1), Polderman, T.J.C. (3) & Haverman, L. (1)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam Reproduction and Development, Amsterdam Public Health, Amsterdam, the Netherlands; (2) Amsterdam UMC, Vrije Universiteit, Epidemiology and Data Science, Amsterdam, the Netherlands; (3) Amsterdam UMC, Vu Amsterdam, Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam Public Health, Amsterdam, the Netherlands; (4) Public Health Service Amsterdam, Dept. of Epidemiology, Health Promotion, and Health Care, Amsterdam, the Netherlands.

Corresponding author: Maud van Muilekom, MSc (m.m.vanmuilekom@amsterdamumc.nl)

Rationale: The impact of lockdown during the COVID-19 pandemic on children's and adolescents' mental and social health is yet unknown. Therefore this study aimed to compare mental/social health of children/adolescents during COVID-19 lockdown versus before, identify associated factors, and qualitatively assess the impact of COVID-19 regulations on daily life.

Methods: In April 2020, children/adolescents aged 8-18y (N=844), representative of the Dutch population, completed six PROMIS® domains (Global Health, Peer Relationships, Anxiety, Depressive Symptoms, Anger, Sleep-Related Impairment) and an open question on the impact of COVID-19 regulations on daily life. PROMIS T-scores and percentages of severe scoring participants were compared to reference data collected before COVID-19 (2018, N=2401) using ANCOVA and Chi-square analyses. Linear regression analysis was performed to identify associated factors, and qualitative thematic analysis to assess the impact of COVID-19 regulations on daily life.

Results: Children/adolescents reported worse PROMIS T-scores on all domains during COVID-19 lockdown compared to before (absolute MD range=2.1-7.1; absolute 95%CI range=1.3-7.9). More children reported severe Anxiety (during 16.7% vs. before 8.6%; RR=1.95; 95%CI=1.55-2.46) and Sleep-Related Impairment (during 11.5% vs. before 6.1%; RR=1.89; 95%CI=1.29-2.78). Worse mental/social health scores during lockdown were found in children/adolescents from a single-parent family, having ≥three children in the family, negative change in work situation of parents due to COVID-19, and having a COVID-19 infected relative/friend. A large majority (>90%) reported a negative impact of COVID-19 regulations on daily life.

Discussion: This study showed that governmental regulations regarding lockdown pose a serious mental/social health threat on children and adolescents that should be brought to the forefront of political decision making and mental health care policy, intervention and prevention.

AKS2021_026

Hyperoxia exposure during viral lower respiratory tract infection at young age alters long-term lung function

Lilien, T.A. (1,2), Gunjak, M. (2,3), van Woensel, J.B.M. (1), Morty, R.E. (2,3), Bem, R.A. (1)

Affiliations: (1) Paediatric Intensive Care Unit, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Lung Development and Remodeling, Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany; (3) Dept. of Internal Medicine (Pulmonology), University of Giessen and Marburg Lung Center, Giessen, Germany

Corresponding author: Thijs Antonius Lilien, MD (t.a.lilien@amsterdamumc.nl)

Rationale: Viral lower respiratory tract infection (VLRTI) is the most common admission reason in the Paediatric intensive care unit, and is associated with long-term lung dysfunction. Patients with severe VLRTI who suffer from hypoxemia, are treated with high fractions of inspired oxygen (hyperoxia). Although often lifesaving, excessive use of oxygen is also known to have long-term adverse effects. So far, there is limited insight of these effects in children. This is important to investigate as lung development continues up to adolescence and lung injury early in life could disrupt this process. In this study it was hypothesized that hyperoxia in infants with severe VLRTI leads to aberrant lung development.

Methods: In a mouse model, mice were intranasally inoculated at postnatal day (P) 7 (infant) with pneumonia virus of mice to induce VLRTI or medium as a control. Mice were then exposed to either room air or hyperoxia (85% O2) from P10 up to P17. Long-term outcome was assessed at P28 (adult). On this endpoint, stereology and FlexiVent were used to analyse lung structure and lung function.

Results: Hyperoxia exposed mice with VLRTI showed a temporary growth arrest with no catch-up phase after recovery of the infection. Weight at P28 was significantly lower compared to control groups. At P28, no difference in parenchyma structure or alveoli number was observed. Analysis of lung function showed no difference in lung compliance or inspiratory capacity, however, a 1.6-1.9 fold increase in airway resistance in the hyperoxia VLRTI group was observed as compared to all other groups ($P<0.01$).

Discussion: In this study, mice with VLRTI who were exposed to hyperoxia during the acute course of disease showed worse outcome both in the acute phase and long-term. Especially striking was the synergistic effect of hyperoxia and VLRTI in increasing airway resistance. This shows potential deleterious effects on long-term lung function and implies possible structural airway pathology.

AKS2021_027

Shock in children in low (middle) income countries: a systematic review and meta-analysis

Assies, R.* (1, 2), Snik, I.* (1), Chimalizeni, Y. (2), Kumwenda, M. (2), Langton, J. (2), van Woensel, J.B.M. (1), Doctor, A. (3), Calis, J.C.J. (1, 2)
* Authors contributed equally

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, the Netherlands; (2) Dept. of Paediatrics and Child Health, College of Medicine, Blantyre, Malawi; (3) University of Maryland School of Medicine, Baltimore, USA

Corresponding author: Roxanne Assies, MD (r.assies@amsterdamumc.nl)

Rationale: Shock is a life-threatening condition and children in low- and middle-income countries (LMIC) may require a different treatment approach than in high income countries (HIC). This systematic review and meta-analysis summarises the prevalence, mortality, aetiology and pathophysiology of shock in children in LMIC.

Methods: We searched for studies reporting on children with shock in LMIC in PubMed, Embase and through snowballing (1 October 2019) and excluded studies in HIC, adults, cardiac surgery patients or iatrogenic causes. Data extraction and critical appraisal were performed independently by two reviewers. We present prevalence data, pooled mortality estimates using random effect models and conducted subgroup analyses per region and disease. Aetiology and pathophysiology data were systematically collected and discussed.

Results: We identified 899 studies and included 59 studies of which six primarily studied shock. Overall 18 different definitions for shock were applied. The prevalence of shock ranged from 1.5% in a paediatric hospital population up to 44.3% in critically ill children. The overall pooled mortality was 18.6% (95% CI: 13.9-23.9%). The aetiology appears to differ from HIC as gastroenteritis, sepsis, malaria and severe anaemia are all more common and often multiple conditions co-exist. The pathophysiology of shock in LMIC is poorly studied but suggests that in addition to hypovolaemia, dissociative and cardiogenic contribution may be key contributors.

Discussion: Shock is a common condition in critically ill hospitalised children in LMIC and associated with a high mortality. The aetiology and pathophysiology appear to be different from HIC. There are limited data on shock in LMIC. This knowledge deficit is compounded by a lack of a uniform bedside definition of shock.

AKS2021_028

Serum and saliva SARS-CoV2 antibody prevalence in children in the Netherlands - COVID KIDS study

Keuning, M.W. (1), de Groen, A.E. (1), Grobben, M. (1), Bijlsma, M. (1), Cohen, S (1), Berman E. (1), de Groof, F. (2), Felderhof, M. (3), Rijpert, M. (4), Molanus, D. (5), Oeij, N. (5), Rispens, T. (6), Plötz, F. B. (7) and Pajkrt, D (1).

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Paediatrics, Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands; (3) Dept. of Paediatrics, Flevoziekenhuis, Almere, The Netherlands; (4) Dept. of Paediatrics, Zaans Medisch Centrum, Zaandam, The Netherlands; (5) Dept. of Paediatrics, Flevoziekenhuis, Almere, The Netherlands; (6) Sanquin laboratory, the Netherlands; (7) Dept. of Paediatrics, Tergooiziekenhuis, Blaricum, The Netherlands.

Corresponding author: Maya Keuning, MD (m.w.keuning@amsterdamumc.nl)

Rationale: In 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) emerged as the cause of a major pandemic. Similar to global numbers, children only represent ~1% of admitted patients due to SARS-CoV2 in the Netherlands. There is a lack of evidence in the dynamics of the systemical and mucosal immune response to SARS-CoV2 in children. To date no large-scale epidemiological studies are known assessing the use of saliva samples in antibody detection. Thus, this prospective multicentre study aimed to assess systemic and mucosal SARS-CoV2 antibody prevalence in children in the Netherlands.

Methods: We simultaneously collected serum, saliva and clinical parameters in a convenience sample of children requiring venapuncture in seven participating hospitals in the North-West region of the Netherlands during 24 consecutive weeks (April 17th to October 2nd 2020). SARS-CoV2 multi-antigen and multi-isotype antibody assays were measured in serum and saliva with a multiplex assay. Serum assays were verified with the Wantai SARS-CoV-2 total antibody enzyme-linked immunosorbent assay.

Results: The preliminary data show that SARS-CoV2 IgG antibody prevalence in serum was 4%. Most seropositive children showed mucosal humoral responses with positive SARS-CoV2 IgA/IgG antibodies in saliva. The highest prevalence was found in the age groups 10-15 years and 16-18 years. Most seropositive children did not report symptomatology related to SARS-CoV2.

Conclusions: The seroprevalence in children (seeking medical care) is similar to the adult seroprevalence in the Netherlands, despite low hospital admission rates. Saliva antibody assays could provide a practical method to SARS-CoV2 antibody surveillance in order to guide future protective public health measurements.

AKS2021_029

Incidence and etiology of Dutch children with a suspected meningoencephalitis

de Blauw, D. (1), Bruning, A.H.L. (2), Wolthers, K.C. (4), van Wermeskerken, A.M.(5), Biezeveld, M.H.(6), Wildenbeest, J.G. (3), Pajkrt, D. (1)

Affiliations: unknown

Corresponding author: Dirkje de Blauw, MD (d.deblauw@amsterdamumc.nl)

Rationale: The aetiology of childhood meningoencephalitis in the Netherlands has changed significantly with the introduction of effective national vaccination programs. In this study we aimed to increase insight in the current incidence, aetiology and outcome of childhood meningoencephalitis in the Netherlands.

Methods: The study was part of the Paediatric and Adult Causes of Encephalitis and Meningitis study (PACEM), a multicohort centre study conducted in three Dutch hospitals between January 2012 and July 2015. This Paediatric study included patients aged < 18 years with a suspected meningoencephalitis. Demographic characteristics, clinical symptoms, neuroimaging, aetiology, treatment and mortality were analysed.

Results: We included 448 children with a median age of 45.5 days (IQR 10.0-365.5). We identified only 70 cases of proven meningoencephalitis (15.6%), of which 63 (90.0%) were of infectious origin. The majority of meningoencephalitis cases was caused by viral pathogens, (61.9%). Enterovirus was the most common viral pathogen (39,7%). No association between mortality or neurological deficits and aetiology of meningoencephalitis was calculated.

Discussion: A proven meningoencephalitis was diagnosed in a small minority of children with a suspected meningoencephalitis. Viral pathogens were the most frequently cause of proven infectious meningoencephalitis.

AKS2021_030

Interprofessional Education – Crossing the boundaries between medicine, nursing and paramedical professions in education and health care

Berkhout, M. (1), Lakerveld, M. (2), Oosterbaan, S. (3), de Vos, R. (4), Geukers, V. (5)

Affiliations: (1) Interprofessional Education (IPE) Program of Amsterdam UMC (Faculty of Medicine) and University of Applied Sciences (Faculty of Health); (2) Dept. of Paediatrics Amsterdam UMC; (3) IPE program OLVG West, Amsterdam, The Netherlands

Corresponding author: Marja Berkhout, MSc (m.a.berkhout@amsterdamumc.nl)

Rationale: Modern healthcare settings demand interprofessional practices (IPP) where professionals integrate their vocational expertise into an integral care plan, across the borders of traditional mono-disciplinary domains. The aims of IPP are: integrated and safer healthcare for patients, higher efficiency of care at system level, and cost reduction. The Faculties of Medicine (Amsterdam UMC) and Health (University of Applied Sciences Amsterdam) have implemented an innovative joint Interprofessional Education (IPE) program where students learn to think, speak and act in terms of IPP-teamwork. They practice the composition of integral, patient-centred care plans in 2 steps: simulation education in mixed undergraduate student groups, and the provision of actual healthcare for real patients in supervised interprofessional learning workplaces (IP-LWP, conform the OLVG-W model) in the master phase. The latter step was made possible by a Comenius Leadership Grant.

Method: We worked out a literature-based project plan, including goals, process and timeline for the development and implementation of IP-LWP's at the departments of Paediatrics and Obstetrics in Amsterdam UMC. Nurses, Paediatricians, gynaecologists, midwives, practice trainers, tutors and workplace managers were involved as stakeholders to self-implement this innovation, with guidance of a project leader.

Results: For the development of IP-LWP's, several factors proved to be important: differences in work cultures and assessments, preparation of tutors as facilitators, and a tailored supervision model for safe IPE and IPP. Also, it was necessary to operationalize facilities, both in- and exclusion criteria of patient groups, as well as the roles and responsibilities of supervisors and students. We developed a supervisor training and an implementation guide to help facilitate the roll-out of the IP-LWP's. In 2021 we aim to open the IP-LWP's at Paediatrics and Obstetrics, later followed by two other departments.

Discussion: At the departments of Paediatrics and Obstetrics of Amsterdam UMC it was feasible to commence the implementation of IP-LWP's, facilitated by a Comenius leadership Grant. Interprofessional collaboration and learning processes at the IP-LWP's will be studied in two PhD-projects, starting 2021.

AKS2021_031

Inflammatory biomarkers in venous thromboembolism as a predictor for outcome

Klaassen, I.L.M., Meijers, J.C.M., Gouw, S.C., Rettenbacher, E., Fijnvandraat, K.J.

Affiliation: Dept. of Paediatric Haematology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands

Corresponding author: Irene Klaassen, MD, PhD (i.l.klaassen@amsterdamumc.nl)

Rationale: Venous thromboembolism (VTE) is more and more a common disease in hospitalized children, with major complications like post-thrombotic syndrome (PTS). Recent evidence suggests that thrombosis and inflammation are interrelated. Therefore, we hypothesized that a stronger inflammatory response at the time of VTE diagnosis may be associated with severity of PTS.

Methods: A retrospective cohort study of all consecutive children (1-18 years), treated at Emma Children's Hospital with a symptomatic VTE between January 2015 and May 2020. The association between inflammatory biomarkers (CRP and/or D-dimer) and PTS was studied as a primary outcome and thrombus resolution and recurrence as secondary outcomes.

Results: In 39/126 patients (♂ 35.9%); mean age 12.9 ±4.8 years) at least 1 biomarker was available at diagnosis of VTE (CRP for 34/39 patients and D-dimer for 21/39 patients). Elevated inflammatory markers were present in 24 (61.5%) patients. Thirteen patients had a CRP >10 mg/l at presentation (range 12,9–335 mg/l, median 64.0, (25.3-221.0)). D-dimer was abnormal in 18 patients (range 1.18–27.1 mg/l, median 5.4 (1.7-11.1)).Ten of 39 patients (25.6%) developed PTS. Nine (9.00%) with increased inflammatory markers, 1 (10.0%) without increased inflammatory markers (RR 5.1 95% CI 1.3-20.5). All but one patients (n=8, mean age 14.6±2.4 years) with high inflammatory biomarkers (CRP >100 mg/l, D-dimer >9 mg/l) at presentation developed PTS.

8/39 Patients (20.5%) had recurrent thrombosis, 6 (75%) with increased and 2 (25%) without increased inflammatory markers (RR 3.2 95% CI 0.7-13.7). There was no association between increased inflammatory biomarkers and thrombus resolution (RR 0.8 95% CI 0.6-1.1).

Discussion: High levels of CRP and/or D-dimer are associated with development of PTS suggesting a correlation between inflammation and VTE outcome. More research is needed to confirm this outcome and might indicate the need for more individualized therapy in the future.

AKS2021_032

Translation from laboratory animals to human poliovirus pathogenesis: A systematic review.

Moreni, G.* (1,2), Aknouch, I.* (1,3), Wolthers, K.C. (1), Sridhar, A. (1), Pajkrt, D. (2)
* Authors contributed equally

Affiliations: (1) Dept. of Medical Microbiology, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Paediatric Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3) Viroclinics Xplore, Schaijk, The Netherlands

Corresponding author: Giulia Moreni, MSc (g.moreni@amsterdamumc.nl)

Rationale: Animal models are extensively being used in research. However, many animal study based results translate poorly into human disease. In this study we aim to review the translation of polio, a human disease caused by the poliovirus as this disease has been extensively studied with the use of animal models. We investigated for the first time how poliovirus infection in animals is comparable to the infection in humans in terms of route of infection, cell entry, replication sites and neurovirulence.

Methods: A systematic review was conducted. Articles of in vivo studies on polio in animal models from PubMed and EMBASE were compared with reviews on poliovirus pathogenesis in humans. The articles were independently screened by two authors based on title and abstract and the final eligibility was addressed on full-text. Quality was assessed using the SYRCLE's risk of bias for animal studies. Comparisons between animal and human study results on route of infection, cell entry, replication sites and neurovirulence were extracted and categorized.

Results: We selected 53 articles on polio animal studies and 15 reviews on human polio infections. The quality assessment showed that animal studies were poorly designed and conducted. Animal baseline characteristics were diverse, animal allocation and housing was not performed methodologically and blinding was not reported or more often not performed at all. A large variety of animal models were used and only few in more than one study. The results of animal and human studies on polio route of infection, cell entry, replication sites and neurovirulence were incongruent.

Conclusion: The lack of normalization in the animal polio studies and the wide use of different animal models in polio research lead to poor comparison and incongruency. It is striking and unexpected that such a well-known and well-studied viral infection like poliovirus is missing a proper standardization in the use of animal models. This could reflect the poor predictive value of animal models.

AKS2021_033

The role of FC gamma receptors in immune tolerance to factor VIII protein in patients with severe haemophilia A and inhibitors – GRIP study

Oomen, I. (1), Voorberg, J. (2), Kaijen, P. (2), Nagelkerke, S.Q. (3), Kuijpers T.W. (3), Fijnvandraat, C.J. (1), Gouw, S.C. (1)

Affiliations: (1) Dept. of Paediatric Haematology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Molecular and Cellular Haemostasis, Sanquin Research and Landsteiner Laboratory, Amsterdam, The Netherlands; (3) Dept. of Blood Cell Research, Sanquin Research and Landsteiner Laboratory, Amsterdam, The Netherlands.

Corresponding author: Ilja Oomen, MD (i.oomen@amsterdamumc.nl)

Rationale: Currently, the only proven strategy to eradicate anti-FVIII antibodies (inhibitors) in haemophilia A, is immune tolerance induction (ITI). Improved understanding of the immunology of inhibitor eradication may drive the design of more immune modulatory treatments. Activation of immune cells by immunoglobulin is determined by the balance in activating and inhibitory receptors for IgG, the Fc gamma receptors (FcγR), generating an activating or tolerogenic immune response. Genetic variations in FCGR genes cause differences in FcγR expression or binding affinity to different IgG subclasses. Therefore, this study aims to investigate how the interaction of FVIII-IC with FcγR directs a certain response of dendritic cells, leading to ITI success/failure in patients with haemophilia A and inhibitors.

Methods: We will perform a explorative study among healthy donors and among Dutch haemophilia A patients with inhibitors who underwent ITI therapy. From every participant, 50 ml EDTA blood will be drawn to generate monocyte-derived dendritic cells (moDC). We will use artificially created FVIII-IC (FVIII-antibodies with A2 and C2 epitopes). Expression of FcγR will be analysed with FACS. Binding and uptake of FVIII-IC by FcγR will be analysed using FITC-labelled antibodies. The cytokines produced by moDC will be analysed using ELISA. Cytokine profiles will be compared between patients with genetic variation in the FCGR genes, including FCGR2A-p.His166Arg and FCGR2C-ORF/Stop.

Results: The primary study outcome is the cytokine profile generated by moDC after binding of FcγR with FVIII-IC. Secondary, we will investigate whether this is related to genetic variation in the FCGR genes.

Discussion: Preliminary data (16 patients), found higher percentages of the FCGR2C-ORF (38% vs 12%) and the FCGR2A-p.166His genotype (75% vs 25%) in patients with ITI failure, compared to those with ITI success. Therefore, we expect to find inflammatory cytokines in donors with these genotypes.

AKS2021_034

Efficacy of non-pharmacological interventions to reduce pain in children with sickle cell disease: a systematic review

Vuong, C.* (1), van Veelen, S.* (1) Gerritsma, J.J. (1) de Groot-Eckhardt, C.L. (1), Peters, M. (1), Verbeek, S.E.M. (2), Fijnvandraat, K. (1)
* Authors contributed equally

Affiliations: (1) Paediatric Haematology, Amsterdam UMC, UvA, Emma Children's Hospital, Amsterdam, the Netherlands; (2) Psychosocial Dept., Amsterdam UMC, UvA, Emma Children's Hospital, Amsterdam, the Netherlands

Corresponding author: Caroline Vuong, MD (c.vuong@amsterdamumc.nl)

Rationale: Pain is the clinical hallmark of sickle cell disease (SCD) and is accompanied by frequent emergency Dept. visits, hospitalizations, psychological sequelae and a decreased health-related quality of life. Although pharmacological treatments to target pain are evolving, children still experience both acute and chronic pain frequently. Therefore, non-pharmacological approaches to target the pain are needed. The aim is to evaluate the effect of these interventions in reducing the frequency and intensity of sickle cell related pain in children with SCD.

Methods: We performed a literature search through June 2020 using the terms 'sickle cell', 'pain', 'psychotherapy', 'analgesic', and 'health service' . We included randomized controlled trials and quasi-experimental studies that investigated the efficacy of non-pharmacological interventions on (1) pain frequency and intensity, and (2) analgesic and health service use in children with SCD.

Results: Eleven articles including 441 participants were included. Nine studies were performed in the outpatient clinic, and investigated the efficacy of cognitive behavioural therapy, biofeedback, and massage. Two studies were performed during hospital admission, and included virtual reality and yoga. Five studies reported significant reductions in the frequency and/or intensity of pain. One of them also reported a significant reduction in analgesics use. Six studies did not report statistically significant positive effects on pain related outcomes.

Discussion: Frequent pain experiences during childhood can cause negative long term effects that can last into adulthood such as higher sensitivity to pain and anxiety and depression. Early intervention in children may influence the pain perception positively. Due to heterogeneity, conclusions can only be carefully drawn about the effectiveness. However, the evidence for non-pharmacological interventions to reduce pain in children with SCD seems promising as complementary medicine.

AKS2021_035

Investigating determinations for navigating tolerance induction in FVIII deficiency – I-DENTIFY: A systematic review and meta-analysis

Oomen, I. (1), Camelo, R. (2), Fijnvandraat, C.J. (1), Gouw, S.C. (1), also on behalf of the GO-ITI consortium. GO-ITI consortium: Carcao, M. (3), Eikenboom, H.C.J. (4), Fischer, K. (5), Leebeek, F. W. G. (6), Lillicrap, D. (7), Mancuso, M. E. (8), Matino, D. (9), Oldenburg, J. (10), Rezende, S. M. (2), Rivard, G. (11), Rydz, N. (12), Voorberg, J. (13)

Affiliations: (1) Dept. of Paediatric haematology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Internal Medicine, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil; (3) Dept. of Paediatric haematology/Oncology and Child Health Evaluative Sciences, Hospital for Sick Children, University of Toronto, Toronto, Canada; (4) Dept. of Thrombosis and Haemostasis, Internal Medicine, Leiden UMC, Leiden, The Netherlands; (5) Dept. of Paediatric haematology, Van Creveld Clinic, UMC Utrecht, Utrecht, The Netherlands; (6) Dept. of haematology, Erasmus UMC, Rotterdam, The Netherlands; (7) Dept. of Pathology and Molecular Medicine, Richardson University, Queen's Laboratory, Kingston, Canada; (8) Dept. of Thrombosis and Haemorrhagic Diseases Center, Humanitas Clinical and Research Center – IRCCS, Milan, Italy; (9) Dept. of Health Sciences, McMaster University, University of Hamilton, Hamilton, Canada; (10) Dept. of Internal Medicine, University clinic Bonn, University of Bonn, Bonn, Germany; (11) Dept. of haematology and Oncology, CHU Sainte Justine, Montreal, Canada; (12) Dept. of haematology and Hematologic Malignancies, University of Calgary, Calgary, Canada; (13) Dept. of Molecular and Cellular Haemostasis, Sanquin Research and Landsteiner Laboratory, Amsterdam, The Netherlands.

Corresponding author: Ilja Oomen, MD (i.oomen@amsterdamumc.nl)

Rationale: Currently, it is not possible to accurately predict which haemophilia patients will successfully achieve tolerance following immune tolerance induction (ITI) therapy, nor which patients will fail ITI. For more effective treatment allocation we need to identify which patients will benefit most from ITI and which patients will not benefit at all. Especially in an era with new treatment modalities become available. Therefore, this study aims to systematically review the current literature concerning genetic and non-genetic determinants for successful ITI therapy in patients with haemophilia A and inhibitors.

Methods: We will perform a comprehensive search using the PubMed, Medline and EMBASE databases. Cohort studies, general haemophilia registries or case-control studies will be included. Furthermore, we will only include studies including patients with hereditary haemophilia A who are treated with ITI therapy. The primary study outcome is the cumulative incidence of successful ITI therapy. The secondary outcome is the cumulative incidence clinically successful ITI therapy. We will identify determinants for ITI success accordingly to the primary and secondary outcome measures. Two independent reviewers will screen all articles for eligibility, perform a quality assignment of all included articles and extract data. I2-statistics will be calculated to assess statistical heterogeneity across studies. If limited clinical and methodological heterogeneity exists, we will pool the results of each study in a meta-analysis.

Results: Cumulative incidences of ITI success will be reported among different categories of potential determinants. Pooled prevalence will be calculated for subgroups for each determinant.

Discussion: Up till now, inconsistence results on most determinants for ITI outcome are reported. Therefore, this study will provide a systematic overview of the literature concerning determinants for ITI outcome.

AKS2021_036

Organ motion in thoracic and abdominal Paediatric radiation therapy – a systematic review

Meijer, K.M. (1), van Dijk, I.W.E.M. (1), Huijskens, S.C. (3), Daams, J. (2), Windmeijer, C.A.A. (1), Balgobind, B.V. (1) & Bel, A. (1)

Affiliations: (1) Dept. of Radiation Oncology, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Medical Library, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3) Dept. of Radiation Oncology, UMC Utrecht, Utrecht, The Netherlands

Corresponding author: Karin Meijer, MSc (k.m.meijer@amsterdamumc.nl)

Rationale: Radiotherapy delivered in multiple fractions is a cornerstone in treatment of Paediatric malignancies. Treating thoracic and abdominal tumours is challenging due to interfractional (day-to-day anatomical variations) and intrafractional (during treatment e.g. breathing) motion. To ensure adequate tumour dose coverage, the target volume is extended with margins, which strongly depend on the extent of organ motion. This study aims to present a literature overview of applied margins and organ motion in patients <18 years.

Methods: A systematic search of MEDLINE, Embase, Web of Science, ClinicalTrials.gov and the International Clinical Trials Registry Platform from 2000 to 2020 resulted in 5102 studies. Using predefined in- and exclusion criteria, primary and secondary study selection based on title/abstract and full text, respectively, was performed independently by three authors. Overall, 112 studies were included, with 96 studies reporting on margin sizes and delineation variability and 16 on organ motion, the latter being presented in this abstract.

Results: From these 16 studies, data on inter- and intrafractional motion from 395 paediatric patients was extracted and summarized in supplementary material S7 (p78) . The studies were heterogeneous concerning study population, age, general anaesthesia, imaging modalities and number of data sets. Cranio-caudal inter- and intrafractional motion ranged from -9.1–10.0 mm and 0.0–17.4 mm, respectively. Motion quantification methodologies differed between studies with regard to measure of displacement (centre of mass, border of organs) and directions. In several studies motion directions were not clearly defined.

Conclusion: Studies on organ motion quantification in Paediatric patients are scarce with a wide variation in studied organs and motion results. Therefore, it remains unclear how margin sizes for each situation should be defined. Next focus is on data extraction of the remaining 96 studies to enhance the knowledge on clinically used margins for various radiation indications.

AKS2021_037

Lower CMV and EBV exposure indicates an under-challenged immune system in children with Kawasaki disease

van Stijn, D. (1), Slegers, A. (1), Zaaijer, H. (2), Kuijpers, T. (1)

Affiliations: (1) Dept. of Paediatric Immunology, Rheumatology and Infectious diseases, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Medical Microbiology, Laboratory of Clinical Virology, Center for Infection and Immunity Amsterdam UMC, UvA, Amsterdam, The Netherlands.

Corresponding author: Diana van Stijn, MD (d.vanstijn@amsterdamumc.nl)

Rationale: Kawasaki Disease (KD) is a Paediatric vasculitis of which the pathogenesis is unclear. The hypothesis is that genetically predisposed children develop KD when they encounter a pathogen which remains most often unidentified or pathogen derived factors. Since age is a dominant factor, prior immune status in children could influence their reactivity and hence the acquisition of KD. We hypothesized that systemic immune responses early in life could protect against developing KD. With this study we tested whether the incidence of previous systemic cytomegalovirus (CMV) or Epstein-Barr virus (EBV) infection is lower in children with KD compared to healthy age-matched controls.

Methods and **Results:** We compared 86 KD patients with an age-matched control group regarding CMV and EBV VCA IgG measurements (taken before or 9 months after IVIG treatment). We found that both CMV and EBV had an almost 2-fold lower seroprevalence in the KD population than in the control group.

Conclusion: We suggest that an under-challenged immune system causes an altered immune reactivity which may affect the response to a pathological trigger causing KD in susceptible children.

AKS2021_038

Coronary CT angiography and cardiac MRI for detection of coronary artery aneurysms in Kawasaki disease

van Stijn, D. (1), Planken, N. (2), Kuijpers, T. (1), Kuipers, I. (3)

Affiliations: (1) Dept. of Paediatric haematology, immunology and infectious diseases, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of radiology and nuclear medicine, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3) Dept. of Paediatric cardiology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands.

Corresponding author: Diana van Stijn, MD (d.vanstijn@amsterdamumca.nl)

Rationale: Kawasaki disease (KD) is an acute vasculitis that mainly affects the coronary arteries. This inflammation can cause coronary artery aneurysms (CAAs). Cardiac assessment consists of risk stratification for the development of myocardial ischemia, based on Z score (luminal diameter of the coronary artery corrected for body surface area). Echocardiography is the primary imaging modality in KD but has several important limitations. Coronary Computed Tomography Angiography (cCTA) and cardiac MRI (CMR) are non-invasive imaging modalities and of additional value for assessment of CAAs with a higher diagnostic yield compared to ultrasound. The objective of this single center study is to determine the difference in diagnostic value of cCTA versus CMR for risk stratification in children with prior KD.

Methods and **Results:** Out of 965 KD patients from our database, a total of 111 cCTAs (104 patients) and 311 CMR (225 patients) have been performed since 2010. For comparison we identified 54 KD patients who had undergone both cCTA and CMR to compare radiologic data interpretation in daily practice. CMR missed 50% of the CAAs that were reported by cCTA imaging and identified 8 patients with CAAs compared to 14 patients by cCTA out of these 54 patients tested.

Conclusions: Our single center study in KD demonstrates that cCTA is the better modality to detect CAAs as it is capable to detect more accurately the presence of CAAs than CMR. However, CMR remains a very valuable imaging tool in KD for the assessment of the cardiac function and fibrosis, which can not be routinely detected with current settings using low-dose cCTA to date.

AKS2021_039

Markerless motion tracking from video recordings for the assessment of dyskinetic movements in cerebral palsy

Haberfehlner, H. (1), Bonouvrié, L.A. (1,2), van der Krogt, M.M. (1), Harlaar, J. (3), Buizer, A.I. (1,2)

Affiliations: (1) Dept. of Rehabilitation Medicine, Amsterdam UMC, Vu Amsterdam, Amsterdam, The Netherlands; (2) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3), Dept. of Biomechanical Engineering, Delft University of Technology, Delft, The Netherlands.

Corresponding author: Helga Haberfehlner, PhD (h.haberfehlner@amsterdamumc.nl)

Rationale: Movement disorders in dyskinetic cerebral palsy (CP) are characterized by (1) dystonia, described as abnormal patterns of posture and/or slow movements and (2) choreoathetosis, characterized by faster involuntary, uncontrolled and recurring movements. The Dyskinesia Impairment Scale (DIS) evaluates the duration and amplitude of dystonia and choreoathetosis. A drawback of the DIS is that scoring needs specialized training and is time-consuming. Extracting features directly from videos might be an option to objectively assess dystonia and choreoathetosis without increasing the burden on patients and assessors.

Methods: Ninety-one videos of 33 participants (mean age 14.3±4.0 yrs; GMFCS IV-V) from the IDYS trial at baseline (T0) and 12 months follow-up (T12) after intrathecal baclofen treatment were used, collected to score DIS. Sequences of twenty seconds were selected from videos during rest, lying down. Body landmarks were tracked using DeepLabCut, an open-source toolbox, based on deep learning. Lower leg length was used as reference to convert pixels to meters. Velocity of both knees and ankles was calculated from the extracted body landmarks. The percentage of time above a threshold velocity of 0.1 meter/second was calculated and summarized as one duration score (MMT). The MMT score were correlated to DIS duration scores of the lower limbs during rest, for dystonia and choreoathetosis, separately, using the Pearson correlation coefficient.

Results: Correlation between MMT score and DIS choreoathetosis duration score was 0.51 at T0 ($p=0.002$) and 0.89 at T12 ($p<0.001$). No significant correlation with the DIS dystonia was found.

Conclusion: Movement assessment using markerless motion tracking is easy, objective and concurrently valid to assess choreoathetosis of lower limbs. Future developments will include parameters of posture and different velocity thresholds to distinguish fast and slow movement, which may allow additional assessment of dystonia.

AKS2021_040

Barriers and facilitators to breastfeeding in moderate and late preterm infants: a systematic review

Carpay, N.C. (1), Kakaroukas, A. (2), Embleton, N.E. (2), van Elburg, R.M (1)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Newcastle Neonatal Service, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom.

Corresponding author: Nora C. Carpay, Medical student (n.c.carpaij@amsterdamumc.nl)

Rationale: Around 10% of all infants are born premature, and most are born between 32-36 weeks of gestation (moderate to late preterm (MLP)). Moderate to late prematurity comes with many short- and long-term risks. Breastfeeding (BF) reduces many of these risks, but studies show that BF rates in MLP infants are lower than in full-term infants. We aimed to conduct a systematic review of studies identifying factors associated with successful BF in MLP infants and interventions that improve BF.

Methods: Systematic search performed by PubMed April 24th 2020. Relevant articles describing barriers to BF in MLP infants and interventions to improve BF were selected. 11 articles on BF barriers and 6 articles about interventions were included. Interventions were categorized according to different outcomes: initiation of BF, continuation for 5 days to 6 weeks, and continuation for ≥3 months. Due to heterogeneity in population, interventions, and outcome measures, a meta-analysis was not performed. The review was conducted according to PRISMA by 2 reviewers (AK, NC).

Results: BF rates were lower in those with lower socio-economic status (SES) and single parent households. Providing parents with access to more information and direct health care support significantly improved BF initiation. Cup feeding instead of bottle feeding had inconsistent effects on initiation and continuation of BF. Continuous skin-to-skin contact/kangaroo care did not affect BF initiation or continuation (supplementary material S8, p79).

Discussion: Risk groups for lower BF rates of MLP infants include mothers with lower SES and single mothers. Interventions that may improve BF include cup feeding, providing parents with more information and direct healthcare support. Key limitations of the included studies are that many studies did not adequately adjust for likely confounders and studies were not blinded. However, this is the first systematic review identifying both risk groups and interventions to improve BF in MLP infants

AKS2021_041

The association between weather conditions and admissions to the paediatric intensive care unit for respiratory syncytial virus bronchiolitis

Linssen, R.S.N. (1, 2), den Hollander, B. (1), Bont, L. (3, 4, 5), van Woensel, J.B.M. (1), Bem, R.A. (1).

Affiliations: (1) Paediatric Intensive Care Unit, Emma Children's Hospital, Amsterdam UMCs, location AMC, the Netherlands; (2) Amsterdam Reproduction & Development (AR&D) and the Amsterdam Infection & Immunity (AR&I) research institutes Medical Centers, location AMC, the Netherlands; (3) Dept. of Paediatric Infectious Diseases and Immunology, Wilhelmina Children's Hospital, UMC Utrecht, the Netherlands; (4) UMCU Laboratory of Translational Immunology, UMC Utrecht, Utrecht, the Netherlands; Dept. of Paediatrics, Wilhelmina Children's Hospital, UMC Utrecht, the Netherlands; (5) Medical Research Council: Respiratory and Meningeal Pathogens Research Unit and Dept. of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Johannesburg, South Africa; Respiratory Syncytial Virus Network (ReSViNET) Foundation, Zeist, the Netherlands

Corresponding author: Rosalie Linssen, MD (r.s.linssen@amsterdamumc.nl)

Rationale: Respiratory syncytial virus (RSV) bronchiolitis forms a leading cause of global child morbidity and mortality. Seasonal RSV outbreaks put high pressure on paediatric intensive care units (PICUs) each year, including in the Netherlands, and this burden appears to be increasing. Weather conditions have strong influence on RSV activity, and climate change has been proposed as a potential important determinant of future RSV-related health care utilisation. In this national study spanning a total of 13 years with 2161 PICU admissions we aimed 1) to identify meteorological variables that were associated with the number of PICU admissions for RSV bronchiolitis in the Netherlands, and 2) to determine if longitudinal changes in these variables over time may have contributed to an observed increase in PICU burden.

Methods: We collected data on all children aged ≤24 months admitted to a PICU in the Netherlands for a confirmed RSV bronchiolitis between 2003 and 2016. Data on the weather were retrieved from Royal Dutch Meteorological Institute website. Poisson regression modelling was used to identify weather variables (aggregated in months and weeks) that predicted PICU admissions and linear regression analysis to assess changes in the weather over time.

Results: Maximum temperature and global radiation best predicted PICU admissions, with global radiation showing the most stable strength of effect in both month and week data. However, we did not observe a significant change in these weather variables over the thirteen-year time period.

Discussion: Based on our study, we could not identify changing weather conditions as a driver for the increased RSV-related PICU burden in the Netherlands during the study period.

AKS2021_042

Risk factors for inhibitor development in non-severe haemophilia A after 50 cumulative exposure days

Abdi, A. (1), Eckhardt, C.L. (1), van Velzen, A.S. (1), Vuong, C. (1), Coppens, M. (2), Laros-van Gorkom, B. (3), Leebeek, F. (4), van der Bom, J.G. (5), Fijnvandraat, K. (1), Gouw, S.C. (1)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Vascular Medicine, Amsterdam UMC, UvA, Amsterdam, Netherlands; (3) Dept. of haematology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands; (4) Dept. of haematology, Erasmus MC, UMC Rotterdam, Rotterdam , The Netherlands; (5) Dept. of Clinical Epidemiology, Leiden UMC, Leiden, Netherlands.

Corresponding author: Amal Abdi, MD (a.abdi@amsterdamumc.nl)

Rationale: The development of neutralizing antibodies (inhibitors) against Factor VIII (FVIII) is a severe complication of haemophilia treatment. Patients with non-severe haemophilia A have a life-long risk for inhibitor development. Yet, no studies looked at risk factors for inhibitor development after 50 exposure days (EDs) to FVIII concentrates. This case-control study aimed to investigate treatment-related risk factors for inhibitor development in non-severe haemophilia A and to assess whether these risk factors were different for early inhibitor development (during first 50 EDs) versus late inhibitor development (after 50 EDs).

Methods: Patients were included from the non-severe haemophilia A cohort of the INSIGHT study (FVIII baseline activity 2-40%). Inhibitor-positive patients (cases) were each matched to 1-4 inhibitor-negative controls by birthdate, cumulative number of EDs and centre/country. We investigated treatment intensity during the last 10 EDs prior to inhibitor development, classified as: surgery, peak treatment (10 consecutive EDs) and high mean FVIII dose (>40 IU/kg/ED). Crude and adjusted odds ratios (aORs) were calculated by binary logistic regression.

Results: From 2709 patients, we included 63 patients with early and 26 with late inhibitor development, matched to 206 and 72 controls, respectively. Both early and late cases were treated more intensively than controls. In early cases, high mean dose was associated with an increased risk for inhibitor development (aOR 2.6, 95% CI 1.4-4.8). In late cases, peak treatment was associated with a higher risk for inhibitor developments (crude OR 4.9, 95 CI 1.5-15.9).

Discussion: Our findings suggest that intensive FVIII treatment may increase the risk for inhibitor development in non-severe haemophilia A up to more than 50 EDs. Therefore, persistent vigilance is required throughout the life-time treatment course.

AKS2021_043

Reliable detection of subtypes of nailfold capillary haemorrhages in childhood-onset systemic lupus erythematosus

Bergkamp, S.C. (1), Schonenberg-Meinema, D. (1), Nassar-Sheikh Rashid, A. (1), Melsens, K. (2, 3), Vanhaecke, A. (2, 3), Boumans, M.J. (4), , P. C. Hissink Muller, P.C. (5), Cutolo, M. (6), Kuijpers T.W. (1), van den Berg, J.M. (1), Smith, V. (2, 3, 7)

Affiliations: (1) Dept. of Paediatric Immunology, Rheumatology and Infectious Diseases, Emma Children's Hospital, Amsterdam University Medical Centres (AUMC), UvA, Amsterdam, The Netherlands; (2) Dept. of Internal Medicine, Ghent University, Ghent, Belgium; (3) Dept. of Rheumatology, Ghent University Hospital, Ghent, Belgium; (4) Dept. of Rheumatology, Maxima Medical Centre, Eindhoven, The Netherlands; (5) Dept. of Paediatric Rheumatology, Leiden University Medical Centre, Leiden, the Netherlands; (6) Research Laboratory and Academic Division of Clinical Rheumatology, Dept. of Internal Medicine, University of Genova, IRCCS Polyclinic San Martino Hospital, Genova, Italy; (7) Unit for Molecular Immunology and Inflammation, VIB Inflammation Research Centre (IRC), Ghent, Belgium

Corresponding author: Sandy Bergkamp, MD (s.c.bergkamp@amsterdamumc.nl)

Rationale: Systemic Lupus Erythematosus (SLE) is a severe chronic disease for which it is necessary to obtain more indicators of disease severity that predict disease damage. Nailfold capillary abnormalities could be such an indicator or biomarker in SLE. Nailfold capillary haemorrhages have been observed in adults and children with SLE as an abnormality that was significantly correlated with disease activity. Recently, different subtypes of capillary haemorrhages have been described in a cross-sectional case-control study of childhood-onset (c)SLE. The aim of this current study was to evaluate the inter- and intra-observer reliability for detection of different subtypes of capillary haemorrhages, as identified by nailfold videocapillaroscopy (NVC) in cSLE patients.

Methods: Five raters blindly evaluated 140 capillaroscopy images from 35 cSLE-patients (diagnosed according to 2012 SLICC criteria). The images were assessed qualitatively (present or absent) and quantitatively (total number) on four different subtypes of haemorrhages: 1) punctate extravasations, 2) perivascular haemorrhage, 3) large confluent haemorrhage and 4) non-definable. As subgroups 1) and 2) were interpreted as a continuous spectrum, a post-hoc analysis with "merged" (mean) kappa/ICC was additionally calculated as one sub-group.

Results: Qualitative assessment showed a kappa 0.65 (95% CI: 0.60-0.70) for "punctate extravasations and perivascular haemorrhages merged" and a kappa 0.78 (95% CI: 0.72-0.83) for large confluent haemorrhages. For the quantitative assessment, ICC was 0.82 (95% CI: 0.76-0.87) for the "merged groups" and ICC 0.93 (95% CI: 0.91-0.95) for large confluent haemorrhages (see supplementary material S9, p80).

Conclusion: Our study shows that different subtypes of capillary haemorrhages in cSLE-patients could be reliably reproduced by different raters. This confirms our recent observation of perivascular extravasations as a subgroup of capillary haemorrhage in cSLE that might reflect endothelial dysregulation.

AKS2021_044

Depression, anxiety and resilience during COVID-19 in patients with cystic fibrosis or primary ciliary dyskinesia and their caregivers

Noij, L.C.E. (1), Haarman, E.G. (1), Hashimoto, S. (1), Terheggen-Lagro, S. (1), Altenburg, J. (2), Verkleij, M. (3)

Affiliations: (1) Dept. of Paediatric Pulmonology, Emma Children's Hospital, Amsterdam UMC, The Netherlands; (2) Dept. of Pulmonology, Amsterdam UMC, The Netherlands; (3) Dept. of Paediatric Psychology, Amsterdam UMC, The Netherlands.

Corresponding author: Lieke Noij, MSc (l.noij@amsterdamumc.nl)

Rationale: The novel coronavirus disease (COVID-19) has since December 2019 spread across the world, leading to implementation of government measures such as national lockdowns and social distancing. These measures are associated with a negative impact on mental health such as higher risks of anxiety, depression and suicide (Choi, et al. 2020). Populations already struggling with higher prevalence of anxiety and depression are patients with cystic fibrosis (CF) or primary ciliary dyskinesia (PCD) and their caregivers (Quittner et al. 2014). The aim of this study was to evaluate the impact of the COVID-19 pandemic on mental health (depression, anxiety and resilience) among this population.

Methods: A quantitative, cross-sectional with retrospective aspect, questionnaire study was performed in adolescents (12-18 years), adults and parents/caregivers of children (0-18 years) with CF or PCD, followed up at Amsterdam UMC. Participants completed five questionnaires on mental health: the Patient Health Questionnaire (PHQ-9) for depression, the Generalized Anxiety Disorder (GAD-7), the Brief Resilience Score (BRS), the COVID-19 Exposure and Family Impact Survey (CEFIS) and a COVID-19-specific questionnaire. Results from the PHQ-9 and GAD-7 were compared to participants' pre-pandemic scores.

Results: 65 participants (23 patients, 42 parents) completed all questionnaires. Prevalence of depression and anxiety during the pandemic were high (34% and 40% respectively), but median PHQ-9 and GAD-7 scores during the pandemic did not differ from the pre-pandemic outcomes. Scores for resilience were within the normal range (see supplementary material S10, p81).

Discussion: Despite the high prevalence of depressive and anxiety symptoms among adolescents, adults and parents of patients with CF or PCD, we did not detect a change in these symptoms during the pandemic. Resilience was within the normal range. Therefore, the current study could not demonstrate a significant impact of COVID-19 on mental health in our population.

AKS2021_045

Exploring physicians' experiences and impact of a group-based intervention to promote physician well-being among Dutch Paediatricians and residents

Rotte, L.G.Y. (1), Smits, M.J. (1), Loots, C.M. (2), Zeevenhooven, J. (3), Frenkel, J. (1), Debets, M.P.M. (4)

Affiliations: (1) Dept. of Paediatrics, Wilhelmina Children's Hospital, UMC Utrecht, Utrecht, Netherlands; (2) Amsterdam UMC, UvA, General Practice/Family Medicine, Amsterdam, The Netherlands; (3) Emma Children's Hospital, Amsterdam UMC, UvA, Paediatric Gastroenterology, Amsterdam, The Netherlands; (4) Research Group Professional Performance and Compassionate Care, Dept. of Medical Psychology, Amsterdam UMC, UvA, Amsterdam, The Netherlands

Corresponding author: Judith Zeevenhooven, PhD (j.zeevenhooven@amsterdamumc.nl)

Rationale: Physicians' well-being is under enormous pressures, but is crucial for physicians themselves, the quality of patient care and the performance of healthcare organizations. Interventions are needed to eliminate physicians' burnout and foster professional fulfilment. This study explored physicians' experiences of such an intervention and the impact on burnout and professional fulfilment.

Methods: The intervention, called the BURNIN Program, was tailored for the Paediatric Dept. of a Dutch tertiary children's hospital and was performed over the course of 2019. The intervention consisted of 4 voluntary workshops addressing 1) talents and motivations, 2) teamwork, 3) core values and authenticity, 4) just culture. Physicians' experiences were qualitatively investigated using feedback forms and semi-structured telephone interviews. The impact of the individual workshops and the total intervention was assessed by pre-post questionnaires, including the Professional Fulfilment Index, assessing professional fulfilment and burnout, and the Utrecht Work Engagement Scale, assessing work engagement.

Results: 51 consultants and residents (about 30%) participated in the intervention. Most attended 1 of the 4 workshops. Key experiences included 1) beneficial impact of insight into own behaviour and core values, and that of colleagues, on work life, 2) creation of a safe and positive environment through group-based intervention with both consultants and residents, 3) practical applicability of workshop content in work environment. The questionnaires revealed no significant reduction in burnout scores or increases in professional fulfilment.

Discussion: The experiences of participants were positive and emphasized a beneficial impact of the BURNIN Program on work life and attitude, but due to the low numbers and lack of a control group, we were unable to quantify the effect of the workshops nor the total intervention on professional fulfilment and burnout.

AKS2021_046

CHildren treated with vincristine: A trial regarding Pharmacokinetics, DNA And Toxicity of targeted therapy In Paediatric oncology patients (CHAPATI).

Uittenboogaard, A. (1), van de Velde, M.E. (1), Njuguna, F. (2), Vik, T. (3), Langat, S. (2), Kaspers, G.J.L. (1, 4).

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, Vu Amsterdam, Paediatric Oncology, NL; (2)Paediatrics, Moi University/Moi Teaching and Referral Hospital, Eldoret, Kenya; (3) Dept. of Paediatrics, Division of haematology/Oncology, Indiana University School of Medicine, Indianapolis, United States of America; (4) Princess Máxima Center for Paediatric Oncology, Utrecht, the Netherlands.

Corresponding author: Aniek Uittenboogaard, MD (a.uittenboogaard@amsterdamumc.nl)

Rationale: Vincristine (VCR) is a cornerstone for treatment of many types of childhood cancer. A dose-limiting side effect of VCR is vincristine-induced peripheral neuropathy (VIPN). To prevent severe VIPN, VCR is dose capped at respectively 2.0 and 2.5 mg/m2 in Caucasian and Kenyan children. However, there are large interindividual differences in VCR metabolism, leading to a wide range of VCR concentrations. VCR is predominantly metabolized by the CYP3A family of enzymes and it has been shown that CYP3A5 high-expressers metabolize VCR more efficiently. 60-70% of African-Americans are CYP3A5 high-expressers, compared to 18-30% of Caucasians. Besides and in agreement with this, black children have a considerable lower risk of developing VIPN than Caucasian children. Combined with the knowledge that black children have worse therapeutic outcome, this has led to the hypothesis that black children might receive subtherapeutic VCR treatment. Therefore, we aim to optimize VCR dosage in Kenyan children with cancer while monitoring VIPN.

Methods: The study will be carried out at the Moi Teaching and Referral Hospital. We aim to include 100 children who are scheduled to receive VCR. VCR concentration will be measured via a finger prick assay and liquid chromatography and mass spectrometry will be performed. The sensitivity of Dried Blood Spot vs. Mitra analysis for the finger prick assay will be determined. The area under the curve will be compared to a reference cohort. The presence of VIPN is being monitored continuously. Based on AUC and VIPN data, the vincristine dosage will be optimized for the next VCR administration. This cycle can be repeated for a maximum of three times.

Results : The trial will start mid 2021.

Discussion: Potential impact: To lower mortality due to cancer in black children all over the world by avoiding subtherapeutic dosing. Optimizing vincristine dosage for not only black but all children: they might also be receiving under- or overtreatment.

AKS2021_047

The Treatable Intellectual Disability App: Update 2020

Hoytema van Konijnenburg, E.M.M. (1), Wortmann S.B. (2), Koelewijn M. (2), Houben R. (3), Ferreira C.R. (4), van Karnebeek C.D.M. (1, 2, 5)

Affiliations: (1) Dept. of Paediatrics, Amsterdam UMC Amsterdam, the Netherlands; (2) Dept. of Paediatrics, Radboud UMC, Nijmegen, the Netherlands; (3) Health2Media; (4) National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA; (5) On behalf of United for Metabolic Diseases, the Netherlands

Corresponding author: Eva M.M. Hoytema van Konijnenburg, MD, PhD (eva.hoytemavankonijnenburg@amsterdamumc.nl)

Rationale: To improve early recognition and intervention for treatable inborn errors of metabolism (IEM) presenting with intellectual disability (ID), an accessible digital tool (www.treatable-id.org) was created in 2012 based on results of a systematic literature review. Advances in technology have catalysed developments of gene discovery and therapeutic interventions, requiring an update of Treatable-ID.

Methods: We performed a scoping literature review of treatable IEMs presenting with ID. Pubmed was searched up to October 2020 to: 1) analyse whether the 89 previously included IEMs still met inclusion criteria (causal therapy with evidence for improvement of ID, epilepsy, survival or neurologic features); and 2) identify treatable IEMs presenting with ID not previously included. A minimum of 2 reviewers were involved and consensus was reached with expert opinion. A level of evidence was assigned to each treatment.

Results: We identified a total of 116 treatable IEMs with ID amenable to causal therapy; 20 IEMs from the previous review were excluded while 47 IEMs were added. The following treatment strategies were identified: nutritional (32%); pharmacological (22%); vitamin and trace element (22%); solid organ transplant (8%); stem cell transplant (4%); enzyme replacement (3%); gene-based (1%) and other (7%). Levels of evidence varied from 1-3 (based on trials, cohort or case-control studies) for 19%; 4 (based on case-series) for 61% and based on a single case-report for 20%.

Discussion: The number of treatable IDs has increased by 25% in 6 years. Although there has been much attention on gene-based and enzyme replacement therapy, the majority of currently available, effective treatment strategies are nutritional. These are relatively cheap, widely available, non-invasive and can be surprisingly effective. We encourage clinicians to use www.treatable-id.org to facilitate diagnosis and intervention for treatable IDs.

AKS2021_048

Cerebral organoids as a model for Enterovirus D68 infection

Depla, J.A. (1,2,3), Mulder, L.A. (1,3), Evers, M.M. (2), Wolthers, K.C. (1) Pajkrt, D. (3) and Sridhar, A. (1,3)

Affiliations: (1) Organovir Labs, Dept. of Medical Microbiology, Amsterdam UMC, Amsterdam, The Netherlands; (2) uniQure Biopharma B.V., Amsterdam, The Netherlands; (3) Dept. of Paediatric Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands.

Corresponding author: Josse Depla, MSc (j.a.depla@amsterdamumc.nl)

Rationale: Enterovirus D68 is a non-polio enterovirus (a positive strand RNA virus) that has caused an increasing number of outbreaks of neurologic disease in the last decade. While it primarily infects the airways leading to respiratory distress, EV-D68 infection can cause acute flaccid myelitis (AFM) in children. Currently, the pathogenesis is largely unclear and a vaccine or effective treatment is missing. We used induced pluripotent stem cell (iPSC) derived cerebral organoids to investigate whether EV-D68 infection is strain dependent. 3D human cell cultures consist of neuronal progenitor cells, neurons, and astrocytes and have been useful in modelling infection by viruses such as Zika virus and SARS-CoV2.

Methods: We infected human cerebral organoids containing NPCs, neurons, astrocytes with EV-D68 strains that are either dependent on solely sialic acid binding for entry: 2042, or strains that are dependent on sialic acid and heparin: 947 and 1348. We measured total viral particles in the cerebral organoid medium with qPCR and infectious particles with TCID50. Cell tropism was studied using confocal imaging.

Results: Only EV-D68 2042 was able to replicate and produce infectious virus in the medium of iPSC derived cerebral organoids. We were able to demonstrate that astrocytes are being infected.

Discussion: We have shown that human cerebral organoids are susceptible to EV-D68 2042. Our results show that cerebral organoids can be used as a model to study EV-D68 tropism and receptor usage in the human brain and in the future to evaluate novel therapeutic strategies.

AKS2021_049

Advances in measuring Paediatric general health: A comparison of the PROMIS® Paediatric Global Health scale (PGH-7) and the Paediatric Quality of Life Inventory (PedsQL).

Luijten, M.A.J. (1,2), Haverman, L. (1), van Litsenburg, R.R.L. (3,4), Grootenhuis, M.A. (3), Terwee, C.B. (2)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Child and Adolescent Psychiatry & Psychosocial Care, Amsterdam Reproduction and Development, Amsterdam Public Health, Meibergdreef 9, Amsterdam, Netherlands; (2) Amsterdam UMC, Vrije Universiteit, Epidemiology and Data Science, Amsterdam, the Netherlands; (3) Princess Máxima Center for Paediatric Oncology, Utrecht, the Netherlands; (4) Emma's Children's Hospital, Amsterdam UMC, Vu Amsterdam, Paediatric Oncology, Cancer Center Amsterdam, Amsterdam, the Netherlands

Corresponding author: Michiel Luijten, MSc (m.luijten@amsterdamumc.nl)

Rationale: To globally standardize the measurement of physical, mental and social health in children, Patient-Reported Outcomes Measurement Information System (PROMIS) investigators developed the Paediatric Scale v1.0 Global Health (PGH-7, nitems=7), which has shown to be sufficiently valid and reliable. In the Emma Children's Hospital the Paediatric Quality of Life Inventory (PedsQLTM, nitems=23) is the most commonly used measure of Paediatric health. The aim of this study was to assess the psychometric properties of the PGH-7 to determine if it would be a suitable and feasible replacement of the PedsQL in clinical practice.

Methods: Children aged 8-18 years (n=2654), representative of the Dutch population were asked to complete the PGH-7 and the PedsQL. To assess structural validity of the PGH-7 a graded response model (GRM) was fitted to the data after checking the assumptions: Unidimensionality, local independence and monotonicity. Item fit of the GRM model was inspected by item misfit. Additionally, convergent validity was assessed by correlating the PGH-7 and PedsQL scores (expected r >.50). Percentage of participants reliably measured was assessed using the standard error of measurement (SEM) <0.32 as a criterion (equals reliability of 0.90). Relative efficiency was calculated (1- SEM2)/nitems) to compare how well both instruments perform relative to the amount of items administered.

Results: In total 1082 (40.8%) children participated. All GRM assumptions were met. The PGH-7 displayed structural and convergent (r=.65) validity. Both questionnaires measured reliably (nPGH-7=74.5%, nPedsQL=76.6%) at the mean and 2SD in clinically relevant direction. The PGH-7 outperformed the PedsQL in terms of relative efficiency (2.6).

Discussion: The PGH-7 displays sufficient reliability/validity in the general Dutch Paediatric population and measures more efficiently than the PedsQL. The PGH-7 is a feasible instrument for assessment of global health in clinical practice.

AKS2021_050

Incidence of delayed haemolytic transfusion reactions in patients with sickle cell disease: The Dutch experience

Gerritsma, J.J. (1), Bongaerts, V. (1), de Groot-Eckhardt, C.L. (1), Biemond, B.J. (2), Nur, E. (2), Heijboer, H. (1), Fijnvandraat, K. (1)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Amsterdam UMC, UvA, Dept. of haematology, Amsterdam, the Netherlands

Corresponding author: Jorn Gerritsma, MD (j.j.gerritsma@amsterdamumc.nl)

Rationale: Red blood cell transfusions remain a cornerstone in the treatment of sickle cell disease (SCD). Delayed haemolytic transfusion reaction (DHTR) is a potentially life-threating complication of RBC transfusion. SCD patients are at relatively high risk of DHTR, due to the high incidence alloimmunization in this population. Since 2011, the Netherlands has introduced extended matching for SCD patients, aiming to reduce alloimmunization rates. We aimed to study the effect of this matching policy on DHTR incidence.

Methods: We performed a retrospective cohort study in the Amsterdam UMC. Patients that received at least one unit as part of an occasional transfusion episode (OTE) since 2011 were included. Records were screened between 3 and 25 days after each OTE for signs of DHTR (i.e. pain, Hb drop, high LDH) using a standardized scoring form. Diagnosed or suspected DHTRs were discussed with an expert panel.

Results: In total, 205 patients were included, receiving 685 OTEs with a total of 1901 transfused units. During the follow-up period, 10 patients were identified to have experienced a DHTR. Six DHTRs were diagnosed at the time of presentation, while four were diagnosed in retrospect. The cumulative incidence of DHTRs was 4.9% per patient over an observation period of 9 years and 4 months, with an incidence rate of 14.6/1000 OTEs. One patient died due to the DHTR. Previous antibody formation was strongly associated with a DHTR (OR 18.6, 95%CI (4.3-80.6)).

Discussion: We have observed significantly lower incidence rates of DHTR compared to current literature. This supports the hypothesis that extended matching further reduces alloimmunization incidence, and thereby the risk of DHTR. Still, almost half of the DHTRs were initially not diagnosed, as symptoms mimicked vaso-occlusive crises. Therefore, the real incidence of DHTR is most likely higher. Transfusion safety is of vital importance in SCD. Therefore, screening for DHTR should receive more attention, as early treatment improves patient outcomes.

AKS2021_051

HCMV infection in cerebral organoids

Mulder, L.A. (1,3), Depla, J.A. (1,2,3), Capendale, P.E (1,3).

Affiliations: (1) OrganoVIR Labs, Medical Microbiology, Amsterdam UMC; (2) UniQure Biopharma B.V., Amsterdam; (3) Dept. of Paediatric Infectious Diseases, Emma Children's Hospital, Amsterdam UMC

Corresponding author: Lance Mulder, MSc (l.a.mulder@amsterdamumc.nl)

Rationale: Human cytomegalovirus (HCMV) is a member of the Herpesviridae family and has a wide prevalence worldwide. HCMV can follow a placental transmitted from mother upon developing child leading to congenital infection. Congenital HCMV (cHCMV) infection can result in long-term neurological sequelae including microcephaly, intellectual impairments, sensorineural hearing loss and ophthalmologic abnormalities. The pathogenesis of cHCMV infection is unknown. Studying the developing brain in vivo is challenging. Pluripotent stem cell technology generating human brain organoid have proven useful tools to approach this challenge. The current study aimed to establish a human brain organoid model to study brain development after HCMV infection. The objective of this study was to establish HCMV infection in an established human organoid model. First, cerebral organoids were generated from the iPS(IMR90)-4 cell line. Then, organoids were infected with HCMV obtained from urine samples.

Methods: Brain organoids were grown for 45 days before HCMV infection. Organoids were washed three times and cultured in their regular medium for 21 days with medium changes every 4-5 days. Since HCMV remains intracellular before lysing the whole cell, whole organoids were studied as well. Medium samples were collected every day and cerebral organoids were collected at Day 3 post-infection (p.i.), Day 10 p.i. and 21 days p.i. to observe viral replication over three weeks.

Results: Medium samples did not show virus replication over time. CT values decreased over time in lysed cerebral organoids, indicating viral replication.

Discussion: We were able to show effective HCMV infection of developing human cerebral organoids making them a validated model to study cHCMV infection. Additionally, in the near future organoids will be generated from HCMV-infected induced pluripotent stem cells to study the effect of infection from initiation of cerebral development.

AKS2021_052

Exploring reasons of adolescents with respiratory disease to participate in clinical research: results of the PICTURES study

Maitland, H.R.C. (1), Hashimoto, S. (2,3), Longo, C. (2), Bartlett, G. (4), Latif, S.L. (2, 3), Terheggen-Lagro, S.W. (3), Vijverberg, S. (2, 3), Maitland-van der Zee, A.H. (2, 3)

Affiliations: (1) Youth advisory board Emma Paediatric hospital, Amsterdam UMCs, UvA, Amsterdam, The Netherlands; (2) Dept of Respiratory Medicine, Amsterdam UMCs, UvA, Amsterdam, The Netherlands; (3) Paediatric Respiratory Medicine, Emma Children's Hospital, Amsterdam UMCs, UvA, Amsterdam, The Netherlands; (4) Dept of Population Health and Outcomes Research, University of Missouri, Columbia MO, United States

Corresponding author: Henriëtte R.C. Maitland, Chair youth council respiratory disease (henriettemaitland@gmail.com)

Rationale: Factors influencing willingness of adolescents with a chronic respiratory disease to participate in clinical research are unknown. In this exploratory study we aim to assess the willingness of adolescents to three hypothetical case studies, as well the agreement between parents and adolescents.

Methods: In total, 20 patients with a chronic respiratory disease (12-17 years) were included in a Paediatric outpatient clinic, 13 were accompanied by a parent who also participated. The participants completed 2 surveys: one on personal characteristics (including disease severity) and one on their willingness to participate in 3 case studies (a quality of life questionnaire study, an observational study with venapunction and a high-risk drug RCT). Multivariate logistic regression was used to study relations between characteristics and willingness to participate, and adolescent choices were compared with their parent's choices.

Results: Adolescents were most likely to participate in the observational study (55%), then the questionnaire study (50%), and only 20% were willing to participate in the drug RCT. For the observational study and the questionnaires study 39% of the adolescents opinions differed from their parents. For the observational study this was predominantly parents who were willing to participate in contrast to adolescents who were not. For the questionnaires study this was the other way around. For the drug RCT there was disagreement in 23%, also mainly adolescents who would participate while their parents would not. The multivariate analysis showed no statistically significant associations.

Discussion: Overall, adolescents are willing to consider participating in clinical studies. The opinions of the adolescents and their parents varied considerably. More research in a larger study population is needed to study reasons for not willing to participate.

AKS2021_053

Patient satisfaction and adherence with Videoconsulting in adolescents with severe Haemophilia : HemChat-study

Beijlevelt, M. (1), Peters, M. (1), Teela, L. (2), Fijnvandraat, K. (1)

Affiliations: (1)Paediatric haematology, Amsterdam UMC, UvA, Emma Children's Hospital, Amsterdam, the Netherlands; (2) Psychosocial Dept., Amsterdam UMC, UvA, Emma Children's Hospital, Amsterdam, the Netherlands

Corresponding author: Marlène Beijlevelt, MSc (m.beijlevelt@amsterdamumc.nl)

Rationale: Children with a severe form of haemophilia start with prophylaxis at a very young age to reduce the risk of joint bleedings, and thus permanent damage to the joints. In adolescence, the life of young people changes drastically. Approximately 25% of the adolescents with haemophilia stops (temporarily) with prophylactic treatments which may lead to an increase of (spontaneous) joint bleedings. Furthermore , face to face outpatient visits are regularly skipped. The objective of this study is to achieve patient satisfaction, to reduce no show's and to increase adherence of medication by offering video consultations compared to face to face consultation at the outpatient clinic.

Methods: This prospective cohort study , started in June 2020. Adolescents and young adults , age 16-25 years with severe haemophilia on prophylaxis with clotting factor concentrates who are known at the Haemophilia Treatment Center Amsterdam, are twice offered a video intervention in a period of 6 months. The video consulting is offered via My Chart in Epic. The pre- intervention data are compared with those during the intervention. Patient satisfaction will be asked via semi-structured interviews.

Results: The study is currently ongoing. Results up to now: Eighteen (72%) adolescents were included with an average age of 20.9 years. The average duration of the video consultations was 28.5 min with a spread of 20-36 minutes. 17% had 2x no show at video consultations, compared to 29% at face to face consultations. Two adolescents who were stopped prophylactic treatment before start of the study restarted during the study period.

Discussion: Video consultations can strengthen the tendency of adolescents to reduce the relationship with the haemophilia treatment centres. Video consultations cannot replace physical examination of the patient.

AKS2021_054

Diaphragm activity pre- and post-extubation in ventilated critically ill paediatric patients, measured with transcutaneous electromyography

van Leuteren, R.W. (1,2,4), de Waal, C.G. (1), de Jongh, F.H.C. (1,5), Bem R.A. (3), van Kaam, A.H (1,2) & Hutten, G.J. (1,2)

Affiliations: (1) Dept. of Neonatology, Emma Children's Hospital, Amsterdam UMC, University or Amsterdam, Amsterdam, The Netherlands; (2) Dept. of Neonatology, Emma Children's Hospital, Amsterdam UMC, Vu, Amsterdam, the Netherlands; (3) Paediatric Intensive Care Unit, Emma Children's Hospital, Amsterdam UMC, University or Amsterdam, Amsterdam, The Netherlands; (4) Amsterdam Reproduction & Development research institute, Amsterdam, the Netherlands; (5) Faculty of Science and Technology, University of Twente, Enschede, The Netherlands

Corresponding author: Ruud van Leuteren, MSc (r.w.vanleuteren@amsterdamumc.nl)

Rationale: While often life-saving, invasive mechanical ventilation (MV) is a risk factor for development of morbidities. Swift extubation is essential, but accurate parameters to assess extubation readiness in children are lacking. As a result, extubation failure rates from 4 to 46% have been reported. Especially in young children, the diaphragm is essential to breathe adequately, but knowledge on diaphragm activity at the time of extubation is scarce. Main study goals were to describe diaphragm activity before and after extubation in critically-ill children and compare success with failed cases.

Methods: Children admitted to the NICU and PICU were included if: MV>24 hours, planned extubation and written parental consent. Extubation failure was defined as reintubation <72 hours. Electrical activity of the diaphragm was measured with transcutaneous electromyography of the diaphragm (dEMG) using skin electrodes. The recording was made from 15 minutes before till three hours after extubation. Peak- (end-inspiratory, dEMGpeak) and tonic activity (end-expiratory, dEMGton) and respiratory rate (RR) were calculated from the dEMG-signal.

Results: 147 children were included (median age 1.9 (0.9-6.7) weeks with 4 (2.2-6.1) ventilator days). Twenty children (13.6%) failed extubation. Overall, dEMGpeak and RR increased significantly after extubation (30.8 and 29.8% increase, both $p<0.05$). Compared to successful extubation, children failing extubation showed a higher dEMGpeak , dEMGton and RR before extubation ($p<0.05$), which increased to a lesser extent after extubation (Supplementary material S11, p82).

Discussion: This study is describing the effect of extubation on diaphragm activity in critically-ill children. Diaphragm activity increased post-extubation and differences were found between success and failed extubation. We propose that dEMG may be a promising tool, combined with other readiness markers. Future studies need to determine the predictive value of dEMG for extubation failure.

AKS2021_055

Configuring SCD care through talk

Dréano, C., M'charek, A.A.

Affiliation: UvA, Amsterdam, the Netherlands.

Corresponding author: Clement Dreano, MSc (c.m.dreano@uva.nl)

Rationale: This paper explores talk as a care practice in the context of Sickle Cell Disease care (SCD). In the Netherlands, SCD is largely unknown in society as a chronic disease that patients live with daily. All the while, research about professional care tends to make visible difficulties of care provision in terms of a barrier to 'transparent' communication between patients and professional caregivers. In this anthropological research, we address the role of language in care practices in yet a different way. We argue that talk between professionals, patients and immediate care-givers is about configuring what matters in living daily with SCD.

Methods: The analysis is based on ethnographic notes from consultations with patients in a Paediatric policlinic in 2005 and in 2019.

Results: To know what it is to live with SCD, professionals are reliant on patients. We discovered that this knowledge of living is crucially developed and shared through talk. We examine three objectives of care 1)Talk as to develop an embodied subjectivity, for the patient and immediate care givers to help know the body and know when a crisis might come up 2) Talk as to help patients care for the relationships between their bodies and their environments 3) Talk as a way of knowing and managing problems, of making the professional sensitive to the life-world of the patient. Through talk, our three objectives of care appear as con-figurations – as objectives of care that are figured out together.

Conclusion: It is important to value talk as a work of care, as SCD care is often dominated in research by curative efforts and prevention paradigm. We discuss talk as a matter of trust and interdependence, and highlight its necessary ongoing-ness, for it to be transformative. That is, to turn objectives of care into daily habits for the patients and care-givers. But also for the practitioners, to learn what is going on. Practitioners are thus in a crucial way at the learning end of talk itself, as it can help them to provide better care.

AKS2021_056

Fecal volatile metabolomics to predict late-onset sepsis in preterm infants: a multi-center case control study

Frerichs, N.M. (1,2), Niemarkt, H.J. (3) Willem P. de Boode, W.P. (4), Veerle Cossey, V. (5), Hulzebos, C.V. (6), van Kaam, A.H. (7,8), Kramer, B.W. (9), van Lingen, R.A. (10), Vijlbrief, D.C. (11), van Weissenbruch, M.M. (7), Wicaksono, A.N. (12), Covington, J.A. (12), Benninga, M.A. (2), de Boer, N.K.H. (13), el Manouni el Hassani, S.* (1,2) and de Meij, T.G.J.* (2)
* Authors contributed equally

Affiliations: (1) Dept. of Paediatric Gastroenterology, Amsterdam UMC, Vu, Amsterdam; (2) Dept. of Paediatric Gastroenterology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam; (3) Neonatal Intensive Care Unit, Máxima Medical Center, Veldhoven; (4) Neonatal Intensive Care Unit, Radboud UMC, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands; (5) Neonatal Intensive Care Unit, University Hospitals Leuven, Belgium; (6) Neonatal Intensive Care Unit, Beatrix Children's Hospital/UMC Groningen; (7) Neonatal Intensive Care Unit, Amsterdam UMC, Vu; (8) Neonatal Intensive Care Unit, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam; (9) Dept. of Paediatrics, Maastricht UMC; (10) Neonatal Intensive Care Unit, Amalia Children's Centre/Isala, Zwolle; (11) Neonatal Intensive Care Unit, Wilhelmina Children's Hospital/UMC Utrecht, The Netherlands; (12) School of Engineering, University of Warwick, United Kingdom; (13) Dept. of Gastroenterology and Hepatology, Amsterdam UMC, Vu, Amsterdam, The Netherlands

Corresponding author: Nina Frerichs, BSc (n.m.frerichs@amsterdamumc.nl)

Rationale: Early detection of late-onset sepsis (LOS) in preterm infants is crucial since timely treatment is the most important prognostic factor. We hypothesize that analysis of faecal volatile organic compounds (VOC), reflecting microbiota composition and function, may serve as non-invasive biomarker for preclinical LOS detection. We aimed to identify LOS-specific VOC profiles and metabolites.

Methods: Faecal samples and clinical data of premature infants (gestational age ≤30 weeks) from nine neonatal intensive care units were prospectively collected up to 28 days postnatally. Samples were analysed by means of Gas chromatography – ion mobility spectrometry (GC-IMS), a pattern recognition technique, and Gas chromatography – time of flight – mass spectrometry (GC-TOF-MS), allowing for identification of unique metabolites. Faecal VOC profiles from LOS infants with gram-negative, gram-positive and coagulase negative staphylococcus LOS were compared with matched controls (based on centre of birth, gestational age, birth weight and postnatal age at LOS onset), up to three days before LOS onset.

Results: 121 LOS infants and 121 matched controls were included and analysed by GC-IMS. Based on sample availability, 34 LOS infants and their matched controls were analysed by GC-TOF-MS. Gram-negative LOS could be discriminated from controls at one and two days before LOS onset (p-value; AUC of 0.01; 0.82 and 0.031; 0.76, respectively) (GC-TOF-MS). VOC differences in this group were most profound for E. coli LOS at one and two days prior to LOS onset (0.024; 0.73 and 0.0001; 0.92, respectively) (GC-IMS). Gram-positive LOS could be discriminated from controls one day prior to LOS (0.003; 0.78) by GC-IMS. Furthermore, GC-TOF-MS allowed for identification of a set of pathogen-specific discriminative metabolites.

Discussion: We observed significant pathogen-specific differences in faecal VOC profiles and metabolites up to three days before LOS onset, underlining the potential as early diagnostic biomarker for LOS.

AKS2021_057

Gut organoids, a promising model to study enterovirus infection and disease pathogenesis

Aknouch, I. (1,2,5), Roodsant, T. (1,3), Navis, M. (4), van der Ark, K. (1,3), Muncan, V. (4), Schultsz, C. (1,3), Stittelaar, K.J. (5), Pajkrt, D. (2), Wolthers, K.C. (1), Sridhar, A. (1)

Affiliations: (1) Amsterdam UMC, University of Amsterdam, Department of Medical Microbiology, The Netherlands; (2) Amsterdam UMC, University of Amsterdam, Emma Children's Hospital, Department of Pediatric Infectious Diseases; (3) Amsterdam UMC, University of Amsterdam, Department of Global Health-Amsterdam Institute for Global Health and Development, the Netherlands; (4) Amsterdam UMC, University of Amsterdam, Tytgat Institute for Liver and Intestinal Research, The Netherlands; (5) Viroclinics Xplore B.V., Schaijk, The Netherlands.

Corresponding author: Ikrame Aknouch, MSc (i.aknouch@amsterdamumc.nl)

Rationale: Enteroviruses (EVs) are a major source of human infections worldwide, with a broad spectrum of disease symptoms, from diarrhoea and skin rash to more severe disease like meningitis and paralysis. Elucidating EV pathogenesis has been limited by the lack of suitable models that faithfully mirror normal human physiology and pathophysiology. Organoids are stem cell-derived in vitro 3D organ models and an excellent system that has potential for studying on EV-host interaction, virus evolution, and antiviral compound testing on a human system.

Methods: The 3D foetal gut organoids are an "inside out" representation of human physiology with the basal side on the outside facing the environment and the apical side facing the inwards. During culture, the proximal and distal organoids are "opened up" and cultured as a monolayer on transwell inserts to establish viral infection. The monolayers were apically exposed to enterovirus A71 (EV-A71) and subsequent viral replication was assessed by quantifying the production of viral RNA and virus replication at several time points over a course of six days.

Results: Using the monolayer transwell system we show that EV-A71 infects the epithelium monolayers from the apical surface. We will present data on infection of the monolayer model with EV-A71, cell tropism of the virus, and monolayer permeability after infection.

Discussion: The human foetal gut derived intestinal organoid model is a powerful model for studying enterovirus infection and related disease pathogenesis. Continued development of the organoids cultures by including components of the normal host tissue microenvironment such as immune cells and blood vessels, will facilitate and simplify studies on human viral pathogenesis, and improve the development of platforms for pre-clinical evaluation of vaccines, antivirals and therapeutics.

AKS2021_058

Predicting neurodevelopment from intraoperative vital functions: a machine learning approach

Roorda, D. (1), Königs, M. (1), Last, J. (2), Thijssen, T. (2), Stevens, M.F. (3), J. Oosterlaan (1)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Emma Neuroscience Group, Dept. of Paediatrics, Amsterdam, The Netherlands; (2) Information studies - Data Science, UvA, Amsterdam, The Netherlands; (3) Dept. of Anaesthesiology, Amsterdam UMC, UvA, Amsterdam, The Netherlands

Corresponding author: Daniëlle Roorda, MD (d.roorda@amsterdamumc.nl)

Rationale: Infants undergoing neonatal surgery are at risk for impaired neurodevelopment. Intraoperative oxygenation and circulation may play a role in this. We aimed to study the predictive value of intraoperative vital functions on neurodevelopment using machine-learning algorithms.

Methods: Motor and cognitive outcomes were measured using the BSID-III, the M-ABC-II, and the WISC-IV. Clinical background variables and intraoperative vital parameter time series were extracted from EPIC. A supervised learning algorithm was used to extract features from the vital parameter time series. Support Vector Machine (SVR) regression was used to predict motor and cognitive outcomes, combining different subsets of variables (i.e., clinical background, static and dynamic features of vital parameters). Performance of the SVR models was evaluated using R2 and RMSE and compared to linear regression models (LR) and to an SVR model predicting the mean (PM).

Results: Removal of artefacts and extracting static and dynamic features from the intraoperative vital parameter time-series was successfully done using a supervised learning algorithm. R2 for SVR models predicting motor outcome ranged from 0.15 – 0.23, with RMSE ranging from 0.94 – 0.99, whereas in LR models R2 ranged from 0.01 to 0.09 and RMSE from 1.25 – 1.91, and in the PM model RMSE was 1.09. R2 for SVR models predicting cognitive outcome ranged from 0.06 – 0.14, with RMSE of 0.72 for all models, whereas in LR models R2 ranged from 0.14 to 0.17 and RMSE from 3.46 – 30.07, and in the PM model RMSE was 0.72.

Discussion: SVR models showed better predictive performance compared to traditional linear regression models. Adding subsets of features from intraoperative vital parameter time series increased predictive performance for the prediction of motor outcomes. Our findings may be explained by small sample sizes, but may also suggest limited impact of intraoperative vital functions on neurodevelopmental outcomes.

AKS2021_059

The Pyridoxine-Dependent Epilepsy Registry: a digital tool to answer rare disease questions

Tseng, L.A. (1,12), Gospe Jr., S.M. (2,3), Bok, L.A. (4), Hartmann, H. (5), Lunsing, R.J. (6), Melaiki, B.T. (7), Groenborg, S. (8), Footitt, E. (9), Coughlin 2nd, C.R. (10), van Karnebeek, C.D. (1,11,12)

Affiliations: (1) Dept. of Paediatrics and Clinical Genetics, Emma Children's Hospital, Amsterdam University Medical Centres, Amsterdam, Netherlands; (2) Dept. of Neurology and Paediatrics, University of Washington, Washington USA; (3) Seattle Children's Research Institute, Seattle, WA USA; (4) Dept. of Paediatrics, Máxima Medical Center, PO Box no. 7777, 5500, MB, Veldhoven, The Netherlands; (5) Clinic for Paediatric Kidney, Liver, and Metabolic Disorders, Hannover Medical School, Hannover, Germany; (6) Dept. of Paediatric Neurology, University of Groningen, UMC Groningen, Groningen, The Netherlands; (7) Prince Sultan Riyadh Military Medical City, Riyadh, Saudi Arabia; (8) Juliane Marie Centre Rigshospitalet University Hospital; (9) Metabolic medicine Dept., Great Ormond Street Hospital, London, UK; (10) Dept. of Paediatrics, Section of Clinical Genetics and Metabolism, University of Colorado School of Medicine, Aurora, Colorado; (11) Dept. of Paediatric Metabolic Diseases, Amalia Children's Hospital, Radboud UMC, Nijmegen, The Netherlands; (12) On behalf of United for Metabolic Diseases, www.umd.nl

Corresponding author: Laura Tseng, MD (l.a.tseng@amsterdamumc.nl)

Rationale: Pyridoxine-dependent epilepsy (PDE) is a rare, epileptic metabolic disorder of lysine catabolism. To unite patients and increase knowledge on this disease, the PDE consortium initiated an online, international PDE patient registry. For PDE, therapeutic delay has been hypothesized to be a factor for more severe phenotype, especially neurodevelopmental status (NDS). Using the PDE registry, our aim was to test this hypothesis and possibly identify PDE as a potential candidate for newborn screening

Methods: An online REDCap registry was initiated in 2014. Inclusion criteria were confirmed PDE due to ALDH7A1 deficiency. Data regarding genotype, phenotype, natural history, diagnosis, treatment and long-term outcomes were collected. Therapeutic delay was defined as ≥ 1 days between presentation and initiation of long-term pyridoxine treatment. Therapeutic delay was correlated with NDS at last follow-up.

Results: 118 subjects from 7 countries were enrolled in the registry (62.1% female). 46.6% was on pyridoxine monotherapy vs 53.4% on additional lysine reduction treatment. The majority of subjects showed a neonatal onset (74%). NDS at last follow-up was delayed in 63/84 subjects (75%). Preliminary results show no significant difference in NDS between the therapeutic and non-therapeutic delay groups.

Discussion: PDE illustrates the conundrums of rare disease research and how digital tools and international collaboration might provide solutions. The PDE registry provides the opportunity for collaborators around the world to enter data, and thus collectively provides insight in natural history, disease course and treatment outcomes. Diet apps, such as www.eiwitkenner.nl, facilitate adherence to these often burdensome nutritional therapies. The PDE Consortium translates knowledge gained via digital tools into consensus guidelines, improving management for this disease. Next on our list is a long-term outcome study on PDE at adult age using a KLIK research website.

AKS2021_060

Efficacy and safety of enteral recombinant human insulin in preterm infants: A randomized, double-blind, placebo-controlled trial

Mank, E. (1), Sáenz de Pipáon, M. (2), Lapillonne, A. (3), Carnielli, V.P. (4), Senterre, T. (5), Shamir, R. (6), van Toledo, L. (1), van Goudoever, J.B. (1), on behalf of the FIT-04 study group

Affiliations: (1) Dept. of Paediatrics-Neonatology, Emma Children's Hospital, Amsterdam UMC, UvA, Vu Amsterdam, Amsterdam, The Netherlands; (2) Dept. of Paediatrics-Neonatology, La Paz University Hospital, Autonoma University of Madrid, Madrid, Spain; (3) Dept. of Paediatrics-Neonatology, APHP Necker Enfants Malades Hospital, Paris Descartes University, Paris, France; (4) Dept. of Paediatrics-Neonatology, Ospedali Riuniti Ancona, Polytechnic University of Marche, Azienda Ospedaliero Universitaria, Ancona, Italy; (5) Dept. of Paediatrics-Neonatology, CHU de Liege, CHR de la Citadelle, University of Liege, Liege, Belgium; (6) Dept. of Paediatrics-Neonatology, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

Corresponding author: Elise Mank, MD (e.mank@amsterdamumc.nl)

Rationale: Enteral insulin may promote intestinal maturation in preterm infants. Insulin is absent in formula and the natural insulin concentration in human milk declines rapidly postpartum. The objective of this double-blind RCT was to assess the effect of two different doses recombinant human (rh) insulin as additive to formula or human milk on time to achieve full enteral feeding for three consecutive days.

Methods: Preterm infants (gestational age (GA) of 26-32 weeks and birth weight (BW) ≥500 grams) were randomly assigned to receive either investigational drug containing low-dose (LD) rh-insulin (400 µU/mL), high-dose (HD) rh-insulin (2000 µU/mL), or placebo for 28 days.

Results: 303 infants were included in the intention-to-treat analysis. Median (IQR) GA was 29.0 (27.7-30.4) weeks and BW was 1210 (1000-1432) grams. Time to achieve full enteral feeding was 10.0 (7.0-21.8) days in the LD group, 10.0 (6.0-15.0) days in the HD group, and 14.0 (8.0-28.0) days in the placebo group and, compared to placebo, significantly shorter in the LD group (p=0.033) and HD group (p=0.0012). Weight gain rates during intervention were not different between the groups (LD: 17.4 (14.0-20.1) g/kg/day), HD: 17.2 (15.0-19.2) g/kg/day, placebo: 17.9 (15.2-19.6) g/kg/day). Necrotizing enterocolitis (LD: 6%, HD: 5%, placebo: 10%) and mortality (LD: 4%, HD: 1%, placebo: 4%) rates were not higher in the intervention groups.

Conclusion: Enteral administration of two different doses rh-insulin, compared to placebo, significantly reduces time to achieve full enteral feeding in preterm infants with a GA of 26-32 weeks.

AKS2021_061

Improving hospital to home transition for Children with Medical Complexity and their families

van de Riet, L. (1), Alsem, M.W. (2), van Karnebeek, C.D. (3,4), van Woensel, J.B.M. (1)

Affiliations: (1) Paediatric Intensive Care Unit, Emma Children's Hospital, Amsterdam UMC, Amsterdam, the Netherlands; (2) Dept. of Paediatric Rehabilitation Medicine, Amsterdam UMC, Amsterdam, the Netherlands; (3) Dept. of Paediatrics and Clinical Genetics, Emma Children's Hospital, Amsterdam UMC, Amsterdam, the Netherlands; (4) Dept. of Paediatrics, Radboud UMC, Nijmegen, the Netherlands

Corresponding author: Liz van de Riet, MD (l.vanderiet@amsterdamumc.nl)

Rationale: Families of Children with Medical Complexity (CMC) have needs that extend well beyond the hospital grounds. The gap between a protective hospital environment and home is large, making the transition from hospital to home particularly challenging. The aim of our study is twofold. First, to systematically map needs and obstacles of CMC families during this transition. Second, to better understand the transition process itself. Both results will help us create a framework for designing interventions to improve this process in the future.

Methods: We combined two study designs. First we performed a systematic review of qualitative evidence to extract transition needs of CMC families from existing literature. An extensive search yielded 1515 papers of which 24 proved eligible for final inclusion. We used meta-aggregation methods to synthesize our findings into categories and formulate relevant overarching domains. Second, we collaborated with a digital design team to look at hospital to home transition from a different perspective. Through an agile work process, we gained new insights and made a prototype of a digital intervention.

Results: Preliminary results from our systematic review show that transition needs can be divided into six domains of care: parental empowerment, care coordination, health & safety, emotional support, social wellbeing and financial support. Furthermore, we found that transition is a continuous process rather than a static moment and that family needs change constantly. A digital tool that targets the six domains and facilitates parent-professional collaboration will improve the transition (Supplementary material S12, p83).

Discussion: While CMC families face different transition needs and obstacles, certain overarching domains of care arise. Identifying them is the first step to creating (digital) interventions that are personalized and flexible and that stimulate interdisciplinary collaboration to ensure a safe and sustainable transition home.

AKS2021_062

Lipoprotein(a) levels in effectively treated perinatally HIV-infected children and adolescents over time

van Genderen, J.G. (1), Van den Hof, M. (1), Jansen, H.P.G. (2), Dallinga-Thie, G.M. (2), van Deventer, S.J.H. (3), Pajkrt D. (1)

Affiliations: (1) Dept. of Paediatric Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, Amsterdam, the Netherlands; (2) Dept. of Experimental Vascular Medicine and Vascular Medicine, Amsterdam UMC, Amsterdam, the Netherlands; (3) Dept. of Gastroenterology, Leiden UMC, Leiden, the Netherlands

Corresponding author: Jason van Genderen, MD (j.g.vangenderen@amsterdamumc.nl)

Rationale: The incidence of cardiovascular disease (CVD) is higher in people living with HIV compared to the general population. Perinatally HIV-infected (PHIV+) children potentially have a greater CVD risk at older age, as their life expectancy increased due to effective therapy. Lipoprotein(a) (Lp(a)) – an independent atherosclerotic marker – is a known risk factor for CVD in the general population. A cross-sectional study found higher Lp(a) levels in PHIV+ children compared to healthy matched controls. To gain further insight in Lp(a) level trends and thus the potential CVD risk for PHIV+ children, we determined their Lp(a) levels – in relation with increasing age – over a period of eight years.

Methods: We determined Lp(a) levels of PHIV+ children who visited our outpatient clinic at the Amsterdam UMC at least twice between September 2012 and September 2020, using the Architect c8000 Abbott (Lake Forest, IL) with a reference value of < 300 mg/L. We assessed intra- and interindividual trends of Lp(a) and its determinants using mixed models.

Results: We included 36 PHIV+ children with a median age (interquartile range) of 8.0 years (5.7 – 10.8) and a mean Lp(a) level of 505 mg/L (95%CI: 371 – 638, p<0.001). We found no association between Lp(a) and age, sex, body mass index or therapy. The intra-individual variability of Lp(a) was 33% (95%CI: 30 – 35).

Discussion: We found fluctuating, but above all significantly higher Lp(a) levels over a period of eight years in PHIV+ children compared to both the reference value and values reported for children with inherited dyslipidaemia. Our findings suggest a higher CVD risk for PHIV+ children. Lp(a) levels could be used to educate patients and parents about the associated higher CVD risk and the need to avoid lifestyle-related CVD risk factors. Ultimately, it would be of interest to develop both antiretroviral therapies that do not influence Lp(a) and specific therapies that lower Lp(a) levels, and thus reduce the CVD risk.

AKS2021_063

High plasma oxalate values not necessarily suggestive for PH

Metry, E.L. (1), Garrelfs, S.F. (1), Oosterveld, M.J.S. (1), Neradova, A. (2), Bijlsma, J. (2), Vaz, F.M. (3), Groothoff, J.W. (1)

Affiliations: (1) Dept. of Paediatric Nephrology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (2) Dept. of Nephrology, Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3) Laboratory Genetic Metabolic Diseases, Amsterdam UMC, UvA, Amsterdam, The Netherlands

Corresponding author: Ella Metry, MD (e.l.metry@amsterdamumc.nl)

Rationale: Patients with end-stage renal disease (ESRD) are known to have higher plasma concentrations of metabolic waste products than healthy individuals. Patients with Primary Hyperoxaluria (PH), a rare congenital cause of ESRD, suffer from hepatic overproduction of the metabolic end product oxalate. Plasma oxalate (POx) levels are determined in the diagnostic and therapeutic work-up for PH. Remarkably, correct interpretation of these values is hampered by the absence of reference values for POx levels in patients with ESRD not attributable to PH.

Methods: In this observational study, we obtained POx values in patients with ESRD due to other causes than PH, to establish reference values in this patient group. We collected blood samples from 120 adults with estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m2 and on maintenance hemodialysis or peritoneal dialysis at the Amsterdam UMC.

Results: While there was a wide variation in POx levels in patients with ESRD, median level was 50 mcmol/L. The lowest values were twice the upper reference limit of those reported in healthy individuals (6.7 mcmol/L).

Discussion: This study shows that elevated POx levels are common in patients with ESRD not due to PH. And that even Pox levels >50 mcmol/L are not necessarily attributable to a diagnosis of PH. This study could lead to a paradigm shift in the diagnostic and therapeutic work-up for patients with ESRD.

AKS2021_064

Parental distress and PTSD in parents of patients with congenital gastrointestinal malformations

Roorda, D. (1,2), van der Steeg, A.F.W. (3), van Heurn, L.W.E. (1), Haverman, L. (4), Oosterlaan, J. (2)

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Dept. of Paediatric Surgery, Amsterdam, The Netherlands; (2) Emma Children's Hospital, Amsterdam UMC, UvA, Follow Me program, Amsterdam, The Netherlands; (3) Princes Maxima Centre for Oncology, Utrecht, The Netherlands; (4) Emma Children's Hospital, Amsterdam UMC, UvA, Psychosocial Dept., Amsterdam, The Netherlands

Corresponding author: Daniëlle Roorda, MD (d.roorda@amsterdamumc.nl)

Rationale: Patients with congenital gastrointestinal malformations (CGIM) receive neonatal surgical treatment, which may psychologically impact their parents in terms of distress and of post-traumatic stress disorder (PTSD).

Methods: Parents were asked to complete the Distress Thermometer for Parents (DT-P) and the Self Rating Scale for Posttraumatic Stress Disorders (SRS-PTSD) before each multidisciplinary follow-up visit of their child. Independent sample t-test, Mann Whitney U test and Chi-square test were used to assess group differences between participants and normative data on sample characteristics, prevalence of clinical distress and PTSD and severity of clinical distress and PTSD. Mixed model regression models were used to identify explaining variables for the risk of clinical distress and PTSD, and for severity of clinical distress and PTSD.

Results: A total of 95 parents (57 mothers and 38 fathers) completed the DT-P and 97 parents (58 mothers, 39 fathers), completed the SRS-PTSD. The prevalence of clinically relevant distress in parents of patients with CGIM (38.0%) was comparable to parents of patients with healthy children (38.2%, X2=0.07, p=.796), but significantly lower than in parents of children with a chronic illness (53.0%, X2=7.42, p=.006) The prevalence of PTSD (14.4%) was significantly higher compared to the Dutch general population (3.8 %, X2=26.37, OR 4.33, p<.001). Fathers had a lower risk of PTSD and less severe symptoms of intrusion, avoidance and hyperactivity. Longer length of hospital stay was associated with more severe symptoms of intrusion, avoidance and hyperactivity.

Discussion: We report a high prevalence of PTSD-symptoms, especially in mothers of patients with CGIM, but no higher prevalence of clinical distress compared to normative data. Structured monitoring of psychosocial wellbeing of parents in follow-up of patients with CGIM is therefore important.

AKS2021_065

Faecal free amino acids as potential early biomarkers for severe necrotizing enterocolitis in preterm infants: a case-control study

Deianova, N.* (1), el Manouni el Hassani, S.* (1), Niemarkt, H.J. (2), Jansen, E.E.W. (3), Bakkali, A.(3), van de Wiel, M. (4), de Boode, W.P. (5), Hulzebos, C.V.(6), van Kaam, A.H. (7), Kramer, B.W. (8), van Lingen, R.A.(9), van Goudoever, J.B. (10), Vijlbrief, D.C. (11), van Weissenbruch, M.M. (7), de Jonge, W.J. (12), Benninga, M.A. (1), de Boer, N.K.H. (13), Struijs, E.A. (3), de Meij, T.G.J. (1)

* Authors contributed equally

Affiliations: (1) Dept. of Paediatric Gastroenterology, Emma Children's Hospital, Amsterdam UMC, UvA, Vrije Universiteit, Amsterdam, the Netherlands; (2) Dept. of Neonatology, Máxima Medical Center, Veldhoven, the Netherlands; (3) Dept. of Clinical Chemistry, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands; (4) Dept. of Epidemiology & Biostatistics, Amsterdam Public Health Research Institute, Amsterdam UMC, Vu, Amsterdam, the Netherlands; (5) Dept. of Neonatology, Amalia Children's Hospital, Radboud UMC, Radboud Institute for Health Sciences, Nijmegen, The Netherlands; (6) Dept. of Neonatology, Beatrix Children's Hospital, Groningen UMC, Groningen, the Netherlands; (7) Dept. of Neonatology, Emma Children's Hospital, Amsterdam UMC, UvA, Vu, Amsterdam, the Netherlands; (8) Dept. of Neonatology, Paediatrics' Dept., Maastricht UMC, Maastricht, the Netherlands; (9) Dept. of Neonatology, Children's Center Isala hospital, Zwolle, the Netherlands; (10) Emma Children's Hospital, Amsterdam UMC, UvA, Vu, Amsterdam, the Netherlands; (11) Dept. of Neonatology, Wilhelmina Children's Hospital, UMC Utrecht, Utrecht, the Netherlands; (12) Tytgat Institute for Liver and Intestinal Research, Amsterdam Gastroenterology & Metabolism, Amsterdam UMC, UvA, Amsterdam, the Netherlands; (13) Dept. of Gastroenterology and Hepatology, Amsterdam UMC, UvA, Vu, Amsterdam, the Netherlands

Corresponding author: Nancy Deianova, MD (n.deianova@amsterdamumc.nl)

Rationale: Necrotizing enterocolitis (NEC) is a devastating disease in premature infants with high mortality in advanced stages (modified Bell's stage IIIA and IIIB). Diagnosis is challenged by non-specific symptoms in the initial phase. There is an unmet need for early biomarkers, as timely diagnosis and initiation of treatment are considered key prognostic factors. Aim of this study was to assess the potential of faecal amino acid (AA), and the amines phosphoethanolamine and ethanolamine (PEA and ETA, resp.) to predict NEC in infants born < 30 weeks of gestation.

Methods: This prospective study was conducted between Feb 2013 and Jan 2018 in 8 neonatal intensive care units in the Netherlands. Demographic and clinical data on feeding type and antibiotic administration were collected during the first month of life. Faecal samples from three to one day(s) before NEC (st. IIIA or -B), and matched control samples, were analysed by targeted high-performance liquid chromatography.

Results: Faecal samples from 23 NEC cases (13 IIIA;10 IIIB) were compared to matched 23 controls. Baseline characteristics, including enteral feeding type and antibiotic use at sampling, were comparable between cases and controls. All branched chained AA (Ile, Leu, Val) were increased in faeces preceding NEC, as well as the essential AA Phe and Trp ($p<0.05$). Finally, non-essential Ala and Tau, non-proteogenic alpha-Aminobutyric acid (AABA) and amine PEA were increased preceding NEC ($p<0.05$). Fecal ETA was decreased ($p=0.009$). Preclinical NEC could be discriminated from controls with an accuracy (AUC) of 0.78 based on Ile and AABA (Supplementary material S13, p84).

Discussion: We observed profound alterations in faecal AA profiles up to 3 days before onset of advanced NEC, compared to controls. Therefore, specific AA could potentially serve as novel biomarkers for imminent NEC and may facilitate early treatment. Further research could point to the origin of these changes.

AKS2021_066

Mortality and causes of death from sickle cell disease in the Netherlands, 1985-2017

Rettenbacher, E. (1), Zaal J. (1), Heijboer, H. (1), van der Plas, E.M.(2), Hof, M.H. (3), Biemond, B.J. (4), Fijnvandraat, K.J. (1)

Affiliations: (1) Dept. of Paediatric haematology, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, the Netherlands; (2) Dept. of General Paediatrics, Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, the Netherlands; (3) Dept. of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, UvA, the Netherlands; (4) Dept. of haematology, Amsterdam UMC, UvA, Amsterdam, the Netherlands

Corresponding author: Eva Rettenbacher, MD (e.rettenbacher@amsterdamumc.nl)

Rationale: In the Netherlands, between 1985 and 2007, secular changes in the health care of patients with sickle cell disease (SCD) have taken place, such as penicillin prophylaxis, nationwide vaccination programs and stroke prevention.

Methods: We investigated the number and causes of death in a cohort of 298 SCD patients, established in 2007, before the introduction of neonatal screening, in order to determine preventable deaths. Preventable death was defined as death due to the lack of antibiotic prophylaxis, vaccination or stroke prevention with transcranial Doppler (TCD) ultrasonography and regular blood transfusion therapy. Patients were diagnosed with SCD before the age of 18 at the Amsterdam UMC. Median age at diagnosis was 5.1 years, 55% of patients were male. The vital status of all patients was determined up to January 2017. To evaluate the age-related event-free survival, a Kaplan-Meier estimator was fitted to the data.

Results: After a total follow-up period of 4565 patient years, 230 patients (77%) were still alive, 45 patients (15%) were lost to follow-up and a total of 23 patients (8%) had died. Estimated survival to 18 years was 91% with a global mortality rate of 0.48 deaths/100 patient years. Leading causes of death were infection (35%) followed by neurological complications (22%) and death in the course of a painful episode (13%). Of the 23 individuals who died, 26% were young adults (18-25 years). Six of the 20 known causes of death were preventable: lack of antibiotic prophylaxis and/or vaccination (n=3), absence of stroke prevention with TCD and regular blood transfusion therapy (n=3).

Discussion: These results strongly suggest the benefit of newborn screening programs and comprehensive care measures for patients with SCD in the Netherlands to prevent future morbidity and mortality.

AKS2021_067

The efficacy of Gut-Directed Hypnotherapy compared to Standard Medical Treatment in Paediatric patients with Functional Nausea: a Multicenter, Randomized Clinical Trial

Browne, P.D.* (1), de Bruijn, C.M.A.* (1,2,3), den Hollander, B. (1), Speksnijder, E. (1), van Wering, H.M. (4), Wessels, M.S. (5), Groeneweg, M. (6), Goede, J. (7), van den Berg, M.M. (8), Tjon A Ten, W. (9), George, E.K. (10), Bevers, N. (11), Frankenhuis, C. (1), Tromp, E. (12), Benninga, M.A. (1), Vlieger, A.M. (13)

* Authors contributed equally

Affiliations: (1) Emma Children's Hospital, Amsterdam UMC, UvA, Paediatric Gastroenterology, Hepatology and Nutrition, Amsterdam, The Netherlands; (2) Amsterdam Reproduction & Development Research Institute, Amsterdam UMCs, Location Academic Medical Center/Emma Children's Hospital, Amsterdam, the Netherlands; (3) Amsterdam UMC, UvA, Gastroenterology and Hepatology, Amsterdam Gastroenterology Endocrinology Metabolism Research Institute, Amsterdam, Netherlands; (4) Dept. of Paediatrics, Amphia Ziekenhuis, Breda, The Netherlands; (5) Dept. of Paediatrics, Rijnstate Hospital, Arnhem, The Netherlands; (6) Dept. of Paediatrics, Maasstad Ziekenhuis, Rotterdam, The Netherlands; (7) Dept. of Paediatrics, Spaarne Hospital, Hoofddorp, The Netherlands; (8) Dept. of Paediatrics, Haaglanden Medical Center, Den Haag, The Netherlands; (9) Dept. of Paediatrics, Maxima Medical Center, Veldhoven, The Netherlands, (10)Dept. of Paediatrics, Northwest Clinics, Alkmaar, The Netherlands; (11) Dept. of Paediatrics, Zuyderland Medical Center, Heerlen, The Netherlands; (12) Dept. of Statistics, St. Antonius Hospital, Nieuwegein, The Netherlands; (13) Dept. of Paediatrics, St. Antonius Hospital, Nieuwegein, The Netherlands.

Corresponding author: Klaartje de Bruijn, MSc (c.m.debruijn@amsterdamumc.nl)

Rationale: Gut-directed hypnotherapy (HT) is effective in Paediatric irritable bowel syndrome and functional abdominal pain. However, the potential effectiveness of HT is unknown for functional nausea, as can be found in children with chronic idiopathic nausea (CIN) or functional dyspepsia (FD). This prospective randomized controlled trial compared the effectiveness of HT performed by qualified therapists with standard medical treatment (SMT) + supportive therapy provided by Paediatricians.

Methods: One hundred children with functional nausea and diagnosed with CIN or FD (8–18 years) were randomly allocated (1:1) to HT or SMT, with a 3-months intervention period. Outcomes were assessed at baseline, 6 weeks, after intervention period and at 6 months follow-up. Children scored symptoms of nausea on a 7-day-diary. Primary outcome was treatment success, defined as at least 50% reduction of nausea at 6 months follow-up. Secondary outcomes included abdominal pain, dyspeptic symptoms, health-related quality of life, anxiety and depression, somatization and adequate relief (AR).

Results: Directly after the 3-months intervention period, treatment success was 45% in the HT group versus 26% in the SMT group (p = .052). At 6 months follow-up, this was 57% versus 40% (p=.099). Scores of dyspeptic symptoms, depression and somatization were significantly lower in favour of the HT group at 6 months follow-up. Moreover, children and parents reported significantly more AR in the HT-group versus the SMT-group at 6 months follow-up (children: 81% vs. 55%, p =.014 and parents: 79% vs. 53%, p =.016).

Discussion: HT was more effective than SMT in reducing symptoms of chronic nausea in children diagnosed with CIN or FD. Therefore, HT should be offered to children with functional nausea as a possible treatment option.

AKS2021_068

The Effects of Preterm Birth on Static Balance Function and its Relationship to Motor Development at Five Years of Age

Henke, C.E., de Kieviet, J.F., van Kaam, A.H., Leemhuis, A.G., Aarnoudse-Moens, C.S.H., Stins, J.F., Oosterlaan, J.

Affiliation: Emma Children's Hospital, Amsterdam UMC, UvA, Amsterdam, The Netherlands

Corresponding author: Celina Eefje Henke, PhD (c.e.henke@amsterdamumc.nl)

Rationale: It is well established that very preterm birth and/or a low birth weight is associated with long-term impairments in neurodevelopmental outcomes, including impairments in motor functioning. One core aspect of motor functioning entails static balance functioning, which is crucially for developing complex motor skills throughout childhood (Lubans, Morgan, Cliff, Barnett, & Okely, 2010). This study aimed to investigate the effects of very preterm birth on static balance function, and its potential underpinning role in impaired motor skills in this population.

Methods: This study compared very preterm born and/or low birth weight children (<30 weeks of gestation and/or birthweight <1500 grams) and term born typically developing controls (>37 weeks of gestation and birthweight >2500 grams). Static balance function was measured using the Wii Balance Board (Nintendo, Kyoto, Japan). The standard deviation of the centre of pressure (CoP) in the medial-lateral (ML) direction and in the anterior-posterior (AP) direction were used as outcome measures. Static balance was assessed under three different conditions: 1) with eyes open, 2) with eyes closed and 3) during a cognitive dual task with eyes open. These conditions were chosen to assess the contribution of visual information processing and cognitive processing abilities to static balance. Dependent variables were subjected to 2 (group) by 3 (condition) ANOVAs.

Results: Thus far static balance function data of 100 preterm born children and of 43 age and sex matched term born controls have been collected. Full results will be available at the time of the symposium.

Discussion: These data will provide insight into the role of static balance function in motor impairment of very preterm born children and allow us to determine the contribution of visual information processing and cognitive processing abilities to static balance function in this population.

AKS2021_069

Linking the proteome to the bleeding phenotype in Mild Haemophilia A

Del Castillo, J. (1,2). Fijnvandraat, K. (1,2), Meijer, A.B. (1,3)

Affiliations: (1) Dept. of Molecular and Cellular Haemostasis, Sanquin Research, Amsterdam, the Netherlands; (2) Amsterdam UMC, UvA, Amsterdam, The Netherlands; (3) Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands

Corresponding author: Jessica Del Castillo, MSc (J.delCastilloAlferez@amsterdamumc.nl)

Rationale: Mild haemophilia A (MHA) is a bleeding disorder caused by deficient plasma levels of clotting factor VIII (FVIII), which is an essential protein in blood coagulation, causing excessive bleeding after minor trauma. Haemophilia A is an hereditary disorder caused by a monogenic mutation in the x-linked F8 gene. In this study we address interindividual response to desmopressin (DDAVP) treatment, that releases endogenous FVIII and its carrier protein von Willebrand Factor from storage pools in endothelial cells.

Methods: We will employ mass spectrometry based proteomics to profile the protein-expression-profiles (PEP) of MHA patients' plasma following DDAVP administration to track cell signatures in plasma..

Results: We have no results yet but we hypothesize that inter-individual variation in DDAVP response is potentially caused by a) the number of binding receptors for DDAVP, b) strength of the signal transduction, c) endothelial cell response

Discussion: We anticipate our assay to be a starting point for more sophisticated biochemical approaches to understand interindividual variation in MHA. Studying the cell signatures in plasma will help gain insight in the, inter-individual variation of the desmopressin response, and thereby potentially explain the bleeding phenotype as well. This may push MHA treatment to the precision medicine era where individual factors will be taken into account before designing and selecting the best available treatment.

AKS2021_070

Modeling HIV-1 neuropathogenesis using iPSC-derived Brain Organoids and iPSC-derived microglia

Capendale, P.E. (1,2), Mulder, L. (1,2), Depla, J. (1,2), Wolthers, K. (1), Shridar, A. (1,2), Ribeiro, C. (4), Pajkrt, D. (1,2)

Affiliations: (1) OrganoVir Labs, Amsterdam UMC, UvA, Amsterdam; (2) Paediatric infectious Diseases, Amsterdam UMC, UvA, Amsterdam; (3) UniQure Biopharma B.V., Amsterdam; (4) Dept. of Experimental Immunology, UvA, Amsterdam

Corresponding author: Pamela Elaine Capendale, MSc (p.e.capendale@amsterdamumc.nl)

Rationale: Prenatally HIV infected children show signs of neurological deficits but whether this is due to direct infection of the neuronal cells or the increased inflammatory response in the brain remains elusive due to the lack of representative models for human-specific viral pathologies. In this study we will develop a complex in-vitro model representing the HIV infected human brain by combining iPSC-derived human brain organoids and microglia. These complex brain organoids will enable us to evaluated the inflammatory response in the brain upon HIV infection and elucidate the specific role of microglia in this process.

Methods: Human iPSC-derived brain organoids are cultured from different ages and different cell type populations. The brain organoids are directly infected with one of three different HIV-1 strains (NL4.3 Bal, SF162 and JR-CSF) or co-cultured with HIV-1 infected iPSC-derived microglia. A viability assay, TCID50 assay Immunocytochemistry (ICC) and fluorescence-activated cell sorting (FACS) are performed to assess the pathological effect of the HIV infection on the cellular characteristics.

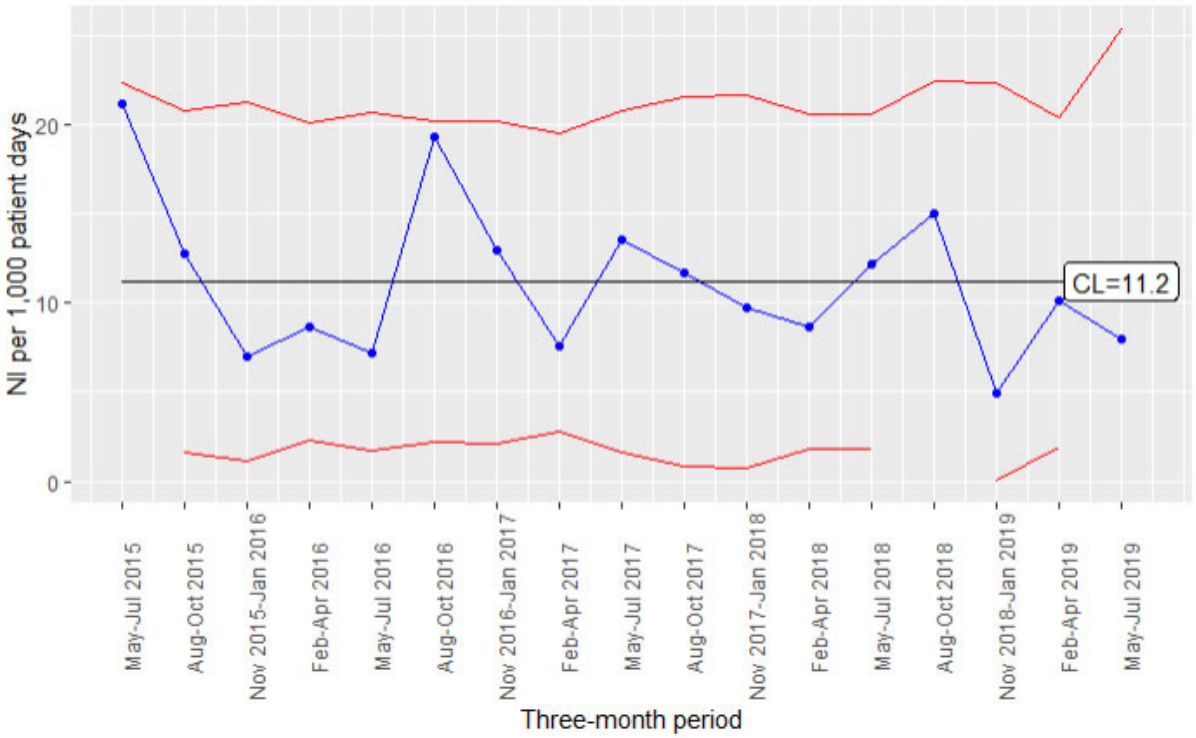
Results: The expected results will show the susceptibility of different cell types present in (complex) brain organoids (e.g. neural progenitor cells, neurons, astrocytes and microglia) to HIV infection with the use of ICC markers SOX2, MAP2 and GFAP, respectively. The difference in susceptibility between cell types of organoids of different ages will be elucidated.

Discussion: Limitations of traditional models such as two-dimensional cell culture systems and in vivo models have constrained researchers to fully understand the molecular and cellular processes behind human-specific HIV related neuropathogenesis that ultimately can lead to cure. The model in this study contains cell types that play an important role in the HIV neuropathogenesis in a 3-Dimensional setting. Mimicking this environment, this model enables us to elucidate the viral tropism and neuropathogenesis of HIV-1.

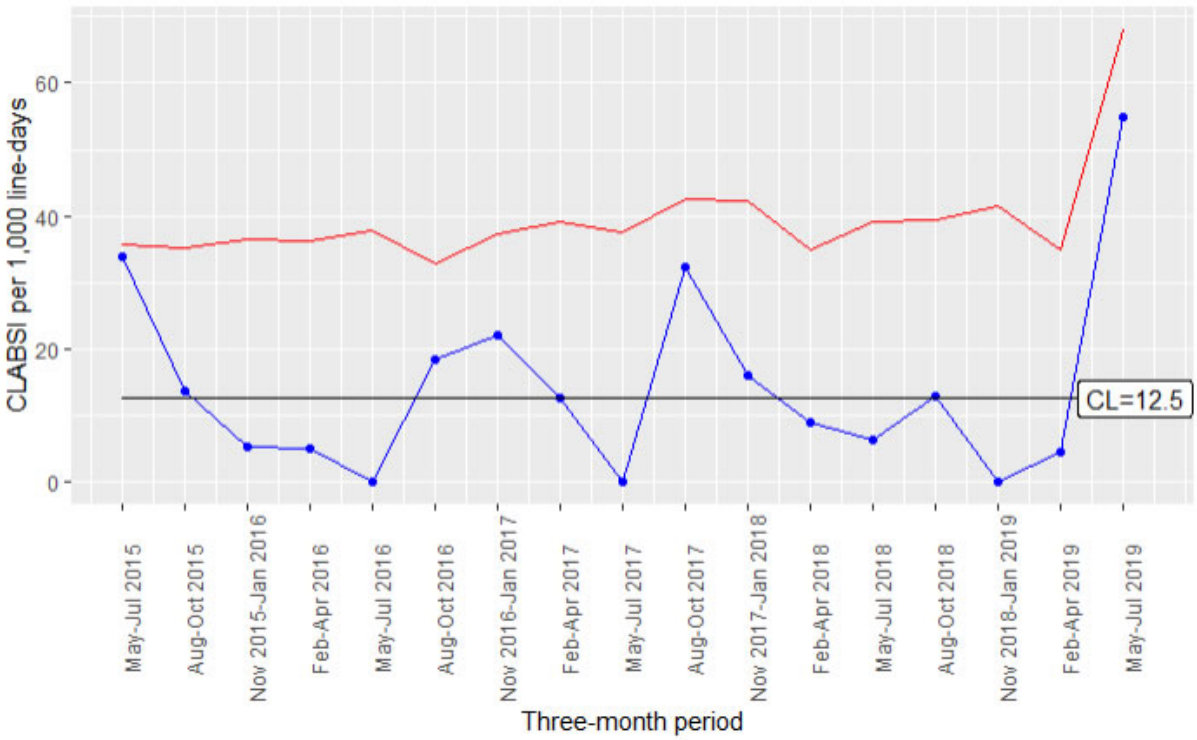
Supplementary figures and tables

AKS2021_004: S1 & S2

S1



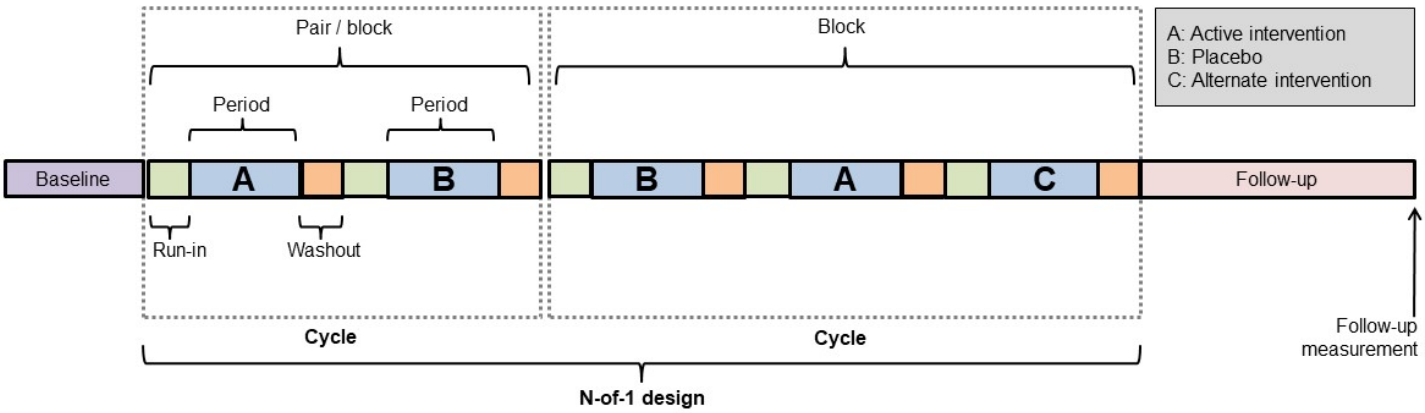
S2



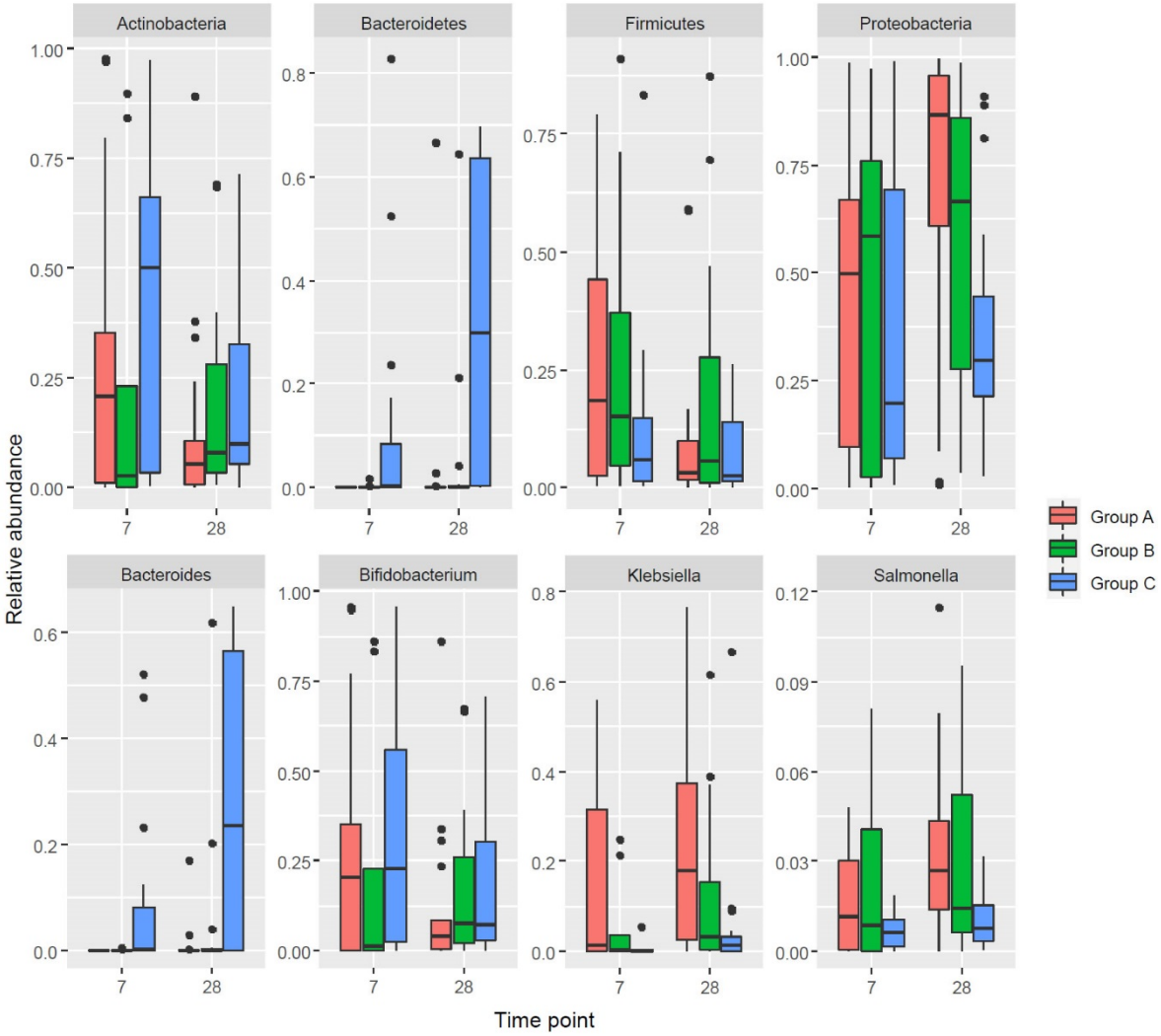
AKS2021_012: S3

	Sensitivity (95%CI)		Specificity (95%CI)	
	Trained physician	Radiologist	Trained physician	Radiologist
Terminal Ileum	40 (14-73)	80 (44-96)	75 (51-90)	95 (72-100)
Ascending Colon	46 (20-70)	10 (5-46)	96 (78-100)	100 (82-100)
Transverse Colon	25 (7-57)	18 (3-52)	100 (82-100)	100 (82-100)

AKS2021_014: S4



AKS2021_017: S5



Abstract figure: Absolute abundance of the four most abundant phyla (*Actinobacteria*, *Bacteriodetes*, *Firmicutes* and *Proteobacteria*) and four genera (Bacteroides, Bifidobacterium, Klebsiella and Salmonella) in faecal samples obtained at 7 and 28 days analysed by whole shotgun metagenomics. No differences were observed between both CS groups on phylum level. The microbiota of vaginally born infants consisted of a higher abundance of *Bacteroidetes* at day 28 ($p = 0.0004$) and a lower abundance of *Proteobacteria* ($p = 0.002$). At day twenty-eight the abundancy of *Bifidobacteria* was significantly lower in intrauterine antibiotic exposed cesarean born infants from group A compared to cesarean born infants from group B ($p = 0.009$). Vaginally born infants differed significantly in numerous genera at day 7 and 28.

AKS2021_023: S6

Mean differences in PedsQL MFS Scores in Perinatally Human Immunodeficiency Virus infected (PHIV), hiv-uninfected controls, children with chronic disease and the general Dutch population.

	Hiv-uninfected controls		*Children with chronic disease*		*General Dutch population.*	
	B*	95% CI	B*	95% CI	B*	95% CI
Fatigue total	-4.520	-14.1 to 5.1	4.613	-4.8 to 14.0	0.837	-5.8 to 7.5
General fatigue	-0.870	-9.5 to 7.7	13.029	1.3 to 24.8	5.333	-1.9 to 12.6
Sleep/rest fatigue	-4.502	-15.4 to 6.4	7.906	-2.6 to 18.4	3.091	-4.9 to 11.0
Cognitive fatigue	-8.187	-22.9 to 6.5	-7.109	-18.1 to 3.9	-5.948	-15.6 to 3.7

*B represents mean difference between PHIV and the comparison group, adjusted for age and gender. Lower scores indicate more severely fatigued. PedsQL MFS; PedsQL multidimensional fatigue scale.

AKS2021_036: S7

S7 Diaphragm and organ motion in cranio-caudal direction (mean (range); mm)								
Interfractional motion								
Study	Patients (N)	Age (years) Mean (range)	Imaging data sets (N)	Diaphragm	Liver	Spleen	Kidneys Right	Kidneys Left
Beltran 2010	10	4.3[c] (1.8–7.9)	CT (10) CBCT (200)	-	-	-	0.5[g]	
Nazmy 2012	9	4.1	CT (9) CBCT (33)	-	0.0 (-7.0–9.0)	-	0.0 (-4.0–10.0)	0.0 (-4.0–8.0)
Huijskens 2015	39	8.9 (1.6–17.8)	CT (39) CBCT (527)	1.1	-	-	0.5	1.5
Huijskens 2017	45	11.1 (2.0–18.0)	CBCT (480)	1.4	-	-	-	-
van Dijk 2017	35	10.3 (3.1–17.8)	CT (35) CBCT (374)	-0.8	-	-	0.7	1.0
Guerreiro 2018	15	4.0 (1.0–8.0)	4DCT (15) CBCT (188)	-	-0.2 (-9.0–8.1)	-1.0 (-9.1–9.6)	-0.2 (-5.6–6.3)	-
Huijskens 2018	12	14.5 (8.6–17.9)	4DCT (20) CBCT (113)	2.2 (-7.0–9.0)	-	-	-	-
Intrafractional motion								
Beltran 2010	10	4.3[c] (1.8–7.9)	CT (10) CBCT (200)	-	-	-	0.5[g]	
Pai Panandiker 2012	11 9	4.1 (2.0–8.0) 12.0 (9.0–18.0)	4DCT (12)[d] 4DCT (9)	5.1 (3.0–10.0) 9.6 (7.0–17.0)	-	-	1.9 (0.6–3.7) 3.9 (1.5–6.3)	-1.7 (0.7–3.4) 3.1 (0.8–4.6)
Pai Panandiker 2013	4	3.0[c]	4DCT (4) 4DMRI (4)	-	-	-	5.25 3.13	3.8 2.8
Seeger 2015	110	1.8	MRI (110)	(2.0–12.0)	-	-	-	-
Kannan 2016	15	4.2 (1.5–10.0)	4DCT (15)	-3.6[e]; -4.4[f]	-2.5	-3.1	-1.9	-1.4
Huijskens 2017	45	11.1 (2.0–18.0)	CBCT (480)	10.7 (4.1–17.4)	-	-	-	-
Uh 2017	30	8.0 (1.0–17.0)	4DMRI (30)	-	4.5 (0.8–10.2)	4.9 (0.6–19.5)	3.1 (1.2–7.7)	3.0 (0.6–13.0)
Boria 2018[a]	8	9.6 (2.0–15.0)	3DCT (8) 4DMRI (8)	-	-	-	-	-
Goo 2018	8	0.3[c] (0.0–3.0)	4DCT (8)	4.5	-	-	-	-
Guerreiro 2018[b]	15	4.0 (1.0–8.0)	4DCT (15) CBCT (188)	-	3.0 (0.6–4.7)	3.2 (0.9–5.5)	0.6 (0.0–3.2)	-
Huijskens 2018	12	14.5 (8.6–17.9)	4DCT (20) CBCT (113)	10.4 11.6	-	-	-	-
Lavan 2018a	15	4.0[c] (1.0–17.0)	4DCT (15)	-	-	-	0.8	0.8
Lavan 2018b	8 12	3.4[c] (1.7–6.1) 7.3[c] (4.1–17.8)	4DCT (8) 4DCT (12)	-	-	-	0.1[h] -3.2[i]	0.4[h] 1.8[i]

[a]tumor motion: 7.1 (1.2–13.5) mm, [b]tumor bed motion: 0.8 (0.0–3.3) mm, [c]median reported, [d]one patient received two 4DCTs, [e]left diaphragm dome, [f]right diaphragm dome, [g]both kidneys, [h]patients treated under general anesthesia, [i]patients without general anesthesia

Table 1: the effect of interventions on the initiation of breastfeeding (at discharge)

Article	Study design	Intervention	Control	n			GA	Endpoint	Outcomes
				I	C	T			
Rocha et al[1]	RCT	Cup feeding	Bottle feeding	44	34	78	32+0 - 36+6 weeks	Hospital discharge	**BF exclusively or partially directly at the breast - n (%)** I: 36 (81.8) | C: 27 (79.4) | P-value: n.s.
Yilmaz et al[2]	RCT	Cup feeding	Bottle feeding	254	268	522	32+0 - 35+6 weeks	Hospital discharge	**BF exclusively or partially at the breast – n (%)** Exclusive BF: I 184 (72.0) | C 123 (46.0) | P-value <0.0001 Any BF: I 252 (99.0) | C 244 (91.0) | P-value <0.001
Estalella et al[3]	Quasi-experimental	Booklet + MDT support	Basic info + support	161	212	372	34+0 - 36+6 weeks	Hospital discharge	**Feeding rate (expressed or directly at the breast) – n (%)** Exclusive BF: I 108 (68.4) | C 106 (50.7) Partial BF: I 41 (25.9) | C 79 (37.8) Formula: I 9 (5.7) | C 24 (11.5) P-value trend: 0.002
Hake-Brooks et al[4]	RCT	Kangaroo care	No kangaroo care	36	30	66	32+0 - 36+6 weeks	Hospital discharge	**BF exclusively or partially – n (%)** Exclusive BF: I 26 (72.2) | C 18 (60.0) | P-value n.s. Partial BF: I 5 (11.1) | C 4 (6.6) | P-value n.s.
Morelius et al[5]	RCT	(Almost) continuous skin-to-skin	Standard skin-to-skin	23	19	42	32+0 - 35+6 weeks	Hospital discharge	**BF rate* – yes/no (% yes)**** I: 18/0 (100) | C: 16/3 (84.2) | P-value: n.s.

I: intervention, C: control, T: total, RCT: randomised controlled trial, GA: gestational age, BF: breastfeeding, n.s.: not significant. MDT: multidisciplinary team

*: breastfeeding was not defined in this study – it is unclear whether this is feeding of breastmilk in any way, or directly at the breast

**: total numbers of patients in results and design do not match due to loss to follow-up

References: 1.Rocha NM, Martinez FE, Jorge SM. Cup or bottle for preterm infants: effects on oxygen saturation, weight gain, and breastfeeding. J Hum Lact. 2002;18(2):132-8., 2.Yilmaz G, Caylan N, Karacan CD, Bodur I, Gokcay G. Effect of cup feeding and bottle feeding on breastfeeding in late preterm infants: a randomized controlled study. J Hum Lact. 2014;30(2):174-9., 3.Estalella I, San Millan J, Trincado MJ, Maquibar A, Martinez-Indart L, San Sebastian M. Evaluation of an intervention supporting breastfeeding among late-preterm infants during in-hospital stay. Women Birth. 2020;33(1):e33-e8, 4.Hake-Brooks SJ, Anderson GC. Kangaroo care and breastfeeding of mother-preterm infant dyads 0-18 months: a randomized, controlled trial. Neonatal Netw. 2008;27(3):151-9., 5.Morelius E, Ortenstrand A, Theodorsson E, Frostell A. A randomised trial of continuous skin-to-skin contact after preterm birth and the effects on salivary cortisol, parental stress, depression, and breastfeeding. Early Hum Dev. 2015;91(1):63-70.

AKS2021_043: S9

Inter-rater scores	**Fleiss' kappa** (qualitative counts)	95% CI	**ICC** (quantitative counts)	95% CI
Punctate&perivascular haemorrhages	0.62	0.57-0.67	0.82	0.76-0.87
Large confluent haemorrhages	0.78	0.72-0.83	0.93	0.91-0.95

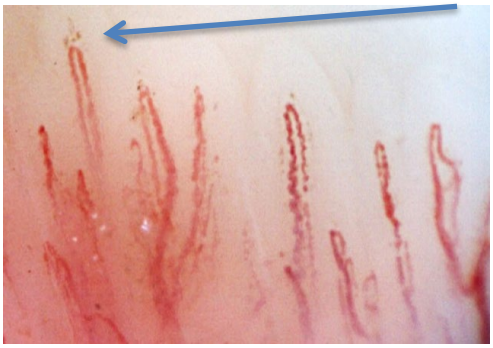
Intra-rater scores	**Mean Kappa** (qualitative counts)	**Mean ICC** (quantitative counts)
Punctate&perivascular haemorrhages	0.70	0.84
Large confluent haemorrhages	0.86	0.96

CI = Confidence Interval

Kappa interpretation:
0.61-0.80 substantial agreement
>0.81 almost perfect agreement

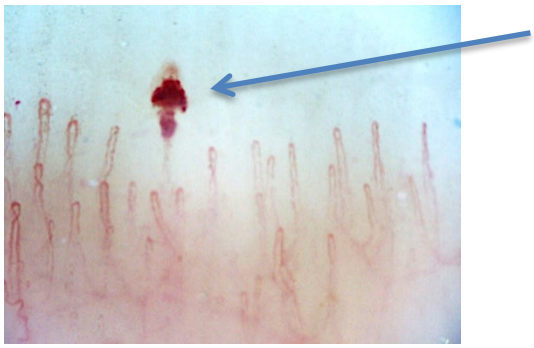
ICC interpretation:
0.76-0.90: good
>0.90 excellent

Part A



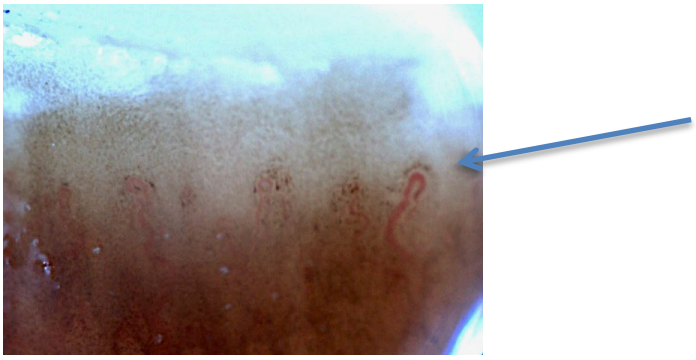
Part A: Subgroup 1; Punctate extravasation

Part C



Part C, Subgroup 3; Large confluent haemorrhage

Part B



Part B, Subgroup 2; Perivascular haemorrhage

AKS2021_044: S10

S10. Outcome scores of questionnaires

Questionnaires	During the pandemic	Pre-pandemic	Wilcoxon ranked-test
PHQ-9 median scores (25-75 percentile)	3.0 (1.00-6.00)	3.0 (1.00-5.75)	p = 0.806
GAD-7 median scores (25-75 percentile)	3.0 (1.00-7.00)	3.0 (1.00-6.00)	p = 0.371
PHQ-9 total scores (n %)	65 (100)	60 (100)	n.a.*
No depression	39 (60)	39 (65)	
Mild depression	20 (31)	16 (26)	
Moderate depression	6 (9)	4 (7)	
Moderately severe depression	0 (0)	1 (2)	
Severe depression	0 (0)	0 (0)	
GAD-7 total scores (n %)	65 (100)	60 (100)	n.a.
No anxiety	41 (63)	36 (60)	
Mild anxiety	16 (25)	18 (30)	
Moderate anxiety	7 (11)	5 (8)	
Severe anxiety	1 (1)	1 (2)	
BRS scores (Mean (SD[×]))	3.30 (0.8)	n.a.	n.a.
CEFIS Impact scores[ϕ] (Mean (SD))		n.a.	n.a.
Patients with CF of PCD	24.2 (11.6)		
Parents of patients with CF or PCD	19.5 (10.6)		

* Not applicable

[×] Standard deviation

[ϕ] CEFIS outcome scores can range from 2 to 70.

AKS2021_054: S11

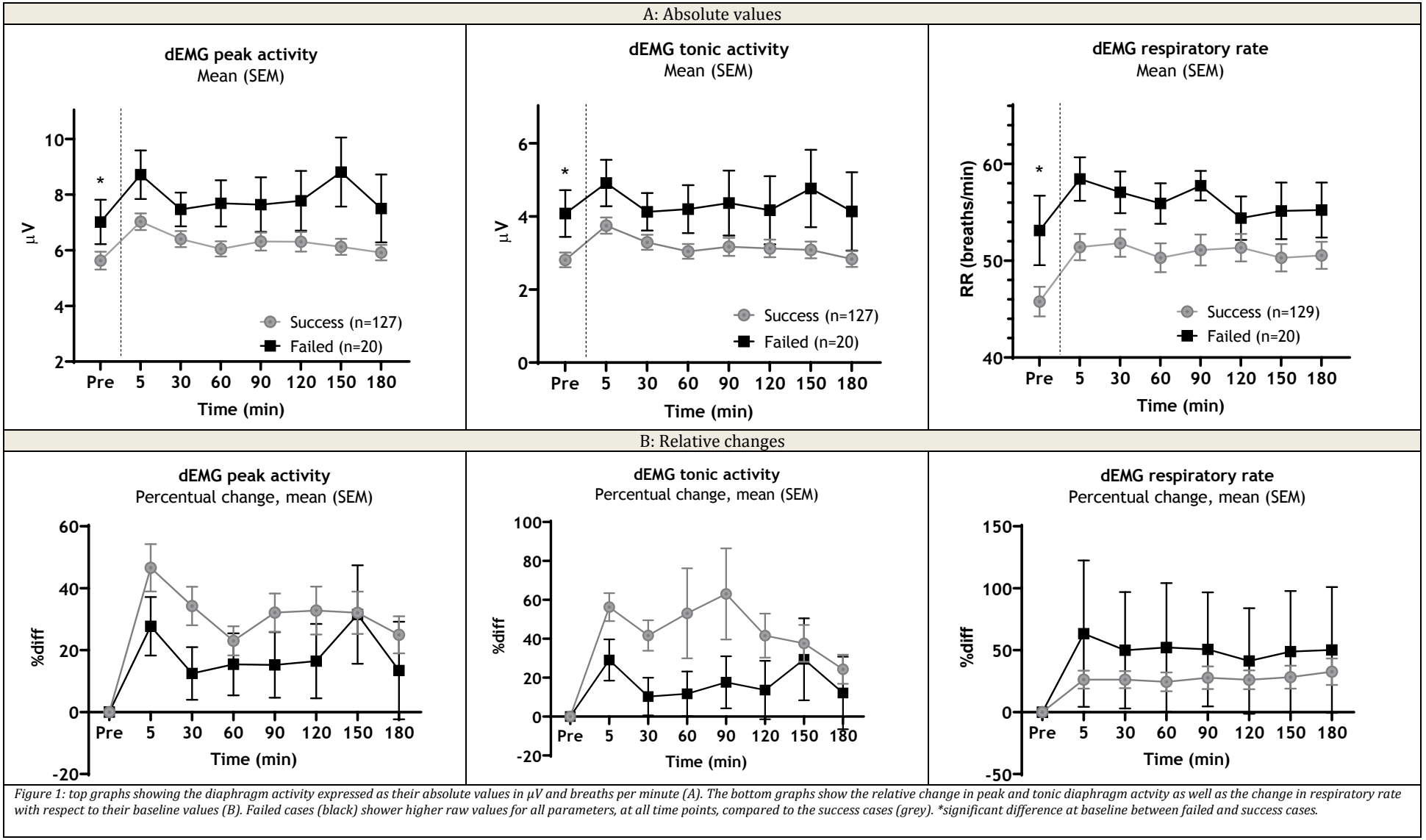
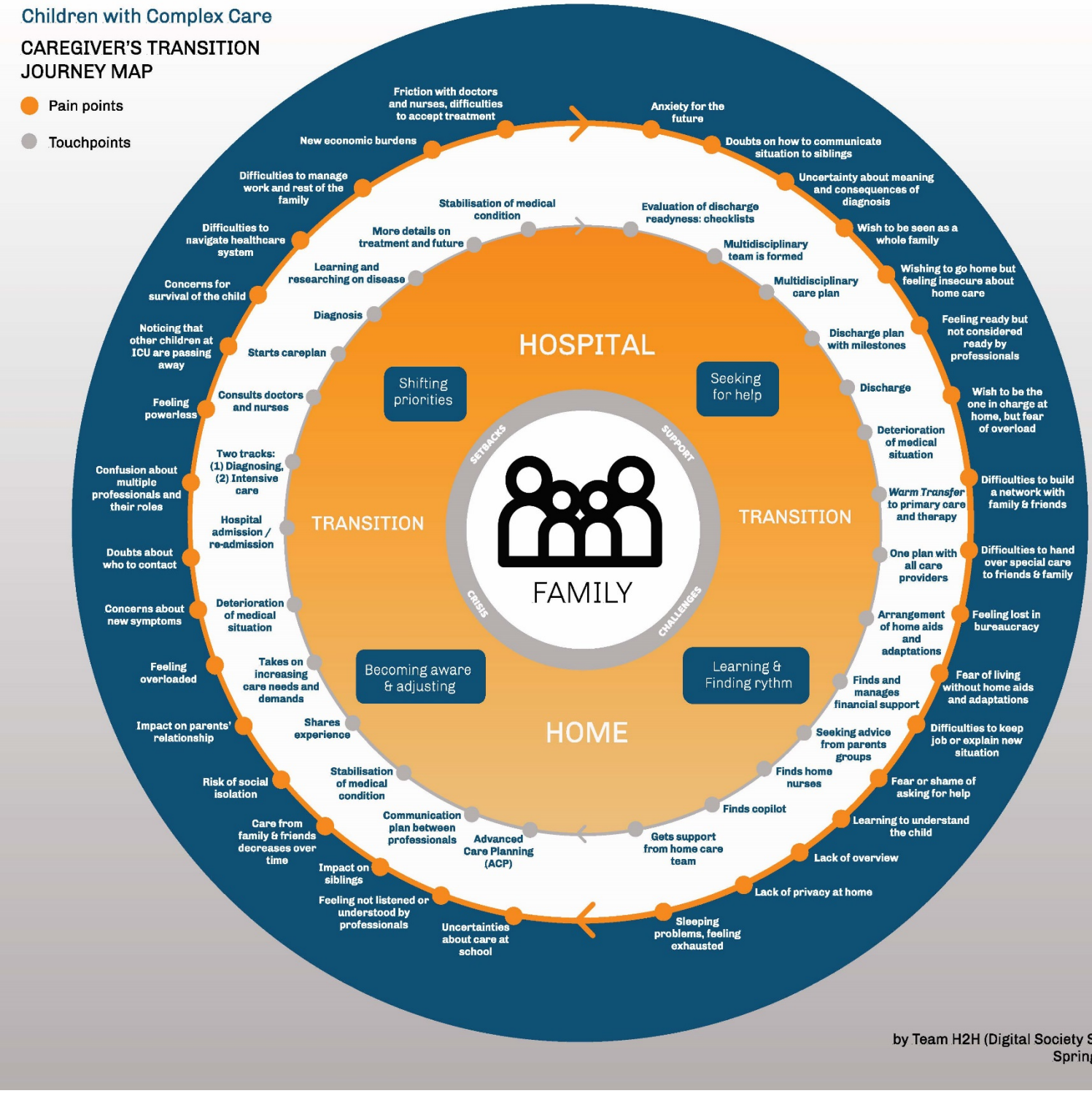


*Figure 1: top graphs showing the diaphragm activity expressed as their absolute values in µV and breaths per minute (A). The bottom graphs show the relative change in peak and tonic diaphragm actvity as well as the change in respiratory rate with respect to their baseline values (B). Failed cases (black) shower higher raw values for all parameters, at all time points, compared to the success cases (grey). *significant difference at baseline between failed and success cases.*


Children with Complex Care
CAREGIVER'S TRANSITION JOURNEY MAP
Pain points
Touchpoints
HOSPITAL
HOME
TRANSITION
TRANSITION
FAMILY
SETBACKS
SUPPORT
CRISIS
CHALLENGES
Shifting priorities
Seeking for help
Becoming aware & adjusting
Learning & Finding rythm
Friction with doctors and nurses, difficulties to accept treatment
Anxiety for the future
New economic burdens
Doubts on how to communicate situation to siblings
Difficulties to manage work and rest of the family
Uncertainty about meaning and consequences of diagnosis
Stabilisation of medical condition
Evaluation of discharge readyness: checklists
Difficulties to navigate healthcare system
More details on treatment and future
Wish to be seen as a whole family
Multidisciplinary team is formed
Learning and researching on disease
Multidisciplinary care plan
Wishing to go home but feeling insecure about home care
Concerns for survival of the child
Diagnosis
Discharge plan with milestones
Feeling ready but not considered ready by professionals
Noticing that other children at ICU are passing away
Starts careplan
Discharge
Wish to be the one in charge at home, but fear of overload
Feeling powerless
Consults doctors and nurses
Deterioration of medical situation
Difficulties to build a network with family & friends
Confusion about multiple professionals and their roles
Two tracks: (1) Diagnosing, (2) Intensive care
Warm Transfer to primary care and therapy
Difficulties to hand over special care to friends & family
Doubts about who to contact
Hospital admission / re-admission
One plan with all care providers
Feeling lost in bureaucracy
Concerns about new symptoms
Deterioration of medical situation
Arrangement of home aids and adaptations
Fear of living without home aids and adaptations
Feeling overloaded
Takes on increasing care needs and demands
Finds and manages financial support
Difficulties to keep job or explain new situation
Impact on parents' relationship
Shares experience
Seeking advice from parents groups
Fear or shame of asking for help
Risk of social isolation
Stabilisation of medical condition
Finds home nurses
Learning to understand the child
Finds copilot
Care from family & friends decreases over time
Communication plan between professionals
Lack of overview
Gets support from home care team
Advanced Care Planning (ACP)
Impact on siblings
Lack of privacy at home
Feeling not listened or understood by professionals
Sleeping problems, feeling exhausted
Uncertainties about care at school
by Team H2H (Digital Society School)
Spring 2020

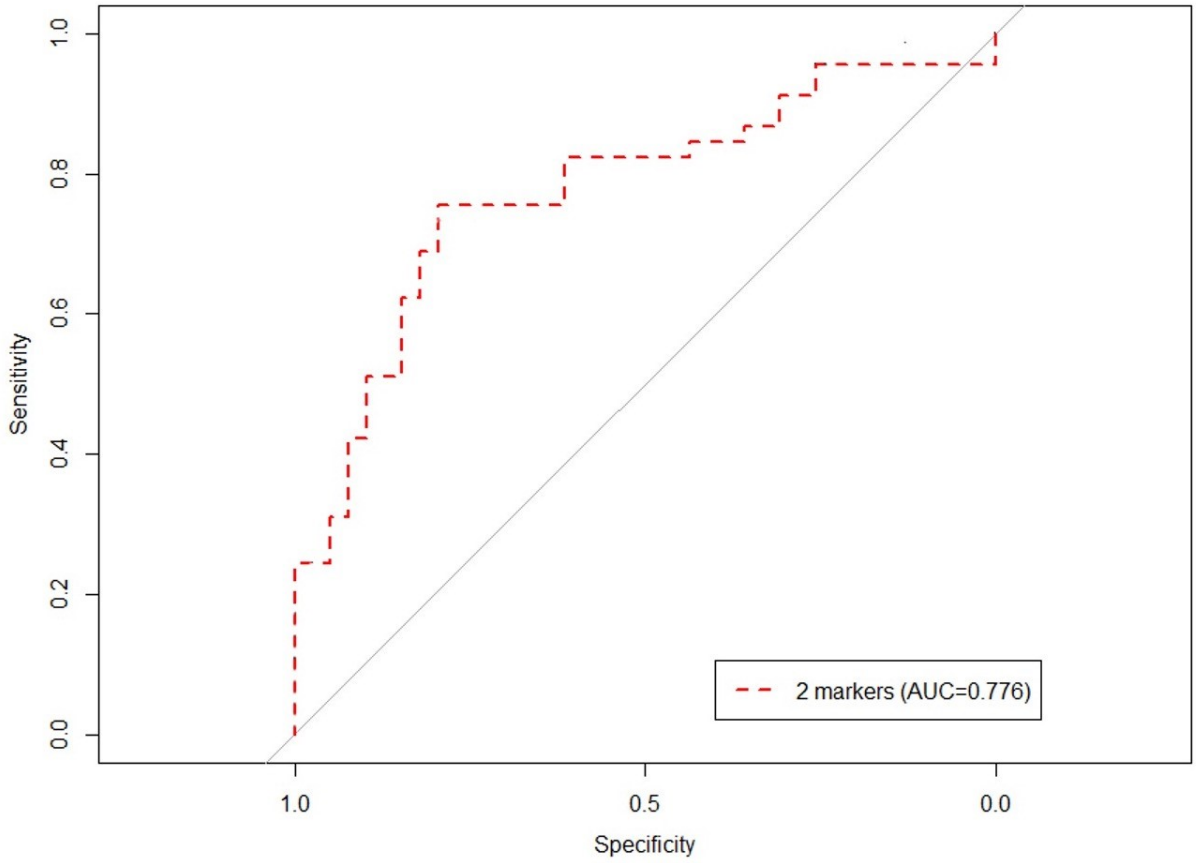


Figure 1 Receiver operating characteristic for weighted cummulative amino acid profiles on three to one day(s) before clinical onset of NEC IIIA/B compared to 1:1 matched controls. Diagnostic accuracy (AUC) for NEC is 0.78, based on isoleucine and alpha-Aminobutyric acid.