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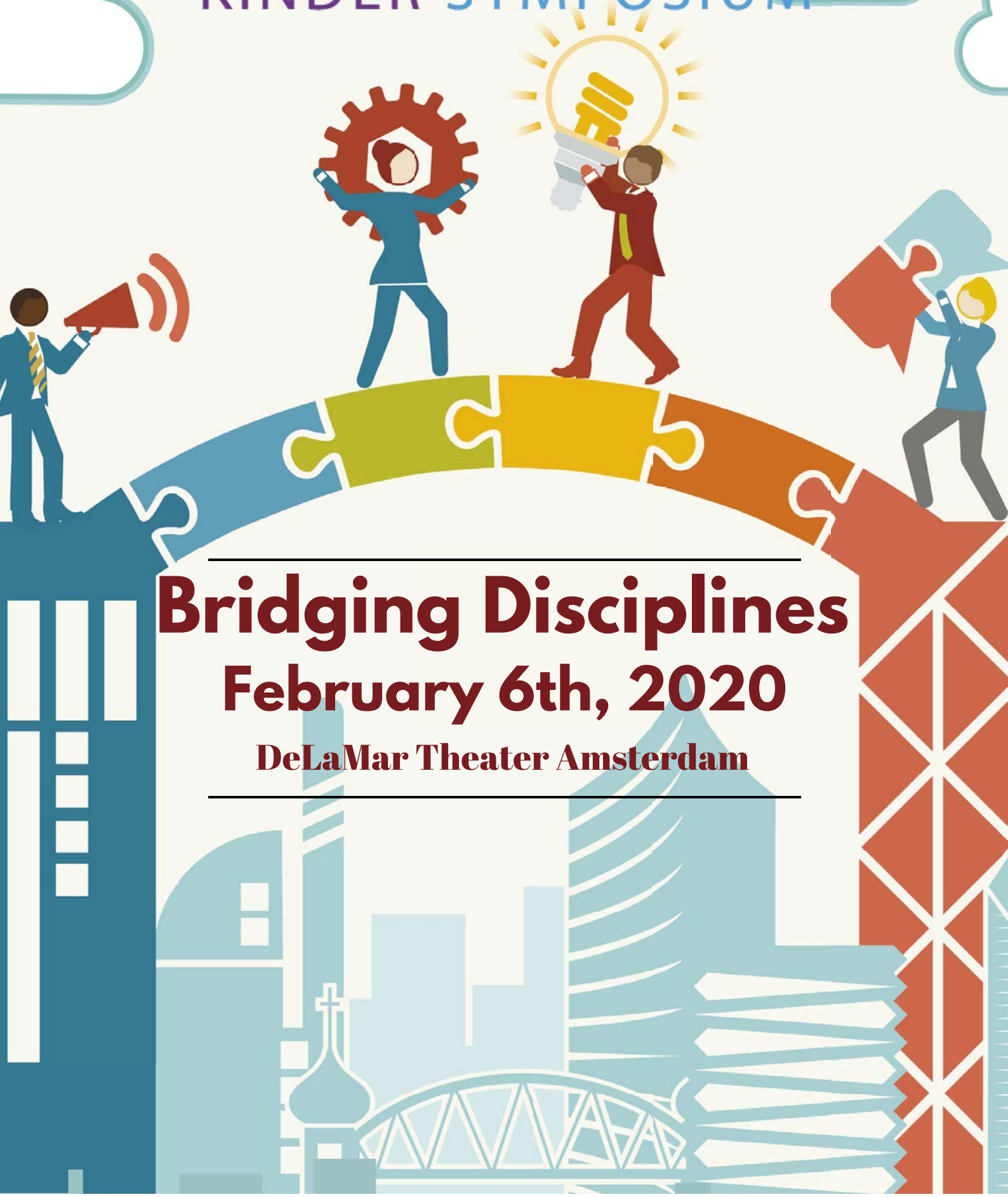

Bridging Disciplines
February 6th, 2020
DeLaMar Theater Amsterdam

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Ninth Amsterdam Kindersymposium, February 6th, DeLaMar Theater

Bridging Disciplines

Amsterdam 2020

Layout: Optima Grafische Communicatie, Rotterdam

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Emma Kinderziekenhuis
Amsterdam UMC

Preface Hans van Goudoever

For the ninth consecutive year, a group of young researchers organizes the Amsterdam Kindersymposium. A teaching course in itself, as it is the second largest conference of the Netherlands with international guest speakers, a speakers dinner, plenary sessions, parallel sessions, prize winning competitions, a masterclass, acquisition of sponsors, organizing the logistics of the venue, putting together the abstract portal and many other things. This has been the tradition from the beginning, as it is the tradition that all Amsterdam research groups, but also important researchers from regional hospitals and other academic hospitals, present their latest findings.
The meeting expands, as we see an increase in abstracts submitted by researchers from other regions and many more pediatricians attending the meeting. The message that is broadcasted by this increasing success is simple: Scientific research is key for progress in medicine. Through research we will continue to improve our treatment of children, through research we will understand the mechanism behind disturbance in functional outcome, through research we will know what treatment is best for the patient as well as the family surrounding him or her.
Again, as in the last five years, the meeting is held in the New DeLaMar theatre, originally built as a school, so the setting could not fit better. Where in the late 1800s, predominantly young children went to school here, after the Second World War, the school was rebuilt into a theater. So teaching and performing on this site, like we will do on February 6th, has its historical roots.
The SLAM presentations are the backbone of the symposium, while the plenary sessions will be held in the view of "Bridging Disciplines". The Committee has invited very interesting speakers, and has selected almost 70 abstracts to be presented, which makes this day a very special one for many.
I wish you all a beautiful day in the DeLaMar Theater at our Amsterdam Kindersymposium 2020.

Hans van Goudoever
Chair, Emma Children's Hospital – Amsterdam UMC

Preface Symposium Commission

With excitement, we invite you to the ninth edition of the Amsterdam Kindersymposium (AKS) in the DeLaMar Theatre in Amsterdam.
This year's theme is **'Bridging Disciplines'** and with this inspiration we have selected several honorable speakers to present their work on topics in and adjacent to the field of pediatrics. Pediatric health care involves many facets and is therefore strongly dependent on multidisciplinary collaborations. With this theme, we aim to fuel synergy between the broad range of specializations with common ground in the field of pediatrics.
Nutricia powers the annual **breakfast session**, where you can enjoy a delicious breakfast while you wake up with inspiring talks about research in the field of pediatric gastroenterology and nutrition.
We welcome **prof. dr. Eli C. Lewis**, our keynote speaker from the Ben Gurion University of the Negev, Israel. He will present his view on "the wisdom of the sick body" which we are eager to learn about!
This year, in addition to the well-known **SLAM-sessions**, we introduce a new session called **'Bridging the Gap'**. With this interactive session, we aim to bridge the gap and bring research closer to clinical practice. With this session, we aim to bridge the gap and bring research closer to daily clinical practice, by presenting a clinical case in which (ongoing) research helped solving a piece of the clinical puzzle.
This year we also introduce the **Takeda lunch symposium**, where we will learn about the nationwide, interdisciplinary teamwork from United for Metabolic Diseases (UMD).
We are looking forward to an inspiring day and hope that you will enjoy the AKS 2020. We would like to thank all that have contributed to making the AKS a great success and we hope to continue and expand this endeavor in the future.

The Amsterdam Kindersymposium Committee 2019–2020,
Laura Tseng, Jorn Gerritsma, Marsh Königs, Mendy Welsink-Karssies, Rinse Barendsen, Floor Veltkamp, Noor de Sonnaville, Marinde van Lennep, Diana van Stijn – Bringas Dimitriades

Program 2020

8:00 – 8:45 Registration, coffee & tea

8:15 – 8:35 **Nutricia Breakfast session**

8:45 – 9:00 **Opening by prof. dr. Hans van Goudoever**

9:00 – 9:30 **Off to a good start! The fundamental importance of the first 1000 days of life**
Prof. dr. Tessa Roseboom, Professor of Early Development and Health, Amsterdam UMC

9:30 – 10:00 **The social contexts of stress and coping**
Prof. dr. Catrin Finkenauer, Professor Youth Studies and scientific director of Dynamics of Youth, Utrecht University

10:00 – 10:25 Coffee break

10:25 – 11:45 SLAM session I

11:50 – 12:35 Professor Heymans Lecture:

The wisdom of the sick body
Prof. dr. Eli C Lewis: Professor and head of the department of clinical biochemistry & pharmacology, Ben-Gurion University of the Negev, Israel

12:45 – 13:45 Lunch

12:55 – 13:20 **Takeda Lunch symposium:**

United for metabolic diseases (UMD)
Prof. dr. C.D. van Karnebeek, Professor of Metabolic Diseases, Radboud University & prof. dr. H.R. Waterham, Professor of Functional Genetics of Metabolic Diseases

13:45 – 14:55 SLAM session II & Bridging the gap session

15:00 – 15:30 **Die ene patiënt (in Dutch)**
Ellen de Visser, Health Journalist, de Volkskrant

15:30 – 15:50 Coffee break

15:50 – 16:20 **PhD thesis: What is the role of parents in treating children with chronic diseases and disabilities?**
Dr. Mattijs Alsem, department of Pediatric rehabilitation, Amsterdam UMC

16:20 – 16:50 **SLAM battle final & Prize ceremony**

16:50 – 17:00 Closing word

17:00 – 18:00 Drinks

Slam session I – Morning (10:25 till 11:45h)

Rode Foyer (–1st Floor)

Chair: Dr. Brigitte de Bie / Annemarie Plaisier

P37	Keulen van, B.	Sexual dimorphism in cortisol production and metabolism throughout pubertal development: a longitudinal study
P38	Haar ter, A.	Health-Related Quality of Life of Perinatally Hiv-Infected Children Growing into Young Adulthood
P39	Orriëns, L.	Nonadherence to Inhaled Corticosteroids: a Characteristic of the Obese-asthma Phenotype in Children?
P40	el Manouni el Hassani, S.	Allantoin: a fecal biomarker for preclinical detection of perforated necrotizing enterocolitis in preterm infants
P41	Muilekom van, M.	Empowering patients: a first step in developing educational videos about PROs in clinical practice
P42	Leuteren van, R.	Relation between esophageal pressure, volume and the activity of the diaphragm in a preterm infant, a physiological study
P43	Linssen, R.	Burden of RSV bronchiolitis in the pediatric intensive care unit – a 13-year national registry study
P44	Chatelion Counet, M.	Kidney failure – an overlooked feature of Down Syndrome
P45	Vijverberg, S.	Drivers and barriers of pediatric patient engagement in respiratory medicine: lessons learnt from establishing a child council
P46	Simons, N.	Child outcomes after amnioinfusion compared with no intervention in women with second-trimester rupture of membranes: a long-term follow-up study of the PROMEXIL-III trial

Slam session I – Morning (10:25 till 11:45h)

Wim Sonneveld zaal (1st floor)

Chair: Dr. Diederik Bosman / Dr. Menno Smit

P47	Roorda, D.	Botulinum toxin injections after surgery for Hirschsprung disease: systematic review and meta-analysis
P48	El Tahir, O.	Executive functioning in later life after childhood bacterial meningitis: a 25-year follow-up
P25	Witkamp, D.	Guanabenz Ameliorates Ataxia in a Mouse Model for Vanishing White Matter
P49	Gathier, A.	Effectiveness of a two-day EMDR treatment for parents of MPS III patients: a study protocol
P50	Assies, R.	Early detection and pathophysiology of shock in Malawian children; A pilot study of new bedside techniques
P51	Roorda, D.	Risk factors of post-operative enterocolitis in patients with Hirschsprungs disease
P52	Apers, W.	Timing of neonatal seizure treatment: a retrospective cohort study.
P53	Verkuil, F.	Exploring contrast-enhanced MRI findings of the wrist in healthy children
P54	Beerepoot, S.	Donor macrophages in transplanted MLD patients support oligodendrocytes, thereby enabling remyelination and improvement of white matter abnormalities on MRI

Slam session I – Morning (10:25 till 11:45h)

Diner Foyer (2nd floor)

Chair: Dr. Koert Dolman / Ilse Luirink

P55	Schoenmaker, M.	Prophylactic anticoagulation in children receiving home parenteral nutrition
P56	Sommers, R.	Viridans group streptococci infections: Are teicoplanin or vancomycin feasible and safe as antibiotic prophylaxis regimen in pediatric leukemia patients? A systematic review
P57	Draijer, L.	Fibrokids Study: Effective screening for NAFLD in children with obesity
P58	Wassenaer van, E.	Diagnostic test accuracy of bowel ultrasound in children with inflammatory bowel disease
P59	Mank, E.	Insulin concentration in human milk in the first days after birth: course and associated factors
P60	Oudejans, E.	Anesthesia in models of Vanishing White Matter
P61	Dooves, S.	Neuronal dysfunctioning in 4H leukodystrophy
P62	Aknouch, I.	The human gut organoid, a promising model to study enterovirus infection and disease pathogenesis
P63	Naafs, J.	Age-specific reference values for plasma FT4 and TSH in term neonates during the first two weeks of life
P64	Zarekiani, P.	Impaired astrocytic functioning in Vanishing White Matter disease and its effect on blood-brain barrier integrity: implications for disease severity

Slam session I – Morning (10:25 till 11:45h)

Mary Dresselhuys Zaal

Chair: Dr. Frans Plötz / Carlijn van der Zee

P65	Kontopodi, E.	The effect of different time-temperature profiles on bioactive proteins during pasteurization of donor human milk
P26	Lijdsman, S.	Brain white matter abnormalities and neurocognitive impairment in children and young adults with severe chronic kidney disease
P66	Henke, C.	Motor interventions in school-aged children with motor impairment: a meta-analysis and meta-regression
P67	Navis, M.	A human 2D organoid model to study gut barrier maturation and host-pathogen interaction in the small intestine
P27	Houdt van, C.	Effects of computerized executive function training in very preterm children: a randomized controlled trial
P68	Brouwer, L.	Echovirus seroepidemiology in the Netherlands
P69	Kerst, S.	Water and ions out of balance: dysfunctional astrocytes in the white matter disease MLC
P28	Kouwenhoven, S.	Metabolic and hormonal markers in 4-month-old infants fed a modified low-protein infant formula: results from a randomized controlled trial
P70	Oomen, I.	Anti-rituximab antibodies with corresponding drug levels in children with B cell mediated diseases treated in the Emma Children's hospital

Slam session II – Afternoon (13:45 till 14:55h)

Rode Foyer (1st floor)

Chair: Carlijn Kraakman / Dr. Emil den Bakker

P71	Passchier, E.	Unraveling the Cellular Signaling Pathways Underlying MLC
P72	Seljogi, D.	Ethnic background is associated with health care consumption in children with asthma
P73	Depla, J.	Stem cell derived brain organoids, a promising model to study Adeno associated viruses for CNS gene therapy
P74	Stellingwerff, M.	Analyzing radiological progression in 252 cases of Vanishing White Matter (VWM)
P75	Boer de, L.	Lipoprotein(a) Levels over Time: a Long-term Follow-up Study of a Large Cohort of Children
P76	Zuurbier, R.	Early life exposure to respiratory viruses: a longitudinal birth cohort study
P32	Heerde van, M Zaal-Schuller, I	**Bridging the Gap Session** End-of-life decision-making for severely disabled children

Slam session II – Afternoon (13:45 till 14:55h)

Wim Sonneveld zaal (1st floor)

Chair: Dr. Jeroen Hol / Dr. Charlotte Ruys

P77	Luijten, M.	From Statistician to Clinician: the feedback of PROMIS® CATs within KLIK
P78	Leuteren van, R.	The feasibility of transcutaneous electromyography of the diaphragm as monitoring technique in the delivery room
P79	Kontopodi, E.	Survey on the operation of European human milk banks
P80	Wissa, M.	The incidence of intracranial hemorrhages in neonates with hemophilia; an assessment of the literature
P81	Koff, E.	The influence of early-life gut microbiome development on vaccine responses
P82	Bruijn de, C.	Fecal microbiota transplantation in adolescents with refractory irritable bowel syndrome; protocol for a pilot randomized, double-blind, placebo-controlled trial
P33	Pajkrt, D. Bruning, A.	**Bridging the Gap Session** Acute Flaccid Paralysis caused by Enterovirus D68

Slam session II – Afternoon (13:45 till 14:55h)

Diner Foyer (2nd floor)

Chair: Dr. Marieke Merelle / Dr. Laura Schouten

P83	Roorda, D.	Intrasphincteric Botulinum toxin injections for post-operative obstructive defecation problems in Hirschsprungs disease: predictors of response
P84	Plug, B.	Heterogeneity of astrocytes in Vanishing White Matter disease: central in white matter lesion repair?
P85	Kos, R.	Targeted analysis of volatile organic compounds for detection of Pseudomonas aeruginosa in cystic fibrosis patients by exhaled breath analysis
P86	Douma, M.	Positive effects of an online cognitive behavioral group intervention on anxiety and depression in parents of children with a chronic illness: a randomized controlled trial
P87	Löwensteyn, Y.	NARSYN trial: intranasal administration of palivizumab against RSV infection
P88	Metry, E.	Transplantation outcomes in patients with Primary Hyperoxaluria Type I
P34	Van den Berg, S. Huybrechts, B.	**Bridging the Gap Session** Treating traumatic injury on children at the emergency department

Slam session II – Afternoon (13:45 till 14:55h)

Mary Dresselhuys Zaal

Chair: Dr. Mariet Felderhof / Dr. Bart Cortjens

P89	Man, J.	Region-resolved quantitative proteomic mapping of the human Vanishing White Matter brain
P90	Navis, M.	The beneficial effect of native whey protein on intestinal integrity and innate defense in the immature intestine of preterm and near-term piglets
P91	Teela, L.	The use of the KLIK PROM portal in clinical care; the patients' and parents' point of view
P92	Brekel van den, N.	Exploring the burden of Ntwetwe virus – a novel orthobunyavirus associated with CNS infections – in Ugandan children
P29	Jong de, A.	Monitoring of micturition and bladder volumes can replace routine indwelling urethral catheters in children receiving intravenous opioids, a prospective cohort study
P30	Termeulen, E.	A scoping review of Inborn errors of metabolism causing progressive intellectual and neurologic deterioration (PIND)
P35	Groothoff, J.W. Garrelfs, S.F.	**Bridging the Gap Session** A crystal clear case, or not?

Plenary sessions

Hosts

Prof. dr. A. Popma

Which study/studies did you do (incl. time period in years)?
I studied Medicine and then specialized in Psychiatry and subsequently in Child and Adolescent Psychiatry.

At which university did you study?
VU University, Amsterdam

When did you obtain your PhD and what was the title of your thesis?
2006: "Neurobiological factors of antisocial behavior in delinquent male adolescents"

Since when are you working at your current institution?
2011

Which publication or grant are you most proud of?
Societal Impact Award 2019 Amsterdam UMC

Which aspects of your work do you like most?
Dealing with human behavior and building relationships, never a dull moment!

What is an important innovation in the field you are working in?
Rebuilding child- and adolescent psychiatry by true co-creation with youngsters and families

What do you like to do after work hours?
Listening and making music; watching and playing football; spending time with my family (and talking about work with befriended colleagues; I have to admit I am a bit of a workaholic ☺)

What are your future plans?
Staying curious and trying to improve a little bit every day

What are you most excited about of this symposium?
Being part of a day that aims to build bridges between disciplines.

What music album did you play most?
Red hot chili peppers – BSSM

What was your favorite concert/show?
The first gig by Moondog Jr. at Lowlands

What is your favorite food?
Burrito's

What is your favorite movie?
Ciske de Rat

Dr. K.J. Oostrom

Which study/studies did you do (incl. time period in years)?
Clinical Neuropsychology (1991–1996)

At which university did you study?
VU University

When did you obtain your PhD and what was the title of your thesis?
2011 Cognition and behavior in children with idiopathic or cryptogenic epilepsy

Since when are you working at your current institution?
Since 2014 VUmc and since 2016 AMC

Which publication or grant are you most proud of?
Most proud of my publications on our ground breaking work for children with cerebral palsy who cannot speak.

Which aspects of your work do you like most?
The combination of both research, clinical work as well as management

What is an important innovation in the field you are working in?
By applying new computerized technologies our research team manages to raise new educational and social perspectives for children who cannot speak and who are severely handicapped

What do you like to do after work hours?
Spending time with family and friends, especially city trips and fun things

What are your future plans?
Not specified yet!

What are you most excited about of this symposium?
The meet & greets amongst passionate young people that will inspire us all

Keynote speaker

Prof. dr. E.C. Lewis

Prof. dr. Eli Lewis is head of the Department of Clinical Biochemistry & Pharmacology and academic faculty member of Basic Sciences at the Faculty of Health Sciences at the Ben-Gurion University of the Negev, Israel. Furthermore, professor Lewis is co-chair of the Wound Healing Hub. Eli Lewis has followed an interesting career path to say the least; he started studying Biology but then emerged himself in Medicine. During his Medicine study (that he almost finished) he got attracted to the field of Immunology, in which he followed a Master program. He then further obtained his PhD in Immunology and became a post-doc on Transplantation and Inflammation. Professor Lewis has initiated his own lab in order to study tissue and immune cells in Israel, focusing on tissue repair and the immune system, including type 1 diabetes, atopic dermatitis and bone-marrow transplantation in children with leukemia. The biggest challenge for professor Lewis has been to convince the scientific community that "some answers are in our bodies already and that deepening too far down an attractive oath doesn't exclude simpler solutions in modern medicine". We are honored that professor Lewis has agreed to fly all the way to the Netherlands to attend the Amsterdam Kindersymposium as our key-note speaker. In his lecture he will talk about **"The wisdom of the sick body"**, in which he says that the most striking conclusion is that humans are apparently inferior to animals in fixing tissues; implicating the need for recombinant therapies using directed evolution.

Speakers

Prof. dr. T. Roseboom

Prof. dr. Tessa Roseboom is Professor of Early Development and Health at the Amsterdam UMC. Her main focus is research, however she also spends her time in teaching and advocacy. Her research is aimed at determining how a child can have the best possible start in life. For example, Professor Roseboom investigates the impact of adverse environmental exposures (stress, under/overnutrition, poverty, medical interventions) in early life on growth, development and health in adult life – and how to optimize the early environment. In her work, professor Roseboom collaborates with many different disciplines such as gynecology, neonatology, pediatrics, internal medicine, psychiatry, epidemiology, public health, sociology and economics. The biggest challenge for her personally has been to balance her professional ambitions with giving her own children the best start in life. With her talk about **"Off to a good start! The fundamental importance of the first 1000 days of life"** she will show us the striking evidence from many different disciplines on the importance of a good start in life. Not only from medical perspective, but also from the fields of Biology and Economics. From biology, medicine and economics– for many different aspects of life; health, learning, behavior, even across generations.

Prof. dr. C. Finkenauer

Prof. dr. Catrin Finkenauer is Professor Youth Studies and scientific director of Dynamics of Youth at the Utrecht University (UU), The Netherlands. The focus of her research lies on youth in changing cultural contexts. The aim of her research is to gain insights in the interactions between individuals and their social and environmental contexts to ultimately improve the lives of children, especially those with chronic diseases and trauma. Her research examines, for example, stress regulation and coping in adolescent-parent relationships, domestic violence and child abuse as well as parenting of traumatized parents. In Dynamics of Youth, professor Finkenauer collaborates with all 7 UU faculties and a large variety of knowledge institutions (e.g. RIVM, NJI, SCP, HU) and stakeholders (e.g., childcare organizations, schools and NGOs). When we asked her what her biggest challenge has been in her career, she answered: "I am my biggest challenge"!". In this lecture, professor Finkenauer will tell **"The social contexts of stress and coping"**, a lecture on how stress manifests between individuals – rather than within individuals – and the effects of this phenomenon.

Dr. M. Alsem

Mattijs Alsem is a pediatric rehabilitation physician in the Amsterdam UMC and also post-doc researcher. In 2018 he received the PhD thesis award from the Netherlands Society of Rehabilitation Medicine. His research involves family empowerment, family integrated care and participation in daily life. In his current position dr. Alsem collaborates with multiple disciplines such as pediatric intensive care, various therapeutic disciplines and he also works with researchers in the "Netwerk Family -integrated Care". Dr. Alsem shared with us that the biggest challenge in his career has been to truly facilitate and practice family-centered care. Dr. Alsem will present on a key-question in his field **"What is the role of parents in treating children with chronic diseases and disabilities?"**, a lecture on the difficulties of facilitating family-centered care, the changes in family needs over time and the uniqueness of family needs.

Motivational speaker

E. de Visser

Ellen de Visser is a medical editor at the Volkskrant. Before becoming a medical editor, she worked as an investigative reporter in the division of Health care. Ellen studied French and Literature in Amsterdam and Paris after which she did a post-doc in Journalism. Her writings cover topics of the medical field, which can be very challenging as it needs to be written in a way that its complexity would reach the general public. Over the years Ellen has published several books; "Genderkinderen" (2010), "Waarom je kat niet mee naar bed mag" (2013) and her latest book "Die ene patient" (2019). For her latest book, which is a bundle of her columns, Ellen interviewed doctors and health care professionals and asked them about **"that one memorable patient"**. During these interviews Ellen found that doctors can learn important lessons from their patients. We are excited to have Ellen at the Amsterdam Kindersymposium as our motivational speaker.

Abstracts selected for the Masterclass

Guanabenz ameliorates ataxia in a mouse model for Vanishing White Matter

D. Witkamp[1], E. Oudejans[1], L. Hoogterp[1], G. Hu-a-ng[1], M.S. van der Knaap[1], T.E.M. Abbink[1]

[1] *Department of Pediatrics, Emma Children's Hospital, Amsterdam UMC, The Netherlands*

Rationale Vanishing white matter (VWM) is a fatal stress-sensitive leukodystrophy, resulting in neurological deterioration and motor problems and mainly affecting young children. VWM is currently untreatable. In this genetic disorder, mutations in the genes encoding eukaryotic initiation factor 2B (eIF2B) result in a deregulated function. eIF2B is essential for mRNA translation initiation and plays an important role in regulation of the integrated stress response (ISR). We found that ISR deregulation is a suitable treatment target. Earlier studies identified guanabenz as a treatment option for VWM. Guanabenz, an FDA-approved drug, has an inhibitory effect on the ISR in neurological disorders with disease-ameliorating consequences. In a recent study using a small number of VWM mice we have found that white matter pathology was ameliorated by guanabenz. However, this initial study was performed with a suboptimal dosage. The aim of the current study is to investigate improvements of guanabenz on hallmarks of VWM in a mouse model using an optimal treatment dosage.

Methods A mouse model for VWM with mutations in eIF2B (2b4he2b5ho) replicates the human VWM phenotype. 16 wild type (wt) mice and 32 2b4he2b5ho mice were i.p. injected daily with either a vehicle or 4.5mg/kg guanabenz from an age of 8 weeks onwards. A third group of 8 wt mice and 16 2b4he2b5ho mice received weekly 10mg/kg guanabenz injections from the same age. Motor skills were assessed at an age of 5–6 months. Animals were subsequently culled for molecular and neuropathological examination.

Results Daily injections of guanabenz 4.5mg/kg increased the body weight of 2b4he2b5ho mice. Motor skills assessed by a balance beam were enhanced by both the weekly as daily dosages. More pronounced improvements were observed in the daily dosage of 4.5mg/kg guanabenz than in the weekly 10mg/kg dosage.

Discussion Guanabenz shows clear improvements on VWM mouse motor skills. Guanabenz shows promise as a viable treatment option for patients with VWM.

Brain white matter abnormalities and neurocognitive impairment in children and young adults with severe chronic kidney disease

S. Lijdsman[1], M. Königs[2], M.S. van Sandwijk[3,4], A.H. Bouts[2], K. van Hoeck[5], H. de Jong[6], J. Oosterlaan[2], F.J. Bemelman[3], K.J. Oostrom[1], J.W. Groothoff[2]

[1] Psychosocial Department, Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, The Netherlands;
[2] Department of Pediatrics, Emma Children's Hospital, Amsterdam UMC Amsterdam, The Netherlands;
[3] Department of Nephrology, Amsterdam UMC, Amsterdam The Netherlands;
[4] Dianet Dialysis Center, Amsterdam, The Netherlands;
[5] Department of Pediatrics, University Hospital Antwerp, Belgium;
[6] Department of Pediatrics, Sophia Children's Hospital, Erasmus MC, Rotterdam, The Netherlands.

Rationale Children and young adults with severe chronic kidney disease (CKD4-5) might be at risk of white matter damage leading to neurocognitive dysfunctioning, which in turn may impact psychosocial development and health-related quality of life. The INPACT study aims to assess the associations to eventually improve psychosocial functioning in these patients. Here we report on the associations between white matter integrity as measured with diffusion tensor imaging (DTI) and neurocognitive functioning of patients on different therapy modes.

Methods This cross-sectional study includes 28 Dutch and Belgian patients with CKD4-5 aged 8–30 years (median=18.5, range=9.1–30.5) on different therapy modes (pre-dialysis: n=8; dialysis: n=8; transplanted: n=12) and 21 healthy controls matched for age, gender and educational level. Measurements consist of DTI scanning (both patients and healthy controls) and neurocognitive assessments (patients only).

Results DTI analysis indicated that CKD4-5, in particular dialysis and transplanted, patients had lower white matter integrity than healthy controls (P<.05). Regarding neurocognitive functioning, IQ were significantly lower in dialysis (p=.045, Cohen's d =1.274) and transplanted patients (p=.031, Cohen's d=1.299) compared to pre-dialysis patients. Longer duration of dialysis was negatively associated with IQ (p=.028, R2=.300) and executive functioning (p=.005, R2=.435). In the cluster affected by CKD4-5, lower white matter integrity was related to poorer IQ (p=.049, R2=.170).

Conclusions Children and young adults with CKD4-5 at risk for brain white matter abnormalities and neurocognitive dysfunctioning. These effects are also clearly present after renal transplantation. Prolonged period of dialysis increases the risk for neurocognitive dysfunctioning. CKD4-5 induced white matter abnormalities are associated with neurocognitive dysfunctioning, which may provide opportunities for cognitive rehabilitation.

Effects of computerized executive function training in very preterm children: a randomized controlled trial

C.A. van Houdt[1,2], A.G. van Wassenaer-Leemhuis[1], J. Oosterlaan[3,4], M. Königs[2], C. Koopman-Esseboom[5], A.R.C. Laarman[6], A.H. van Kaam[1,6], C.S.H. Aarnoudse-Moens[1,2,4,7]

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[4] *Vrije Universiteit Amsterdam, Clinical Neuropsychology section, Van der Boechorststraat 7, Amsterdam, The Netherlands;*

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[6] *Emma Children's Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, Neonatology, de Boelelaan 1117, Amsterdam, The Netherlands;*

[7] *Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Psychosocial Department, Meibergdreef 9, Amsterdam, The Netherlands*

Rationale Very preterm (VP) children show deficits in attentional, academic, behavioral and emotional functioning compared to term-born peers. Executive function (EF) problems are thought to underlie the deficits in these domains. Aim of the current study was to examine effects of a computerized EF training (BrainGame Brian) on attentional, executive, academic, behavioral and emotional functioning and self-perceived competence in VP children.

Methods In our multi-center, double-blind, placebo and waitlist controlled randomized trial, we included VP children (< 30 weeks of gestation) aged 8 to 12 years with parent rated attention problems. Children were randomized to EF training, placebo training or waitlist. Outcome measures were assessed at baseline, at the end of the training program and five months after finishing the training. Outcome measures were parent and teacher rated attentional, executive, behavioral and emotional functioning, neuropsychological tests of attentional, executive and academic functioning and self-perceived competence rated by children themselves. Data were analyzed on intention-to-treat basis with linear mixed model analyses.

Results 85 children were included in the trial and randomized to EF training (29), placebo training (26) or waitlist (30). Basic characteristics at the start of the study did not differ between the groups. For children in the EF training group, significant improvements were found across training sessions in the EF training tasks. Despite these improvements, we found no significant differences in improvement over time between the EF training, placebo training and waitlist for any of the outcome measures.

Discussion This study does not support the use of computerized EF training programs in VP children to improve attentional, executive, academic, behavioral or emotional functioning or self-perceived competence. Future studies should investigate whether more real-world like EF training can be effective in VP children.

Metabolic and hormonal markers in 4-month-old infants fed a modified low-protein infant formula: results from a randomized controlled trial

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Rationale High protein intake in early life is associated with increased childhood obesity risk. Dietary protein intake may affect endocrine and metabolic responses. We aimed to determine the effect of a modified low-protein (mLP) infant formula on growth factors at the age of 4 months.

Methods Term infants received mLP (1.7 g protein/100 kcal) or a specifically designed control formula (CTRL) (2.1 g protein/100 kcal) until 6 months of age in a double blinded RCT. A breast-fed (BF) group served as reference. Glucose, insulin, leptin, IGF-1, IGF-BP1, -BP2 and -BP3 levels were measured at the age of 4 months. Groups were compared using linear regression analysis.

Results No significant differences in plasma parameters were observed between the formula groups (n=53 mLP; n=44 CTRL) while protein intake was significantly different. Insulin and HOMA were higher in both formula groups compared to the BF group (n=36 BF) (P <0.001). IGF-BP1 was lower in both formula groups compared to the BF group (P <0.01). We found a lower IGF-BP2 level in the CTRL group compared to the BF group (P <0.01) and a higher IGF-BP3 level in the mLP group compared to the BF group (P 0.03). There were no significant differences found in glucose, leptin and IGF-1. Adjustment for sex did not change our results.

Discussion At 4 months of age, there are no significant differences in growth factors between infants fed mLP formula and infants fed CTRL formula. In addition, there are distinct differences in fasting plasma parameters between formula-fed and breast-fed infants.

Monitoring of micturition and bladder volumes can replace routine indwelling urethral catheters in children receiving intravenous opioids, a prospective cohort study

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Rationale Opioids can cause acute urinary retention (AUR). Great variation exists in the routine placement of indwelling urinary catheters(IUC) in children receiving intravenous (IV) opioids in daily practice. We aim to determine the incidence, risk factors and time to event of AUR in children receiving IV opioids. We hypothesis that children receiving IV opioids do not routinely require an IUC.

Methods In our prospective observational study we included children aged 0–18 years old receiving IV opioids continuously and/or via patient-controlled analgesia for at least four hours. Main exclusion criteria were receiving epidural analgesia or admission to the NICU.
AUR was defined as the inability to void over eight hours with a bladder volume larger than expected for age, confirmed by ultrasound. Univariable and multivariable logistic regression analysis were performed. The time to AUR was analyzed by cumulative incidence.

Results We included 207 participants. Median age was 7.6 years (IQR 0.9–13.8). Morphine IV was the administered opioid in 199 (96.1%) of participants. The incidence of AUR was 31/207 (15.0%), with 19/65 (29.2%) in PICU patients and 12/142 (8.5%) in non-PICU patients. The number needed to treat was one IUC per seven participants, one IUC per four PICU patients and one IUC per 12 non-PICU patients. PICU admission (adjusted OR=4.5, 95% CI 1.8–11.5, p=0.001) and daily maximum fluid intake (adjusted OR=0.8, 95% CI 0.7–0.9, p=0.002) were significantly associated with AUR. Median time to AUR was nine hours (IQR 7.1–13.3). AUR occurred within 24 hours in 28/31 (90.3%) of AUR cases.

Discussion Good monitoring of micturition and bladder volumes can replace routine IUC insertion in children receiving IV opioids, even in PICU patients who have a significant increased risk of developing AUR. This monitoring is of the greatest importance during the first 24 hours of IV opioid administration.

A scoping review of Inborn errors of metabolism causing progressive intellectual and neurologic deterioration (PIND)

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Rationale Progressive intellectual and neurological deterioration (PIND) is a rare but severe childhood disorder, characterized by loss of intellectual or developmental abilities, and requires quick diagnosis to ensure timely treatment to prevent irreversible neurological damage. Inborn errors of metabolism (IEMs) are associated with PIND and often treatable, however not commonly screened for with biochemical urine/blood tests.

Methods We performed a PubMed search on IEMs presenting with PIND in individuals aged 0 to 18 years. We applied stringent selection criteria and subsequently derived information on encoding genes, pathways, clinical and biochemical signs and diagnostic tests from IEMbase (www.iembase.org) and other sources.

Results The PubMed search resulted in 2,152 articles and a review of references added another 19 articles. After applying our selection criteria, a total of 85 IEMs presenting with PIND remained. For 44 IEMs (52%) diagnosis can be achieved through generally accessible metabolic blood and urine screening tests; the remainder requires enzymatic and/or genetic testing. 7 PIND associated IEMs are included in newborn screening (NBS) panels of various countries. Treatment targeting the underlying pathophysiology is available for 35 IEMs (41%). All treatment strategies are reported to achieve stabilization of deterioration, and a subset improved seizure control and neurodevelopment.

Discussion With this literature review we aim to create an overview of IEMs presenting with PIND in children, to aid clinicians in accelerating the diagnostic process. Clearly IEMs constitute the largest group of genetic PIND conditions and have the advantage of detectable biomarkers as well as amenability to treatment. Thus, the clinician should keep IEMs at the forefront of the diagnostic workup of a child with PIND. With the ongoing discovery of new IEMs, expanded phenotypes, and novel treatment strategies, continuous updates to this work will be required.

Abstracts accepted for the Bridging The Gap Session

End-of-life decision-making for severely disabled children

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End-of-life decision-making (EoLDM) for severely disabled children is subject of research in Emma Children's Hospital. It focuses on how parents of severely disabled children are involved in EoLDM and on how they prefer to be involved. The presented case illustrates how it improves the EoLDM process in practice.

The patient is a girl of 14 years old. At 7 months of age, her parents worried about her development. After 2 years of uncertainty the diagnosis Rett syndrome was made. At 5 years of age she was admitted to the PICU because of respiratory insufficiency. Weaning from mechanical ventilation (MV) proved to be difficult. The medical team raised the question whether, in the case of problems, MV should be withhold in order to protect the girl from discomfort while there was no prospect of returning to a reasonable quality of life (QoL). In conversations with the intensivists, parents expressed their concern that the estimation of their daughter's QoL by the medical team was mainly based on the decreased QoL during her admission. They also felt that their opinions were not considered to be important and felt pressured to accept the decision not to initiate MV again.

After discharge from hospital, the girl improved. She did not require MV for several years. Mother started discussing her doubts concerning treatment limitations with their pediatrician. She stated: 'I know when her time has come and when I have to stop fighting for her. It was decided to reevaluate the decision to withhold MV. Now conversations started with discussing the wishes of parents in case their daughter would become critically ill again. Parents felt that they were listened to and that were acknowledged as experts of their daughter. Both parents and physicians felt that by openly discussing their divergent opinions, this challenged them to explore alternative pathways that were suitable for the girl's specific situation. Finally, the decision was made to reverse all treatment limitations.

Acute Flaccid Paralysis caused by enterovirus D68

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In 2018, an enterovirus D68 (EV-D68) outbreak with reports of Acute Flaccid Paralysis (AFP), also referred to as Acute Flaccid Myelitis (AFM), was observed in Europe and the USA. AFP is a neurological disorder, and when caused by poliovirus known as poliomyelitis. EV-D68 belongs to the same Enterovirus (EV) virus family as poliovirus and is classified as a Non-Polio (NP)EV. In the Netherlands, two cases of AFM associated with EV-D68 infection have been reported during this outbreak will be discussed during this session. EV-D68 infection has a biennial endemic elevation. Awareness and knowledge among clinicians about AFP and enterovirus related paralysis is therefore required. In addition, we describe whether active surveillance of AFP is necessary and what steps need to be taken to achieve this. Active surveillance will aid in policy making regarding the development of effective treatment and prevention strategies of AFP.

Treating traumatic injury on children at the emergency department

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Background For children a visit to the Emergency Room (ER) can be accompanied by fear, pain and stress, so-called procedural distress. Scientific research tells us that children experience needle-related procedures as most traumatic. To prevent procedural distress it is essential to prepare a custom-made plan that matches the procedure, the level of anxiety and age of the child.

Main findings A 17-month-old toddler is presented at the ER with a fingertip injury on his left hand.
A classic story of getting a finger stuck in the door. The diagnosis is a partial nail luxation. To maintain the nail, it is of great importance that the nail is placed back and stitched accurately. For this reason, sedation is required.

Management At arrival on the ER, a topical anaesthesia is lubricated on the location of the injection of the local anaesthesia. The sedative of preference is Dexmedetomidine intranasal. This is primarily sedative and brings only minimal analgesic effects. After checking the depth of sedation, the procedure can start. A single volair block with lidocaine, buffered in sodium bicarbonate is placed. This is injected using a 30G injection needle. After an exposure time of 10 minutes, we can start with replacing the nail. After successfully replacing the nail the finger is bandaged. We let the child awake from his sedation in his own pace.

Summary Fear and pain are unnecessary and harmful for the recovery and confidence of the patient. At OLVG we strive for a pain and stress-free treatment for every child. A multidiscipline collaboration at the hospital is of great essence.

A crystal clear case, or not?

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Background A 63-year old male presented with acute-on-chronic renal failure. The patient had a history of recurrent kidney stone episodes since the age of six years.

Main findings A renal biopsy was performed and showed massive oxalate deposition, which suggests oxalate nephropathy as the most likely explanation for the sudden decline in renal function. The serum creatinine level was 1236 µmol/L and plasma oxalate was 133 µmol/L. No secondary cause of hyperoxaluria was present (e.g. fat malabsorption) and further genetic testing confirmed the diagnosis of primary hyperoxaluria type 1 (PH1).

Management: PH1 is caused by a deficiency of the liver specific enzyme alanine:glyoxylate aminotransferase (AGT). At hand, the only curative option for PH1 is a liver-transplantation, which corrects the disease-causing enzymatic defect. In the majority of cases this would be the treatment modality of first choice, but there is one exception. A subgroup of patients do not have a complete deficiency of AGT, but their disease is caused by a mitochondrial mistargeting and pyridoxine (Vitamin B6) can correct this trafficking-defect. Unfortunately, this patient was diagnosed at time of advanced renal failure, which takes away the possibility to monitor the response to pyridoxine therapy by urine oxalate excretion. This resulted in a difficult clinical dilemma, whether to perform a sole-kidney transplantation (purely based on his late-onset and genotype) or opt for the more invasive combined liver-and kidney transplantation.

Follow-up For this reason, we performed a novel stable isotope method to assess residual AGT-activity in vivo. Based on our experiment we concluded that this patient was indeed pyridoxine-responsive and we recommended a sole-kidney transplantation. He successfully received a kidney-transplant and on examination his urine oxalate excretion remained normal under treatment with pyridoxine (Vitamin B6).

Abstracts accepted for the Slam Sessions

Sexual dimorphism in cortisol production and metabolism throughout pubertal development: a longitudinal study

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Rationale Sex differences in disease susceptibility might be explained by a sexual dimorphism in hypothalamic-pituitary-adrenal axis activity, which has been postulated to emerge during puberty. The aim of this study is to assess the contribution of pubertal development to sexual dimorphism in cortisol production and metabolism.

Methods Participants, born between 1995 and 1996, were enrolled from the population-based Netherlands Twin Register. At the ages of 9, 12 and 17 years (self- of researcher-reported) Tanner pubertal stage was assessed, and early-morning urine samples were collected. Cortisol metabolites were measured with GC-MS/MS, and ratios were calculated, representing the activities of various enzymes involved in the metabolism of cortisol, such as A-ring reductases, 11β-HSDs and CYP3A4. Cortisol production and metabolism parameters were compared between sexes for pre-pubertal (Tanner stage 1), early-pubertal (Tanner stage 2–3) and late-pubertal (Tanner stage 4–5) stages.

Results 218 participants provided 542 urine samples. Cortisol production decreased with pubertal progression in both sexes and did not differ between sexes at any pubertal stage. A-ring reductase activity was lower in girls than in boys at late-pubertal stage. Activities of 11β-HSDs favored cortisone in girls at early- and late-pubertal stages. Cytochrome P450 3A4 activity did not differ between sexes.

Discussion Prepubertally, sexes were similar in cortisol metabolite excretion rate and cortisol metabolite ratios. During puberty, as compared to boys, in girls the activities of A-ring reductases declined and the balance between 11β-HSDs progressively favored cortisone. Therefore, our findings suggest that the sexual dimorphism in cortisol may be explained by rising concentrations of sex hormones.

Health-related quality of life of perinatally HIV-infected children growing into young adulthood

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Rationale Previous evaluation of the Dutch NOVICE-cohort showed no difference in Health -Related Quality Of Life (HRQOL) between children perinatally infected with HIV (pHIV) and matched HIV-negative controls, yet more PHIV were HRQOL impaired. Furthermore, studies in young pHIV adults show less favorable HRQOL. We suggest HRQOL of pHIV-children can change over time during their development into young adulthood. Therefore, the aim of our study is to assess HRQOL of the same pHIV-children over a 5-year period.

Methods In this follow-up study, we approached all NOVICE-participants to repeat HRQOL assessment after 5 years. Controls were matched for age, sex and socioeconomic status. We assessed HRQoL with a self-report version of the PedsQL™ 4.0. We analyzed 4 scale scores (Physical, Emotional, School and Social functioning), the Psychosocial Health Summary Score and the Total Scale Score of all participants who completed both assessments. We tested differences in scale scores between pHIV, controls and the Dutch healthy norm at both time-points. We used linear mixed models analyses (LMEM) to test whether the change in scores over time differed between pHIV and controls.

Results Fifteen/33 (45.5%) pHIV and 17/37 (45.9%) controls completed both assessments. Participants had a mean age of 13.09 years at baseline and 17.62 years at follow-up. At baseline, pHIV scored significantly better than HIV- controls on Emotional functioning and Total Scale Score. After 5 years, pHIV scored significantly better than HIV- controls on all scales, except Social functioning. PHIV did not differ from the Dutch healthy norm on either time-point. LMEM showed no difference in change over time for any of the PedsQL scales.

Discussion PHIV adolescents receiving appropriate health care, remain to experience a good HRQOL when they develop into young adulthood. This routine health care of pHIV children in the Netherlands might even advance their HRQOL beyond that of healthy peers with similar socioeconomic backgrounds.

Nonadherence to inhaled corticosteroids: a characteristic of the obese-asthma phenotype in children?

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Rationale Overweight children with asthma tend to respond less well to inhaled corticosteroids (ICS) than normal-weight children. Intentional nonadherence to ICS might be a consequence of this. Therefore, we assessed whether excess weight was associated with general, unintentional, and intentional nonadherence to ICS in children with asthma.

Methods We analyzed data from 566 children aged 4–13 years with asthma from the cross-sectional PACMAN study, who used ICS as maintenance therapy. General nonadherence was measured objectively with the proportion of days covered (PDC<50%) and subjectively with the Medication Adherence Rating Scale (MARS<21) reflecting parent-reported nonadherent behavior. Unintentional and intentional nonadherence outcomes were defined as forgetting to take medication and deliberately changing or skipping doses, respectively, from specific items of the MARS. The association between excess weight (BMI≥85th percentile) and general, unintentional, and intentional nonadherence was estimated using logistic regression. Estimates were stratified by asthma severity and age group.

Results Excess weight was associated with a trend towards increased odds of parent-reported nonadherent behavior (OR 1.54; 95%CI 0.84–2.81) and objectively measured general nonadherence, but only in moderate-to-severe asthma (OR 1.71; 95%CI 0.84–3.48). The odds of intentional, but not unintentional, nonadherence seemed to be greater in children with excess weight than normal weight (OR 1.94; 95%CI 0.94–4.01), and the association appeared to be stronger in younger (OR 2.17; 95%CI 1.00–4.73) versus older children (OR 1.18; 95%CI 0.36–3.94).

Discussion Excess weight was associated with general nonadherence to ICS, but only in children with moderate-to-severe asthma, and nonadherent behavior, which seemed to be intentional.

Allantoin: a fecal biomarker for preclinical detection of perforated necrotizing enterocolitis in preterm infants

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Rationale Necrotizing enterocolitis (NEC) carries high mortality and morbidity rates in preterm and very low birth weight infants. Timely diagnosis of NEC remains an unmet challenge, but is of outmost importance, as early treatment initiation is a key prognostic factor. We aimed to identify noninvasive diagnostic fecal biomarkers to detect severe NEC (stage III) prior disease onset.

Methods This prospective multicenter case-control study was embedded in an ongoing study, in which infants born below 30 weeks of gestation are eligible to participate. Fecal samples and clinical data were collected daily, from birth up to 28 days postnatally. For the current study, infants diagnosed with NEC stage III were included and matched to controls, based on gestational age, center of birth and day of life. We performed untargeted and targeted fecal metabolic analyses on samples collected up to three days prior to clinical diagnosis of NEC by means of liquid chromatography(LC)-high resolution mass spectrometry(MS) and LC- tandem MS (LC-MS/MS).

Results In total, 22 NEC cases (14 NEC IIIA and 8 NEC IIIB) and 22 matched controls were included. Allantoin, a marker for oxidative stress, was identified as most discriminative metabolite. Between three days until one day before NEC IIIB, a gradual increase in median allantoin/uric acid levels (t-3 0.14, t-2 0.87 and t-1 0.89) was observed compared to controls. The allantoin/uric acid levels were highest one day before NEC (P< 0.05 vs controls).

Discussion Fecal allantoin/uric acid ratios is a novel noninvasive preclinical diagnostic biomarker for severe NEC, which may provide opportunities for timely treatment initiation.

Empowering patients: a first step in developing educational videos about PROs in clinical practice

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Rationale The importance of discussing Patient Reported Outcomes (PROs) during consultation is increasingly acknowledged. Although the KLIK PROM portal (www.hetklikt.nu) assists in discussing PROs, it remains challenging for pediatric patients/parents to initiate conversations about PROs themselves. To empower patients/parents in discussing PROs during consultation with the healthcare provider (HCP), educational videos are developed. A first step is gaining insight in 1) PROs patients/parents find difficult yet important to discuss 2) experienced barriers/facilitating factors in discussing PROs.

Methods A mixed-method design is used: A) Focus groups were held with adolescents (12–18y) with a chronic health condition and parents (children 0–18y), from the Emma Children's Hospital and registered on the KLIK website. Audio recordings were transcribed and analysed using MAXQDA. B) A self-composed questionnaire was sent to quantitatively assess the study aims.

Results A) Eight adolescents and 17 parents participated. Most often mentioned difficult yet important PROs to discuss were 'home situation/family', 'psychological functioning', 'future perspectives', 'school', 'sexuality'. Perceived barriers were presence of parents/child during consultation, perception of available time, emotions during consultation and insufficient skills of patients/parents/HCPs. Perceived facilitating factors were preparation of consultation, completing PROMs before consultation, possibility of asking questions through email and talking to HCP without parents/child. B) Results of the questionnaire are presented at the symposium.

Discussion The outcomes will inform the development of educational videos, which aim to empower pediatric patients/parents to discuss the PROs they find difficult and important and to support them in overcoming the barriers they experience in discussing these PROs. The ultimate goal is to further optimize communication between patients/parents and HCPs.

Relation between esophageal pressure, volume and the activity of the diaphragm in a preterm infant, a physiological study

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Methods Respiratory support is used in preterm infants to reduce work of breathing (WOB). Measuring WOB requires invasive measurement of transpulmonary pressure. Therefore, clinicians use respiratory rate and distress, to assess WOB. A non-invasive method to measure WOB is lacking. Transcutaneous electromyography of the diaphragm (dEMG) is able to detect changes in diaphragm activity, potentially reflecting WOB. This study describes the relation between esophageal pressure (Pes), tidal breathing and diaphragm activity in a preterm infant.

Results Pes, volume and dEMG were recorded simultaneously in a preterm infant (gestational age 29+6 weeks, weight 1115 grams) while supported by nasal continuous positive airway pressure, without supplemental oxygen. Pes was measured with a fluid-filled (retracted) feeding tube connected to a pressure sensor. Volume was measured with calibrated respiratory inductance plethysmography (RIP) bands. Three skin electrodes were used to measure dEMG. Breath-by-breath analysis resulted in an average respiration loop of the relation between dEMG activity and volume and Pes changes.

The measurement set-up was able to retrieve, Pes, volume and dEMG tracings in a preterm infant. RIP-calibration was done with moderate accuracy (R2 fit of volume vs. RIP 0.83). The EMG-pressure loop showed a pressure drop at the start of muscle contraction and a pressure increase during expiration (diaphragm relaxation). The dEMG-volume loop showed ramp inspiratory activity (RIA) of the diaphragm before actual inspiratory volume was measured. The median RIA time of the diaphragm was 194 (246–152) ms. Post-inspiratory activity of the diaphragm was seen, indicating active contraction to maintain end-expiratory lung volume.

Discussion This study describes the physiological relation between the electrical activity of the diaphragm and the esophageal pressure and volume respectively. Based on these results dEMG seems a promising candidate for non-invasive WOB monitoring in preterm infants.

Burden of RSV bronchiolitis in the pediatric intensive care unit – a 13-year national registry study

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Rationale Respiratory syncytial virus (RSV) bronchiolitis is one of the most common infections in children. Although the number of RSV-bronchiolitis admissions to the general pediatric ward is declining, it is not clear whether this is also the case in the pediatric intensive care unit (PICU). Thus, we aim to determine the burden in time of RSV-bronchiolitis for the PICU in the Netherlands. Our secondary aim is to define the potential impact of maternal vaccination on severe RSV-bronchiolitis.

Method We performed a multicenter registry study of children ≤24 months admitted to the PICU for RSV-bronchiolitis from 2003–2016. We extracted demographic, (co)morbidity and clinical data, performed linear regression analysis on time trends. We identified the children that potentially could have benefitted from a maternal vaccination strategy as the children ≤3 months old and without a history of premature birth.

Results We recorded 2161 PICU admissions for RSV-bronchiolitis. Severe comorbidity was present in 321 (14.8%) children and 37 (1.7%) children died. The annual number of RSV-bronchiolitis PICU admissions significantly increased, with an increase of approximately four children per year (SE=1.27, p=0.01). Concurrently the number of children with a comorbidity remained stable (p=0.56) while the number of children that received non-invasive respiratory support increased with almost nine children per year (SE=1.08, p=0.00). We identified 1697 (79%) children who could potentially have benefitted from maternal vaccination.

Discussion The burden of RSV-bronchiolitis for the PICU has increased, but this does not seem to be related to increased comorbidity and may be due to changes in clinical practice such as the increased use of non-invasive respiratory support. Maternal immunization against RSV may have major impact on the prevention of life-threatening RSV-bronchiolitis and subsequent RSV related morbidity and mortality.

Kidney failure – an overlooked feature of Down Syndrome

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Rationale Life expectancy of patients with Down syndrome has increased significantly in the last decades. Down syndrome is associated with a fourfold risk of urinary tract abnormalities, still data on renal dysfunction in Down syndrome patients are conflicting. The present study was set out to assess kidney function in a large pediatric tertiary Down syndrome clinic.

Methods Retrospective analysis of data were collected during routine visits at the DS clinic of VU medical center. All patients aged between 2 and 18 years in whom serum creatinine had been measured were eligible for inclusion. Exclusion criteria were glucocorticosteroid use, neuromuscular disease or primary referral to a nephrologist or urologist. Kidney function was assessed using the full-age spectrum equations, i.e. eGFRcreat (107.3 / [sCr (mg/dL)/Q (age- or height-based normal value)]) and eGFRcys= (107.3 / sCys (mg/L)/0.82). In a subgroup of 74 patients, a total of 236 serial creatinine measurements with a minimum interval of 2 years were analysed by linear mixed modelling.

Results Serum creatinine was available in 189 patients (63% boys, aged 10.8 ± 5.0 years) and cystatin C in 143 children (64% boys). Mean eGFR was 83.6 ± 16.7 mL/min/1.73m² and mean eGFRcys was 87.3 ± 12.0 mL/min/1.73m². Based on eGFRcreat 32% of the patients had CKD stage I, 62% stage II and 6% stage III. There was no relation between kidney function and co-morbidity (i.e. celiac disease, congenital heart disease, hypothyroidism or history of leukemia). Serial measurements showed a significant decline of eGFRcreat (slope −2.11 ml/min/1.73m² /year [95% CI −2.51 to −1.70], $p < 0.0001$).

Discussion Mildly to moderately impaired renal function is a common finding in children with Down syndrome. The progressive loss of GFR is troublesome and calls for regular monitoring of kidney function both in children and in adults with Down syndrome to identify potentially treatable risk factors for disease progression such as hypertension and microalbuminuria.

Drivers and barriers of pediatric patient engagement in respiratory medicine: lessons learnt from establishing a child council

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Rationale Involving young people in decision-making processes is important for developing environments, policies and interventions that fit their needs and daily reality. Despite the growing awareness of its importance, there is a knowledge gap of health care professionals and researchers on how to meaningful engage children. The aim of this study was to explore drivers and barriers for establishing an advisory council for adolescents with a chronic respiratory disease.

Methods A responsive evaluation was performed of the process of starting the child council. Data collection consisted of interviews with child council members, facilitators and respiratory physicians, observations of council meetings, group discussions, and diary notes over a period of 22 months. Council members (n=9, aged 11–18 years) all had a chronic respiratory disease (ranging from mild-to-severe). Two hour council meetings took place in the Emma's Children Hospital after school hours. Data were analyzed using thematic analysis.

Results Drivers of children to engage are fun, peer-support and improvement of care and research. Youth engagement could be seen as a group-intervention with children with a disability, which is more than peer-support, because it also focusses on social impact. However, organizing youth engagement is not easy for facilitators due to a range of boundaries in the bio-medical context and the complexity to work with children in a domain that is owned by adults.

Discussion Youth engagement is a relevant and beneficial way to organize peer-support for children. Side effect is that institutions could learn from the ideas of children. Implementation of youth engagement in medical academia requires structural embedding and continuous evaluation.

Child outcomes after amnioinfusion compared with no intervention in women with second-trimester rupture of membranes: a long-term follow-up study of the PROMEXIL-III trial

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Rationale To assess the effect of transabdominal amnioinfusion or no intervention on long-term outcomes in children born after second-trimester prelabour rupture of the membranes (PROM between 16 0/7 – 24 0/7 weeks) and oligohydramnios. A follow-up of infants of women who participated in the randomized controlled trial: PPROMEXIL-III (NTR3492).

Methods Surviving infants were invited for neurodevelopmental assessment up to five years of corrected age using a Bayley Scales of Infant and Toddler Development or a Wechsler Preschool and Primary Scale of Intelligence. Parents were asked to complete several questionnaires.

Results Neurodevelopmental outcomes were measured. A Mmild delay was defined as −1 standard deviation (SD), a severe delay as −2SD. Healthy long-term survival was defined as survival without neurodevelopmental delay or respiratory problems.

Results In the amnioinfusion group 18/28 children (64%) died versus 21/28 (75%) in the no intervention group (relative risk (RR) 0.86; 95% confidence interval (CI) 0.60 to 1.22). Follow-up data were obtained from 14/17 (82%) children (10 amnioinfusion, 4 no intervention). In both groups 2/28 (7.1%) had a mild neurodevelopmental delay, no severe delay was seen. Healthy long-term survival occurred in 5/28 children (17.9%) after amnioinfusion versus 2/28 (7.1%) after no intervention, RR OR 2.50 (95% CI 0.53 to 11.83). When analysing data for all assessed survivors, 10/14 (71.4%) survived without mild neurodevelopmental delay, and 7/14 (50%) were classified as healthy long-term survivor.

Discussion In this small sample of women suffering second-trimester PROM and oligohydramnios amnioinfusion did not improve long-term outcomes. Overall 71% of survivors survived without a mild neurodevelopmental delay.

Botulinum toxin injections after surgery for Hirschsprung disease: systematic review and meta-analysis

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Rationale A large proportion of patients with Hirschsprung disease experience persistent obstructive symptoms and are at risk for Hirschsprung-associated enterocolitis after corrective surgery. To improve faecal passage, internal anal sphincter relaxation Botulinum toxin injections (BTI) can be used.

Methods A systematic review and meta-analysis was done, including 14 studies representing 278 patients. Random-effects meta-analysis was used to aggregate adverse and positive effects of BTI on obstructuve symptoms and enterocolitis.

Results Botulinum toxin injections are effective in treating obstructive symptoms in on average 66% of patients (ER=0.66, p=0.004, I2=49.5, n=278 patients). Type of Botulinum toxin, average dose, average age at first injections and proportion of patients with associated syndromes were not predictive for this effect. Mean duration of improvement after one BTI was 6.4 months and patients needed on average 2.6 procedures. There was a significant higher response rate within one month after Botulinum toxin injections compared to more than one month after Botulinum toxin injections (ER=0.79, vs. ER=0.46, Q=19.37, p<0.001). Botulinum toxin injections were not effective in treating enterocolitis (ER 0.58, p=0.65, I2=71.0, n=52 patients). There were adverse effects in on average 17% of patients (ER=0.17, p<0.001, I2=52.1, n=187 patients), varying from temporary incontinence to mild anal pain.

Discussion Findings from this systematic review and meta-analysis indicate that Botulinum toxin injections are effective in treating obstructive symptoms and that adverse effects were present, but mild and temporary.

Executive functioning in later life after childhood bacterial meningitis: a 25-year follow-up

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Rationale Bacterial meningitis (BM) in children remains a life –threatening infection that may cause evident sequelae.

The most common severe to moderate sequelae are sensorineural hearing loss, neuromotor disabilities (e.g. spasticity) and mental retardation. Subtle sequelae that might occur are mainly academic and/or behavioural disabilities, cognitive impairment and fine motor problems. Executive functions are skills necessary for purposeful, goal-directed activity and problem-solving. As BM can affect the brain and cause potential brain damage this study aimed to explore executive functioning of childhood BM survivors in young adulthood.

Methods In this cross-sectional follow-up study young adults (n=947) of a historical childhood BM cohort were invited to complete a self-report measure of executive functioning (EF), the BRIEF-A. Multivariate analyses of covariance were used to evaluate the association between executive problems identified with the BRIEF-A and meningitis-causing pathogens and age at illness.

Results Nearly half of the patients (n=474) (48.7%) reported executive problems. Patients with S. pneumoniae scored worse than patients with N. meningitidis on subscales working memory (WM) (F 5,253, p=0.22) and Plan/Organize (P&O) (F5,051, p=0.025). Patients with S. agalactiae and E. coli scored worse on the subscale Initiate (F7,464, p=0.00) compared to patients with other pathogens. Age at illness was not associated with problems in EF.

Discussion Our study indicated that survivors of childhood BM reported significantly more executive problems on the BRIEF-A depending on meningitis-causing pathogen. However, these results must be interpreted with caution because this study lacks a control group and because of the fact that young adults often report high levels of psychological distress which could influence their executive functioning profile.

Effectiveness of a two-day EMDR treatment for parents of MPS III patients: a study protocol

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Rationale Parents of mucopolysaccharidosis III (MPS III) patients often face traumatic events followed by short and long term stress responses. Based on a former study of our study group 22% of these parents have post-traumatic stress disorder (PTSD) compared to 3.8% in the general population. Hence, evidence based trauma treatment such as Eye Movement Desensitization and Reprocessing (EMDR) is essential. Parents of MPS III patients are often overburdened and not able to follow intensive psychological treatment. Therefore, this abstract describes the study protocol for investigating the effectiveness of a short, two-day EMDR treatment for these parents.

Methods Twenty-five parents of MPS III patients that are treated in the Emma Children's Hospital will complete online questionnaires using the KLIK PROM portal at the start of the study (T0). After three months waiting list they are invited for an intake and complete questionnaires again (T1). The two-day EMDR treatment, consisting of 4 sessions and with one week between treatment days, will start within one week after intake. Questionnaires are completed again two weeks (T2) and three months post-treatment (T3). PTSD symptoms are the primary outcome, measured by the PTSD checklist for DSM-5. Secondary outcomes are psychopathology (Brief Symptom Inventory), parenting stress (Parenting Stress Questionnaire) and parental distress (Distress Thermometer for Parents).

Results Pre-post and pre-follow up change scores on PTSD symptoms will be used as primary outcome to assess the effectiveness of the treatment program. Secondary outcomes are pre-post and pre-follow up change scores on psychopathology, parenting stress and parental stress.

Discussion This abstract outlines the study protocol for a two-day EMDR treatment for parents of MPS III patients. If this treatment is effective, it can improve the psychosocial well-being of these parents and might also be offered to other parents in paediatric settings.

Early detection and pathophysiology of shock in Malawian children; a pilot study of new bedside techniques

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Rationale Shock is associated with a high morbidity and mortality in children in low-income countries. This increased mortality may be explained by the lack of a simple definition of shock and the controversy regarding fluid resuscitation in shock. The latter stems from the FEAST trial findings of increased mortality in African children with shock receiving a fluid bolus. These results remain unexplained and unrepeated and highlight our poor understanding of the pathophysiology of shock in children. To improve outcome, we require simple means to detect shock and an improved understanding of its pathophysiology.
Bedside techniques have been developed in recent years but need to be validated in a low resource setting. Heart Rate Variability (HRV) and Capillary Reserve Index (CRI) were able to detect and predict shock in high income settings. A bedside ultrasound protocol (pediatric-Rapid Ultrasound in Shock, p-RUSH) was developed to describe pathophysiology and to guide treatment of shock. We aim to evaluate the use of these techniques in Malawian children.

Methods This pilot study has been conducted in Queen Elizabeth Central Hospital, a tertiary level Paediatric emergency department in Blantyre, Malawi. We aim to include 40 children (2 months to 16 years) presenting with shock, according to the FEAST definition. After informed consent HRV and CRI findings will be collected and compared to commonly used vital parameters. We will describe means and ranges and compare results between survivors and non-survivors. A rapid bed side ultrasound according to the p-RUSH protocol will be performed before starting fluid therapy. A second investigator will read the images and we will assess the inter-observer agreement using the kappa statistic. We will evaluate our algorithm defining the type of shock (hypovolemic, cardiac, obstructive, distributive, dissociative or mixed).

Discussion If proven successful these methods will be validated in a larger study.

Risk factors of post-operative enterocolitis in patients with Hirschsprungs disease

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Rationale Hirschsprung-associated enterocolitis (HAEC) is a severe inflammation of the bowel, accounting for morbidity and mortality in patients with Hirschsprungs disease. The aim of this study was to identify incidence of pre- and post-operative HAEC in our population, as well as to identify patient and clinical characteristics that are associated with a higher risk of developing post-operative HAEC.

Methods A retrospective cohort study was performed. A total of 146 patients that were treated for Hirschsprungs disease between 2000 and 2017 were included. Data on patient characteristics and clinical characteristics were retrieved from the medical records. The number of HAEC episodes was calculated. Patients with a history of HAEC were compared to patients without a history of HAEC. Logistic regression was used to test potential predictors of post-operative HAEC. Kaplan-Meier and Cox-regression were used to assess time between surgery and first post-operative HAEC episode.

Results We identified 15 out of 146 patients with pre-operative HAEC (10%) and 31 out of 146 patients with post-operative HAEC (21%), accounting for 47 episodes of post-operative HAEC. Incidence over the years fluctuated. Length of post-operative hospital stay was on average 6.5 days longer for patients that developed a post-operative HAEC compared to those who did not (U=1872.5, p=0.047). There were no predictors of post-operative HAEC identified. The more days of post-operative hospital stay, the earlier the first post-operative HAEC episode occurred (HR=1.14, 95%CI 1.012 – 1.281, p=0.032).

Conclusion HAEC incidence was relatively low in our population. No predictive clinical factors could be identified, suggesting that there are no subgroups of patients with a higher risk of developing post-operative HAEC.

Timing of neonatal seizure treatment: a retrospective cohort study

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Rationale Neonatal seizures are common and caused by a variety of underlying disorders. There is increasing evidence that neonatal seizures result in further brain damage. The aim of this study was to describe the time interval between diagnosis of amplitude-integrated electroencephalography (aEEG) confirmed seizures and administration of anti-epileptic drugs (AEDs).

Methods In this single-centre retrospective cohort study, full-term infants (n=106) admitted to a level III neonatal intensive care unit between 2012–2017 with seizures confirmed on two-channel aEEG and corresponding raw electroencephalography (EEG) trace, treated with AEDs, were studied. The time-interval between the first seizure on the aEEG registration, confirmed by the researcher, and AED administration was calculated. Factors associated with treatment <1 hour and seizure recognition were analysed.

Results The median time interval of initiating treatment of aEEG confirmed seizures was 01:50h (interquartile range (IQR) 00:43h – 4:30h). Treatment of aEEG confirmed seizures was initiated <1h in 34/106 infants (32.1%), between 1–2h in 21/106 infants (19.8%), 2–4h in 23/106 infants (21.7%), 4–8h in 14/106 infants (13.2%) and ≥ 8 hours in 14/106 infants (13.2%). Seizures treated <1h were significantly more often recognized by the seizure detection algorithm (SDA) compared to seizures treated >1h (67% versus 42%, p=0.02) and showed more clinical signs (79.4% versus 37.5%, p<0.01). There was no difference for out of office hours (23.5% versus 22.2%, p=0.88).

Discussion With only 32.1% of the seizures being treated <1h, there is room for improvement. aEEG is a helpful tool for diagnosing seizures 24/7. Timely treatment occurred more often when seizures were clinical or recognised by the SDA, there was no difference for out of office hours. Training off staff is needed to optimise recognition of seizures on aEEG.

Exploring contrast-enhanced MRI findings of the wrist in healthy children

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Rationale To analyze contrast-enhanced (CE) MRI findings of the wrist in healthy children, focusing on the synovial- and tenosynovial membrane. Furthermore, we assessed the presence of joint fluid, bony depressions and medullary changes suggestive of bone marrow edema (BME).

Methods We included 20 healthy children (15 females; age range: 7.5–17.6 years), unaffected by arthritic-related-disorders, who underwent CE-MRI of the wrist. Various imaging characteristics of the synovium, tenosynovium, joint fluid, bone tissue and bone marrow were evaluated using existing MRI-scoring systems.

Results The level of synovial- and tenosynovial enhancement was scored as being normal in 17/20 (85%) and 18/20 (90%) children respectively (median total score for each characteristic: 0). The presence of >2 mm joint fluid was observed in 11/20 (55%) children in at least one of the joints assessed. Bony depressions were present in all 20 children (median number of depressions: 9). Signal changes suggestive of BME were observed in 6/20 (30%) children.

Discussion The results of our study provide new insights in the contrast-enhanced physiological heterogeneity of the wrist in the healthy pediatric population. The level of synovial- and tenosynovial enhancement was scored as being normal in the majority of 20 children, but some enhancement and thickening can be found in the growing wrists of healthy children. Given the substantial occurrence of joint fluid, bony depressions and medullary changes suggestive of BME in healthy children, these features should be interpreted with care in clinical setting.

Donor macrophages in transplanted MLD patients support oligodendrocytes, thereby enabling remyelination and improvement of white matter abnormalities on MRI

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Rationale Hematopoietic cell transplantation (HCT) is a partially effective therapy for patients with metachromatic leukodystrophy (MLD), a disorder characterized by deficient arylsulfatase A (ASA) activity and sulfatide storage. We examined the time course of white matter abnormalities on magnetic resonance imaging (MRI) after HCT, and investigated brain tissue to define the therapeutic effects of HCT on tissue level.

Methods The MRI scans of 15 successfully transplanted MLD patients with at least 1 available MRI examination before and 3 after HCT were retrospectively evaluated with the MLD-Loes score. Brain tissue was obtained at autopsy from 2 transplanted and 6 non-transplanted patients, and 2 age-matched controls. The presence of donor cells, ASA, and sulfatide storage and digestion was examined by immunohistochemistry and microscopy. Myelin content, oligodendrocyte numbers and macrophage phenotypes were also assessed. An unpaired t-test, linear regression or Mann-Whitney U-test was performed to evaluate differences between the transplanted, non-transplanted and control group.

Results MRI white matter abnormalities initially deteriorated, but improved (n=7) or stabilized (n=8) from approximately one year post-HCT onwards (mean follow-up=82 months). In the autopsy obtained white matter of transplanted patients, we found metabolically competent donor macrophages that were immunopositive for ASA. These macrophages preferentially expressed markers of alternatively-activated, anti-inflammatory cells compared to macrophages in non-transplanted patients. Besides, transplanted patients showed higher numbers of oligodendrocytes and remyelination.

Discussion In successfully transplanted MLD patients, brain white matter abnormalities may improve on MRI for years. HCT leads to the presence of donor macrophages with the metabolic ability to degrade sulfatides in the white matter. Besides, their anti-inflammatory phenotype may support oligodendrocyte survival and differentiation, thereby enabling remyelination.

Prophylactic anticoagulation in children receiving home parenteral nutrition

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Rationale We aimed to evaluate the efficacy and safety of prophylactic anticoagulation in children with home parenteral nutrition.

Methods All children, 0–18 years, treated with home parenteral nutrition at the Amsterdam UMC were followed from April 2010 – July 2019. Patients received prophylactic anticoagulation as part of routine care. Primary outcome measures were occurrence of catheter-related thrombosis and occurrence of bleeding. Bleeding was divided in major, clinically relevant nonmajor and minor bleeding. Major bleeding was defined as fatal bleeding or bleeding in a critical organ, a decrease in hemoglobin >2 g/dl or requiring surgical intervention. Clinically relevant nonmajor bleeding was defined as bleeding that required administration of a blood product or a non-surgical intervention to restore hemostasis. Secondary outcomes were: number of catheter occlusions and number of catheter-related infections.

Results 63 patients were included. Median age at start of parenteral nutrition was 7.7 months (IQR 4.3 – 50.5). A total of 82610 catheterdays were studied. Low molecular weight heparin was used in 61 patients (97%) at the start of the study and in 46 patients (73%) at the end of the study. The remaining patients used a vitamin K antagonist. A total of 14 patients developed 19 catheter-related thromboses. There were 0.2 catheter-related thromboses per 1000 catheterdays, 0.4 bleedings per 1000 catheterdays, 0.9 catheter occlusions per 1000 catheterdays and 0.9 catheter-related bloodstream infections per 1000 catheterdays. In total, 35 bleedings occurred, of which 5 were major and 16 clinically relevant nonmajor. Cumulative event free survival after 5 years was 73% for thrombosis, 69% for bleeding, 32% for occlusion and 51% for infection.

Discussion Our study shows prophylactic anticoagulation, in children receiving home parenteral nutrition, is effective in preventing catheter-related thrombosis and shows a low rate of bleeding complications.

Viridans group streptococci infections: Are teicoplanin or vancomycin feasible and safe as antibiotic prophylaxis regimen in pediatric leukemia patients? A systematic review

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Rationale Bacterial infections in pediatric leukemia patients are common. Viridans group streptococci (VGS) sepsis occurs in 25–30% of these patients. The DCOG wrote a clinical guideline to prevent infection in children with leukemia by giving them oral antibiotic prophylaxis against the VGS. However the incidence of VGS infections is still high. We compared currently used prophylactic antibiotic regimes with teicoplanin or vancomycin prophylactic regimens to decrease the incidence of VGS bacteremia and sepsis in pediatric oncology patients.

Methods A computer-based search was done in PubMed and Cochrane databases to find studies describing prophylactic antibiotic regimens to prevent leukemic children from VGS infections. All papers were selected by defined in- and exclusion criteria. All studies were critical appraised. Data extraction included study characteristics, patient characteristics and relevant outcomes.

Results Five studies were included: Boztug, Brunet, Kurt, Nolt, Inaba. We investigated the incidence of VGS bacteremia and VGS sepsis per different antibiotic regimen to evaluate vancomycin or teicoplanin as antibiotic prophylactic regimen against VGS. The studies Nolt and Inaba gave an odds ratio of 0.04 (CI 95%: 0.01–0.1) for VGS bacteremia by use of teicoplanin/vancomycin prophylaxis regimens compared to other regimens ($P<0.00001$). The studies Boztug and Brunet gave an odds ratio of 0.03 (CI 95%: 0.00–0.24) for VGS sepsis by the use of teicoplanin/vancomycin prophylaxis regimens ($P=0.001$). ICU admissions, mortality and VRE data was collected. However, this data could not be compared because of missing information.

Discussion Glycopeptides like vancomycin and teicoplanin are shown to be feasible to use as prophylactic antibiotic regimens to prevent pediatric leukemia patients from VGS bacteremia and sepsis. Further prospective studies are necessary to prove the quality of vancomycin and teicoplanin as antibiotic prophylaxis regimens against VGS.

Fibrokids Study: effective screening for NAFLD in children with obesity

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Rationale Non-alcoholic Fatty Liver Disease (NAFLD) is a common complication of obesity. Due to the increasing prevalence of obesity, NAFLD is now the most common chronic liver disease worldwide and is currently the second leading indication for liver transplantation for adults in the USA. The spectrum of NAFLD ranges from simple steatosis, to steatohepatitis and might eventually result in fibrosis or cirrhosis. Most children will have simple steatosis and will not progress to more advanced stages. Advanced fibrosis is reported in up to 17% of children referred to liver centres after screening. However, these studies are at high risk of selection bias. NAFLD also increases the risk of type 2 diabetes and cardiovascular disease at adult age. The high prevalence and important long term health risks make NAFLD highly suitable for screening. However, due to the limited data on the prevalence and progression of liver fibrosis in pediatric NAFLD and the lack of data on the cost-effectiveness of screening, current guidelines differ in their advice on screening and are not evidence based. We aim to determine the prevalence of fibrosis in children with obesity and to evaluate existing guidelines in the screening for NAFLD in order to generate data that can lead to a more comprehensive and effective screening strategy for NAFLD in children.

Methods We will prospectively include 600 children with obesity referred to the AMC by one of the 15 participating hospitals in the Netherlands. These children will be evaluated for NAFLD using serum ALT according to the NASPGHAN 2017 screening guideline. Fibrosis will be detected by measuring liver stiffness using FibroScan®. We will evaluate the usefulness of two additional fibrosis measurements and determine the costs of detecting one case of fibrosis. Lastly, we will evaluate children's self-reported discomfort of the fibrosis measurements and assess the burden and worry prior and after the visit to the outpatient clinic.

Diagnostic test accuracy of bowel ultrasound in children with Inflammatory Bowel Disease

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Rationale Currently used non-invasive tools for monitoring children with inflammatory bowel disease (IBD), such as faecal calprotectin, do not accurately reflect the degree of intestinal inflammation and do not provide information on disease location. Ultrasound (US) might be of added value. This study aims to determine the diagnostic accuracy, optimal use and patients' experience of ultrasound (US) as a diagnostic tool for disease severity and extension for Inflammatory Bowel Disease (IBD) in children.

Methods A cross-sectional study in 125 pediatric patients with (suspicion of) IBD. We will determine the diagnostic accuracy of US using ileo-colonoscopy as reference standard for colon and terminal ileum and MR enterography (MRE) for small bowel and build an easy-to-use US score composed of different US features. In addition we will determine the patients' experience of US, MRE and endoscopy examinations

Discussion We expect that US – using an easy-to-use US score – will be able to assess disease severity and extension with high sensitivity and specificity. We expect that the patients' burden of undergoing an US is limited compared to endoscopy and MRE. Therefore US is a valuable diagnostic tool to monitor pediatric IBD.

Insulin concentration in human milk in the first days after birth: course and associated factors

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Rationale Human milk is better tolerated than formula in preterm infants. Insulin (not present in formula) has been suggested as a key factor, as it seems to stimulate gut maturation and thereby feeding tolerance. Therefore, it might serve as supplement for formula or additive to fortifiers. However, human milk insulin concentration directly following birth is unknown, so exact dosage schemes are difficult to establish. The objective of this study was to quantify milk insulin concentration following term (≥37 weeks) and preterm delivery (<32 weeks), and to assess the effect of diurnal rhythm and pre-pregnancy body mass index (BMI).

Methods Milk was collected from 25 non-diabetic mothers (preterm, n=15; term, n=10) at serial time points in the first five days and on day 10 postpartum. Milk insulin concentration was measured by using luminescence immunoassay. Generalized estimating equations were used to analyze milk insulin concentration over time.

Results Milk insulin peaks (up to 2614 pmol/L) were observed on day 1, which rapidly declined to 207 (110–437) pmol/L on day 3, followed by a gradually decline to 121 (58–236) pmol/L on day 10. Preterm delivery did not affect milk insulin concentration (β −0.005 (−0.580–0.570); p=0.988). Obese mothers (BMI ≥30 kg/m²) had a higher milk insulin concentration over time compared to non-obese mothers (BMI <30 kg/m²) (β 0.711 (0.213–1.209); p=0.005). Insulin concentration increased in the morning (β 0.169 (0.092–0.246); p<0.001), and declined throughout the night (β −0.082 (−0.109–−0.055); p<0.001).

Discussion Milk insulin course is characterized by a rapidly decline in the first three days, followed by a gradually decline until day 10 postpartum. Concentration is affected by diurnal rhythm and pre-pregnancy BMI, but not by gestational age at birth.

Anesthesia in models of Vanishing White Matter

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Rationale Vanishing White Matter (VWM) is a fatal leukodystrophy mainly affecting children. The disease is characterized by chronic neurological deterioration and episodes of rapid decline caused by stresses. To diagnose and follow the disease progression patients undergo MRIs, during which anesthetics are commonly used. The inhalational anesthetic sevoflurane is preferred, but patients' parents have indicated that it worsens patient recovery. Sevoflurane is known to have an impact on VWM-related molecular pathways, which may explain its effect on disease course. We aim to investigate the effects of sevoflurane on molecular pathways and pathophysiology in VWM disease models.

Methods We will use in vivo and in vitro models. For the in vivo study we compared sevoflurane effects to a control anesthetic and an untreated group. Anesthesia was performed in wild type (WT) and symptomatic VWM mice (2 hours). We measured breath rate, body weight, and analysed coordination and gait on the balance beam and Catwalk tests. Post mortem tissue was collected for downstream analyses. For the in vitro study we will assess the effects of sevoflurane on the expression of ATF4, a key protein in the VWM-related molecular pathway.

Results Sevoflurane significantly lowers breath rate in VWM and WT mice compared to the other anesthetic and the untreated group. We did not find statistically significant effects of the two anesthetics when comparing the body weight and balance beam performance of VWM mice to the untreated group. The in vitro studies are currently ongoing.

Discussion Based on the current in vivo study, sevoflurane did not affect body weight and gait parameters in VWM mice. Our initial in vivo set-up may not fully grasp the events that occur in VWM patients undergoing sevoflurane anesthesia. Therefore, we will focus on molecular changes during in vivo anesthesia that are conserved between VWM mice and VWM patients.

Neuronal dysfunctioning in 4H leukodystrophy

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Rationale 4H leukodystrophy is a genetic white matter disorder with a progressive disease course. Most patients present with delayed motor development and ataxia and have hypomyelination and cerebellar atrophy. However, recent studies indicate that a number of patients show no hypomyelination but have grey matter involvement. In this study neuronal pathology of 4H patients was examined in a human cell culture system.

Methods Previously we made induced pluripotent stem cell (iPSC) lines from 4H patients and (age and gender matched) controls. These iPSCs were differentiated into cerebellar granule neurons and into a mixed culture of glutamatergic and GABAergic neurons. Neurons were analyzed by whole transcriptome analysis with RNA sequencing and neuronal maturation was assessed by looking at neuronal maturation markers.

Results The differentiation of iPSCs into cerebellar granule cells was not affected by 4H mutations. RNA sequencing analysis revealed a number of differentially expressed genes. An interesting candidate gene for involvement in 4H pathophysiology is ARX. We are currently analyzing neuronal maturation of the mixed differentiation.

Discussion Neuronal involvement may be important in 4H disease development. We have developed human cell culture models to study neuronal pathology, and showed that ARX is differentially expressed in 4H cells. ARX plays a role in SHH signaling which is important for the development of granule cells, interneurons, oligodendrocytes, teeth and eyes; all organs that can be affected in 4H patients. In future studies we will study the effect of modulating SHH pathway on neuronal pathology and look at interaction with neurons and oligodendrocytes, to study whether neuronal defects can underlie the hypomyelination observed in 4H patients. Insight into neural cell types involved in 4H will help to identify cellular targets for therapy development.

The human gut organoid, a promising model to study enterovirus infection and disease pathogenesis

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Rationale Enteroviruses (EVs) are a major source of human infections worldwide, with a broad spectrum of disease symptoms, from diarrhea 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 fetal 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.

Conclusion The human fetal 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.

Age-specific reference values for plasma FT4 and TSH in term neonates during the first two weeks of life

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Rationale Congenital hypothyroidism (CH) is a common, preventable cause of mental retardation, which is detected in many neonatal screening programs. Upon suspicion of CH, free thyroxine (FT4) and thyroid stimulating hormone (TSH) concentrations are measured. CH can be of thyroidal or central origin (CH-T and CH-C, respectively). While CH-T diagnosis is based on an elevated TSH with a low FT4, CH-C diagnosis is based on a low FT4 without a clearly elevated TSH. Currently, neonatal reference intervals (RIs) for FT4 and TSH are lacking. Age-specific RIs would greatly improve the diagnostic process, especially for CH-C. We aim to establish RIs for plasma FT4 and TSH in term neonates at day 3–7 (t=1) and day 13–15 of life (t=2; day of birth=0). The study was particularly designed to provide a reliable FT4 lower limit to facilitate CH-C diagnosis. In the Netherlands, the screening is performed at day 3–7 and neonates with an abnormal result suspect for CH-C are referred on average at day 14; time points were chosen accordingly.

Methods Blood was collected from 120 neonates at two time points. For missed time points, additional participants were included (total number of participants>120). FT4 and TSH were measured with an electrochemiluminescence immunoassay (Cobas, Roche Diagnostics, Switzerland; adult RI for FT4 12–22 pmol/L, TSH 0.5–5.0 mU/L). RIs were calculated with MedCalc for Windows (version 18.5, Belgium). If data were not normally distributed, the non-parametric percentile method was used.

Results From 146 participants (49% female) ≥1 measurement was available. 95% RIs for FT4 were 20.5–37.1 pmol/L (t=1) and 15.3–26.5 pmol/L (t=2). 95% RIs for TSH were 1.0–8.4 mU/L (t=1) and 1.4–8.6 mU/L (t=2).

Discussion FT4 concentrations differ significantly between the first and second week of life, with a FT4 lower limit of 20.5 pmol/L at day 3–7 and 15.3 pmol/L at day 13–15. Both lower limits are considerably higher than the adult RI lower limit for the same assay.

Impaired astrocytic functioning in Vanishing White Matter disease and its effect on blood-brain barrier integrity: implications for disease severity

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Rationale Vanishing White Matter (VWM) is a detrimental leukodystrophy that mostly affects young children. It is characterized by global loss of the white matter (WM). Stressors, such as head trauma, acute fright and fever provoke the disease onset and cause episodes of severe neurological deterioration during which the patient may die. VWM is caused by mutations in genes encoding for subunits of eukaryotic translation initiation factor 2B, which has a housekeeping function and is expressed throughout the body. Previous studies have demonstrated that the WM deterioration is caused by dysfunction of astrocytes, which are crucial for homeostasis in the central nervous system (CNS) and maintenance of the blood-brain barrier (BBB) integrity. The BBB is a vascular structure that separates the CNS from the periphery and prevents the entrance of harmful compounds into the CNS and is responsible for clearance of waste from the CNS. The BBB is comprised of specialized polarized brain endothelial cells (BECs) that are sealed together with tight- and adherens junctions. These BECs are encapsulated by the basal and basement lamina, pericytes and astrocytes. Under pathological conditions there could be disruption of the BBB on several levels via impairment of these different components that comprise the BBB. Therefore, we hypothesize that due to the astrocytic dysfunction the BBB in VWM is compromised and could possibly affect the disease severity and progression. Using immunohistochemical analysis of human post-mortem material we demonstrate that there are alterations at the BBB of VWM patients.

The effect of different time-temperature profiles on bioactive proteins during pasteurization of donor human milk

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Rationale To ensure safety, donor milk is generally processed by holder pasteurization (HoP) at 62.5°C for 30 min. This temperature-time combination negatively affects the activity of some important bioactive milk components. Long warming up and cooling down times (lag-times) may further affect the bioactive properties of pasteurized milk. High-Temperature-Short-Time (HTST), a treatment with shorter processing times (72°C-15"), may be a suitable alternative to HoP. We aimed to compare the effects of different heating processes on the bioactive proteins and the safety of human milk.

Methods Five pasteurization methods were conducted: First, to compare HoP and HTST and secondly, to study the influence of lag-time by comparing pasteurization methods with the same holding time as HTST (72°C-15"), but with different heating up and cooling down times. Protein concentration was measured with a BCA assay and further characterization was obtained with LC-MS/MS measurements. BSSL and ALP activities were also measured. To investigate the effect of lag-time on the bacteriostatic properties, human milk samples previously treated with the five heating methods were inoculated with 2100 CFU/ml E.coli K12 and S.aureus.

Results HTST generally performed better than HoP. Protein retention was impaired with increasing lag-times ($p<0.05$). All pasteurized samples were ALP negative, with a significantly low BSSL activity (<10%). Raw milk had similar bacteriostatic properties to HTST treated samples, while for HoP samples, E.coli and S.aureus growth rate was double compared to both HTST and untreated samples ($p<0.05$).

Discussion The difference in lag-time was more important in the preservation of bioactive proteins than the difference of the heating processing itself among the investigated methods. A treatment with considerably short lag-times, such as HTST, may reduce the thermal damage caused to the bioactive proteins compared to HoP, without affecting safety.

Motor interventions in school-aged children with motor impairment: a meta-analysis and meta-regression

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Rationale Motor problems frequently occur in school-aged children and may have an impact on daily life functioning; besides interfering with physical capacities and participation in activities, it may negatively impact self-worth (Piek, Baynam, & Barrett, 2006). This systematic review and meta-analysis aggregated all existing studies on the effectiveness of interventions aimed at remediating motor problems in school-aged children.

Methods An electronic search of four databases (PubMed, Embase, Cochrane and Web of Science) was conducted to retrieve (a) randomized controlled studies (b) that investigated the effectiveness of interventions aimed at remediating motor problems (c) in school-aged children (4–12 years) (d) in whom motor impairment was established using standardized measures and/or diagnostic criteria. Reference lists of published articles were searched to identify additional studies. Two reviewers independently assessed study eligibility and quality using the Cochrane Collaboration's risk-of-bias tool. Motor performance scores were analyzed using random effects meta-analysis and standardized mean differences (SMD) were calculated. Random effects meta-regressions were performed to study the associations between SMDs and sex, age at intervention and intervention dose, duration and frequency.

Results A total of 14 studies met all inclusion criteria, with a total of 295 children in the intervention groups and 331 controls. Large intervention effects were found for motor performance (SMD = 0.86, 95% CI: 0.46 – 1.25, $p < 0.001$). Additionally, age significantly explained heterogeneity in effect size across studies ($\beta = 0.29$; 95% CI: 0.11 – 0.47, $p<0.01$), effects being more robust in interventions used in older children. Sex and intervention characteristics did not significantly moderate the intervention effects.

Discussion Motor interventions have strong beneficial effects on motor performance in children with motor impairment, especially so in older children.

A human 2D organoid model to study gut barrier maturation and host-pathogen interaction in the small intestine

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Rationale The intestinal barrier consists of a single layer of polarized epithelial cells, covered by a layer of mucins and separates the intestinal content from the rest of the body. In infants the intestinal barrier is underdeveloped and consequentially infants are more susceptible to conditions such as infectious diarrhea, necrotizing enterocolitis and allergic gastroenteropathy. Moreover, appropriate maturation of the infant's intestinal barrier is essential because barrier dysfunction in childhood is a critical factor in predisposition to chronic intestinal and autoimmune diseases.

Methods To study the functions of epithelial barrier during early stages of life, primary human fetal intestinal cells were validated as a source of polarized epithelium using transwell inserts. Specifically, we generated proximal and distal gut monolayers and characterized this model with respect to epithelial cell types (qPCR, immunofluorescence), epithelial polarization (immunofluorescence) and epithelial barrier function (TEER, FITC-Dextran). In addition, the potential of viral replication and bacterial translocation after apical infection with enterovirus A71 (EV71) and listeria monocytogenes, both enteric pathogens, was evaluated.

Results Our data reveal that the fetal intestinal organoid monolayer preserved all characteristics of the 3D culture including epithelial cell heterogeneity, epithelial polarization and gene expression profiles. Moreover, these intestinal monolayers appeared to build a tight barrier in time. Replication of EV71 was observed in this model with no difference between proximal and distal cultures. Finally, L. monocytogenes displayed higher translocation in distal cultures compared to proximal cultures, followed by a distinct pro-inflammatory IL-8 response.

Discussion In conclusion, the human 2D organoid model described here can be a valuable tool in the field to study early life intestinal barrier maturation and host-pathogen interactions.

Echovirus seroepidemiology in the Netherlands

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Rationale Enteroviruses (EVs) are highly prevalent viruses worldwide. They mostly cause mild disease, but some EVs (a.o. EV-A71, EV-D68 and several echoviruses) are also known to cause severe neurological infections. Little is known about the circulation patterns of the >100 different serotypes of EVs. However, recently a model was constructed based on EV prevalence data in Japan, accurately predicting EV prevalence and outbreaks in the coming two years.
Here, we present our results of a recently conducted seroprevalence study in a healthy Dutch population. Together with prevalence data, this data will be used to model prevalence of seven EVs in the Netherlands.

Methods We received 500 serumsamples from healthy children and adults from the Netherlands, collected by the Dutch National Institute for Public Health and the Environment (RIVM) in 2006/2007 and in 2016/2017. We performed neutralization assays for seven EVs (i.e. Echo 6 (E6), E9, E11, E16, E18, E25 and E30) and calculated neutralising titers for each sample.

Results The seropositivity rates for the seven viruses ranged from 48% (for E6) to 97% (for E30). Seropositivity rates were lower in children than in adults. Geometrical mean titers (GMTs) were higher in children and declined with increasing age for all viruses. Both in seroprevalence percentage and GMTs, no significant differences were observed for the two timepoints.

Discussion We can conclude that the seven included EVs are highly prevalent in the Netherlands. The increasing seropositivity rates and decreasing GMTs with age, underline the vast circulation of the included viruses mainly in (young) children. Together with prevalence data on these viruses, collected by the RIVM, this data will be used to model and predict the circulation and possible outbreaks of these viruses in the Netherlans in the coming years.

Water and ions out of balance: dysfunctional astrocytes in the white matter disease MLC

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Rationale Electrical signaling, caused by flow of ions between intra- and extracellular compartments, is the essence of brain functioning. The maintenance of a proper distribution of ions and water in the brain is to a great extent attributed to astrocytes. Dysfunctional astrocyte ion and water homeostasis leads to chronic white matter swelling in a group of neurological diseases, for which the white matter disease 'Megalencephalic leukoencephalopathy with subcortical cysts' (MLC) is a prototype. MLC patients develop macrocephaly and show severe motor disabilities. Mutations in either MLC1 or GLIALCAM underlie 95% of MLC cases. The proteins MLC1 and GlialCAM are co-localized in astrocytes, together with other proteins involved in ion and water homeostasis. Research on isolated cells suggests that defective astrocyte volume regulation and disturbed chloride currents are central to MLC. However, whether astrocytes exhibit aberrant electrophysiology in the intact MLC brain, and how astrocyte dysfunction exactly underlies disrupted homeostasis of water and ions remains to be investigated.

Methods Here we took advantage of an MLC mouse model in which the gene encoding GlialCAM is knocked out (Glialcam-null mouse). Using transduction with custom AAV virus, we fluorescently labeled astrocytes in adult Glialcam-null and wildtype control mice. Next, patch clamp recordings were performed from astrocytes in acute brain slices.
Using patch clamp recordings, we explored potential electrophysiological alterations in astrocytes in Glialcam-null mice. In addition, we investigated whether astrocytes in the mutants responded differently to a cell swelling-inducing hypotonic stimulus.

Discussion This study forms a crucial step in checking the validity of discoveries made in isolated cells to the intact brain. By recording directly from astrocytes in intact tissue we are able to better understand to what extent disrupted astrocyte physiology in this disease can explain clinical phenotypes observed in MLC patients.

Anti-rituximab antibodies with corresponding drug levels in children with B cell mediated diseases treated in the Emma Children's hospital

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Rationale The anti-CD20 monoclonal antibody rituximab (RTX) is widely used. Lack of efficacy appears to be related to the formation of anti-drug antibodies (ADA). This seems to be correlated with the failure of B cell depletion or the occurrence of anaphylactic reactions. However, it is unknown which patients are at risk for developing ADA, and if the presence of ADA affect RTX drug levels. Therefore we conducted this study to investigate if there is a correlation between the development of ADA and low RTX serum concentrations, explaining therapeutic failure.

Methods This is a retrospective cohort study in children with B cell mediated diseases treated with RTX. Patients were recruited from the following pediatric departments; rheumatology/immunology, nephrology and hematology, between 2006 and August 2019. Blood samples were collected during the follow-up period. Assays for RTX serum concentrations and ADA were performed by Sanquin Diagnostics. Autoantibodies were detected by the hosting immunology laboratory. Data were analyzed using SPSS version 24.

Results Twenty-nine patients were included in the study, of whom ten were ADA-positive (34.5%). Half of these ten patients were diagnosed with SLE. Undetectable low concentrations RTX were only found in ADA-positive patients ($p<0.005$). Anti-dsDNA, anti SS-A, anti RNP and anti Sm autoantibodies were more prevalent in ADA-positive patients ($p=0.045$, $p=0.038$, $p=0.038$ and $p=0.036$, respectively). No B cell depletion was found in six of the positive patients (OR 24, $p=0.009$). Severe anaphylactic reactions only occurred in ADA-positive patients.

Discussion ADA leads to undetectable low serum concentrations and a higher probability for anaphylactic reactions. ADA monitoring should be done in patients who are more prone to develop ADA or in patients without B cell depletion. Furthermore, when ADA are detected, continuation of treatment seems reasonless and our recommendation is to consider changing the therapy.

Unraveling the cellular signaling pathways underlying MLC

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Rationale Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare white matter disease. Patients develop macrocephaly in the first year of life and show slow cognitive decline, epilepsy, ataxia and spasticity. On MRI patients show increased brain water content and subcortical cysts. At the cellular level the brain white matter appears vacuolated. MLC is caused by mutations in either the MLC1 or the GLIALCAM gene. MLC1 and GLIALCAM are mainly expressed by astrocytes, cells crucial for ion and water homeostasis in the brain. The function of these proteins is unknown. Previous studies showed that mutations in MLC1 and GLIALCAM cause disturbances in astrocyte volume regulation, leading to chronic swelling of astrocytes. Here we want to further understand the cellular signaling pathways involved in astrocyte volume regulation, and how these are disrupted in MLC. Our final aim is to find a therapeutic target for MLC treatment.

Methods We have set up two in vitro experimental pipelines to study astrocyte volume regulation. We load cultured primary astrocytes with the fluorescent compound Calcein-AM, and use fluorescence quenching as a measure of cell volume changes. By exposing these astrocytes to a hypotonic solution, we can measure the swelling and subsequent volume regulation in these astrocytes. This allows us to instantly measure the effects of different compounds on astrocyte volume dynamics, and link this to MLC pathology.

Results Experiments are currently ongoing. Based on previous data we hypothesize to find effects of compounds affecting ion channels involved in volume regulation, water channels and compounds affecting the cell cytoskeleton.

Discussion Assessing the effects of these manipulations will lead to a better understanding of the molecular mechanisms underlying MLC. In the long run this might allow us to hypothesize potential therapeutic interventions for this disease.

Ethnic background is associated with health care consumption in children with asthma

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Rationale Childhood asthma is associated with a high health care utilization and high socioeconomic burden. Social characteristics might influence how often parents utilize health care facilities for their child's asthma (Urguhart A. et al, J Asthma, 2019).
This study was conducted to assess whether ethnicity is associated with the frequency of health care utilization of pediatric asthma patients in the Netherlands.

Methods For this cross-sectional analysis we used data from the PACMAN-study, a community pharmacy-based cohort of Dutch children (6–12 years) with regular use of asthma medication. Parental reported frequent (defined as ≥2 visits/year) health care consumption for asthma in the past year was assessed based on visits to the general practitioner, pediatrician, pulmonologist and emergency room (ER). Multivariate logisitic regression was used to asses wether there is an association between ethnic background and health care utilization. Ethnic background was defined as Dutch (both parents native/non-immigrant) and non-Dutch (at least one parent foreign/immigrant). Odd ratio's were adjusted for covariates age, asthma and/or atopy in family, medication use, ACQ and parental educational level.

Results In total, 959 children (62% male, age 8.4 ± 2.4 years, 73.6% with Dutch ethnicity) were included in the analysis. Having a non-Dutch ethnic background was associated with frequent visits to the general practitioner (OR 1.64; CI 1.19–2.27), to the pediatrician (OR 1.58;CI 1.10–2.28) and to the pulmonologist (OR 1.88; CI 1.12–3.16). There was no association between ethnicity and ER visit (OR 0.64; CI 0.25–1.66).

Discussion Ethnic background of patients influences the amount of health care consumption, independently of asthma control, medication use or atopic status.

Stem cell derived brain organoids, a promising model to study Adeno associated viruses for CNS gene therapy

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Rationale The development of gene therapies for central nervous system (CNS) disorders is challenging because it is difficult to translate efficacy and toxicity findings in current in vivo and in vitro and in vivo methods to the clinic. Brain organoids are 3D, induced pluripotent stem cell (iPSC)-derived cell cultures. They have a human origin and harbor the different cell types found in the brain, such as mature neurons, astrocytes, neural progenitors and even oligodendrocytes. Importantly, brain organoids can form secondary structures that represent different brain regions. These features provide a more relevant physiological environment as compared to 2D cell lines. The fact that brain organoids are of human origin and their applicability for assays with higher throughput, give them a further advantage as compared to animal models. Brain organoids can be derived from iPSCs from patients and healthy controls, thereby allowing to generate disease-specific models. To date, brain organoids have been very useful in studying multiple viruses including ZIKA virus.

Methods We have studied the spread, tropism and transduction efficiency of brain cells by adeno associated viruses (AAV) using brain organoids and are comparing different AAV capsids based on different serotypes in their ability to transduce brain organoids.

Results Our results show the effective transduction of neurons and neural progenitors in the brain organoid, both via administration to the medium and by direct injection.

Discussion These preliminary results suggest that brain organoids can become an important tool in the development of AAV-based therapies targeting CNS diseases.

Analyzing radiological progression in 252 cases of Vanishing White Matter (VWM)

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Rationale VWM, caused by recessive mutations in any of the EIF2B1-5 genes, is one of the more common leukodystrophies. The clinical spectrum is broad. Patients with a lower age of onset (AoO) generally have a faster disease course. A large set of MRI scans of patients with VWM has so far not been analyzed.

Methods Genetically confirmed and clinically phenotyped VWM patients were divided according to AoO: <1 y (group 1), 1–2 (2), 2–4 (3), 4–8 (4), 8–18 (5) and >18 (6) y. MRI scans were available from 1985 on. The ventricle-skull ratio (VSR) was measured to determine brain atrophy. We visually scored the aspects of white matter (WM) (normal, FLAIR hyperintense, rarefied, or cystic) as percentages of the total cerebral WM, resulting in an aspect score (0–30, 0 being 100% normal, 30 being 100% cystic). Segmentation into normal, FLAIR hyperintense, rarefied/cystic WM, and CSF is being performed using FMRIB Software Library. Violation of normality led us to report medians and Kruskal-Wallis analyses to determine differences in disease duration, VSR, and aspect scores between groups.

Results 422 scans of 252 patients were analyzed. Disease duration and VSR were different between groups (both $p<0.001$). Group 1 had the shortest (0.26 y) and group 6 had the longest (5.8 y) disease duration. Group 2 and 3 had the lowest (0.85) and group 6 had the highest VSR (1.10). The aspect score was assessed in 303 scans of 200 patients. There was a difference between groups ($p<0.001$); group 1 had the highest (17.8) and group 6 had the lowest aspect score (12.9). First analyses suggest a faster WM disease course in patients with a lower AoO.
Patients with a lower AoO have more WM rarefaction and cystic degeneration, even after a short disease duration. Patients with a higher AoO show more WM atrophy, as indicated by a higher VSR.

Discussion Our research underlines the heterogeneity in VWM. This information can be used to inform patients and may serve as a reference in future clinical trials.

Lipoprotein(a) levels over time: a long-term follow-up study of a large cohort of children

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Rationale Lipoprotein(a) [Lp(a)] is associated with an increased risk of cardiovascular disease, such as myocardial infarction. In general, Lp(a) is measured only once in a lifetime, assuming that it is mostly genetically determined and thus stable over time. However, in our pediatric cohort we observed something else and therefore we evaluated in a large cohort of children whether Lp(a) levels increase with increasing age and whether Lp(a) levels fluctuate within individuals.

Methods We performed a retrospective follow-up study of all children that visited the pediatric lipid clinic of the Academic Medical Center between 1989 and 2017. Children were referred to the pediatric lipid clinic for a possible diagnosis of dyslipidemia. Children were eligible if Lp(a) was measured before the age of 18. To evaluate Lp(a) levels over time we used a mixed models analysis in which we corrected for medication use.

Results In total, we included 2,820 children in our analysis. 2,159 children used no lipid-lowering medications (1) and 581 children used statins (2). Mean Lp(a) at the age of 8 was 135 mg/L in the first group and increased with 13% up to a level of 135 mg/L at the age of 18. Mean Lp(a) at the age of 8 was 128 mg/L in the second group and increased with 30% up to a level of 167 mg/L at the age of 18. In addition, intra-child variability was 1.78, meaning that if the true Lp(a) level of a child is for example 500 mg/L, 95% of the measured Lp(a) will lie between 282 mg/L and 889 mg/L.

Conclusion Lp(a) increases during childhood in both groups, whereas the greatest increase was observed in the statin group. Furthermore, we found that Lp(a) fluctuated greatly within children. These findings suggest that Lp(a) is not at all stable in children and one single measurement may not accurately reflect the 'true' Lp(a) value and thereby the Lp(a)-mediated risk of cardiovascular disease. Therefore, we suggest measuring more than once in a lifetime.

Early life exposure to respiratory viruses: a longitudinal birth cohort study

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Rationale Respiratory tract infections (RTI) in children (<5y) are mainly caused by viruses. Respiratory syncytial virus (RSV) and human metapneumovirus (hMPV) are considered to be the most pathogenic viruses. Rhinovirus (RV), in contrast, is the most commonly detected virus, although often found in asymptomatic children as well. Little is known about the health consequences of (a)symptomatic presence of respiratory viruses early in life.
Objectives: To examine exposure to respiratory viruses in the first year of life and relate exposure and timing thereof to development of symptomatic infections in a longitudinal birth cohort.

Methods In a prospective birth cohort of 115 infants, we characterized a panel of 17 respiratory viruses longitudinally from birth to 12 months of age (11 consecutive sample moments and up to three RTI moments; in total, n = 1,287 samples) by quantitative RT-PCR. Associations between viral presence and symptoms of an RTI were tested by generalized estimating equation (GEE) models.

Results RV was the most commonly detected virus, and often found in multiple consecutive sample moments, suggesting prolonged periods of infection. RV was negatively associated with RTI symptoms (GEE: OR 0.41 [0.17–0.98]). In contrast, hMPV, RSV, parainfluenza (PIV) 2 and 4, RSV, and HKU corona were highly associated (OR > 10; $p<0.05$) with RTI symptoms. Despite the asymptomatic behavior of RV, early life detection was associated with increased susceptibility to respiratory complaints in the first year of life (Kaplan-Meier survival analysis: $p=0.021$).

Discussion Early life rhinovirus presence is negatively associated with RTI symptoms but is associated with future susceptibility for respiratory complaints. Further studies on potential ecological or immunological mechanisms explaining these findings are needed.

From Statistician to Clinician: the feedback of PROMIS® CATs within KLIK

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Rationale KLIK is an evidence-based Patient Reported Outcome Measures (PROM) portal. Health-Related Quality of Life (HRQOL)/symptoms/psychosocial functioning questionnaires are completed by patients and discussed by Health Care Providers (HCPs) during consultation. To reduce patient burden, new PROMs (pediatric PROMIS computerized adaptive tests (CATs)) were made available in KLIK. For the use of PROMIS in clinical practice new feedback options are required. The aim of this study is to develop these feedback options for individual item and domain score feedback.

Methods HCPs using KLIK were eligible for this multi-method study. Literature-based feedback options were shown for individual items and domain scores. HCPs were asked about interpretability/comprehensibility/(color)design/completeness of these options. Additionally, a questionnaire was sent out to HCPs to collect additional information on whether estimates should be included in the visual feedback.

Results Six focus groups were held (n=27) and analyzed by two researchers in MaxQDA. HCPs report that individual item feedback is preferred for using PROMIS in clinical practice. Presenting the full item banks, with responses (in traffic light colors) of administered items, was described as their optimal feedback option. Clinicians preferred separate graphs per domain score, ranked in order of importance over any of the textual representation of domain scores. These graphs should include normative lines/SD lines/traffic light colors/same directionality of all domains. There was disagreement about including numerical scores within graphs. Most clinicians preferred not seeing estimates (69.6%).

Conclusion Overall, simplicity was considered most regarding the feedback method. The Dutch-Flemish PROMIS National Center and KLIK research group will design and evaluate the optimal feedback option to successfully implement PROMIS in KLIK.

The feasibility of transcutaneous electromyography of the diaphragm as monitoring technique in the delivery room

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Rationale Cardio-pulmonary transition is monitored in the delivery room (DR) with pulse oximetry (PO) and/or chest impedance (CI). However, CI and PO do not measure respiratory effort, an essential factor to titrate respiratory support. Electromyography of the diaphragm (dEMG) measures the activity of the diaphragm and might be helpful to determine respiratory effort. It also measures HR, potentially improving monitoring compared to CI, but it needs to be established if dEMG provides accurate data on HR in the DR.

Methods Infants with a gestational age (GA) > 26 weeks, in need for cardio-respiratory support were enrolled. CI, PO and dEMG measurements were started directly after birth. Time between device application and the first read out of the corresponding HR was calculated (Δt). HR was calculated based on the dEMG signal and the raw CI-waveform. Numerical HR, from CI- and PO, was acquired from the patient monitor. All HR-readings were compared using intra-class correlation coefficient (ICC) and Bland-Altman (BA) analysis (with limits of agreement (LOA)).

Results Fourteen infants (GA 32.5 ± 3.0 weeks; birth weight 1743 ± 790 g) were included so far. Due to errors in data storage, not all CI tracings were stored (6 raw CI and 1 numeric CI missing). Δt was equal for dEMG and raw CI signal (both with median (IQR): 10.1 (10.1–10.3) seconds), while numerical CI was slower (12.0 (8.1–13.7) seconds). HR detection of PO was slower compared to dEMG and CI with a median of 35.9 (16.3–67.7) seconds. dEMG monitoring showed high accuracy with an ICC of 0.98 for dEMG vs. raw CI; 0.96 for dEMG vs. numerical CI; and 0.96 for dEMG vs. numerical PO. BA analysis showed high agreement between dEMG and raw CI (mean difference (LOA): −0.5 (6.8) beats/minute).

Discussion This study suggests that dEMG monitoring in the DR is feasible and provides fast and accurate data on HR. Future studies should investigate the additional value of dEMG in assessing respiratory effort and titrating respiratory support in the DR.

Survey on the operation of European human milk banks

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Rationale When mother's own milk is unavailable, banked donor human milk should be provided to high risk infants admitted in neonatal units. The European Milk Bank Association (EMBA) has currently 226 registered donor human milk banks, located in 28 European countries. Most of them operate based on regional or national guidelines, as currently there are no published European-wide guidelines. We aimed to collect data on the human milk banking practices affecting the quality and safety of banked donor milk in Europe.

Methods An online-based questionnaire consisting of 35 questions was sent out to all 226 milk banks and an EMBA Survey Group was formed in 2018 to support this task. The questions were divided into 5 categories: Donation, handling, storage, processing and microbiological testing of donor milk.

Results A total of 112 milk banks, from 20 out of the 28 countries (Austria, Belgium, Bulgaria, Denmark, Estonia, France, Germany, Greece, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Spain, Sweden, Switzerland, United Kingdom) completed the survey. Differences were observed in most aspects of donor milk banking. With respect to milk screening, only 28% of milk banks bacteriologically test every container of donated milk and only a 44% performs a serological screening for CMV (cytomegalovirus). A wide variation in donor milk processing parameters was observed, such as the heating up time to the pasteurization temperature (62.5°C), which was between 20 minutes and more than 1 hour, the cooling down time, the volume of milk treated within a pasteurization cycle and milk pooling.

Discussion Our findings suggest that there is still a wide variability in milk bank practices across Europe and there is an urgency to uniform practices to increase safety and efficacy of donor milk banking.

The incidence of intracranial hemorrhages in neonates with hemophilia; an assessment of the literature

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Rationale Hemophilia is a congenital bleeding disorder which causes patients to be more likely to bleed. Birth is the first traumatic risk factor and hemostatic challenge a hemophilic newborn has to cope with. Sometimes it may result in an intracranial hemorrhage (ICH), a severe complication that is associated with a high mortality and a risk of irreversible neurological damage and life-long disability. Information on the incidence of these bleeds could help to establish additional guidelines and guide future decision-making in neonates with hemophilia, in order to prevent ICH's and neurological sequelae.Therefore, the aim of this review is to systematically analyze and critically appraise the current literature available with regard to incidence of intracranial hemorrhage in neonates (up to 28 days) with hemophilia.

Methods A search was performed in the PubMed database. At first studies were screened for title and abstract. Subsequently, studies that were deemed relevant were screened on full text. The most important eligibility criterion was that the research article should provide the possibility for calculation of crude incidence of intracranial bleeds in neonates with hemophilia. For this, two numbers were needed, namely cohort size and number of ICH cases. Patient characteristics of ICH cases were also collected and presented.

Results The search yielded 103 results, of which 16 were relevant and included in this systematic review. This study found that the incidence of intracranial hemorrhages in neonates with hemophilia was 2.0%. The mortality of intracranial hemorrhage in this group was found to be 3.9%.

Discussion However, the evidence was limited to retrospective cohort studies mainly and large prospective studies are needed to determine an accurate incidence of intracranial hemorrhage in neonates with hemophilia.

The influence of early-life gut microbiome development on vaccine responses

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Rationale Antibody responses to vaccination are highly variable between individuals. This inter-individual variation remains poorly understood. We assessed associations between early-life development of the gut microbiota and antibody responses to vaccination.

Methods In a prospective cohort study of 123 healthy infants, we characterized gut microbiota development from birth until age 2 months using 16S rRNA sequencing. We related this to post-vaccination salivary immunoglobulin G (IgG) concentrations specific to pneumococcal serotypes (Ps) 6b, 7f and 14 at age 12 months, as well as meningococcus type C (MenC) at age 18 months, as measured by a fluorescent bead-based multiplex immunoassay.

Results Higher vaccine responses were associated with vaginal birth (MenC), breastfeeding (Ps6b, Ps7f, Ps14) and female sex (Ps7f). Within the first months of life, high abundances of Bifidobacterium, Escherichia coli and Bacteroides were related to higher vaccine responses, while high abundances of Streptococcus and Clostridium were related to lower vaccine responses. These biomarker species were in turn driven by early-life exposures including birth mode and feeding type.

Discussion Our results suggest that early-life exposures affect gut microbiota development, which is in turn associated with antibody responses to vaccination. This is in line with the idea that microbial exposure in the earliest phase of life, within the critical window of opportunity, may influence immune development and later-life health.

Fecal microbiota transplantation in adolescents with refractory irritable bowel syndrome; protocol for a pilot randomized, double-blind, placebo-controlled trial

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Rationale Irritable bowel syndrome (IBS) is a common chronic medical condition, with a suggested peak prevalence in adolescents. Despite available pharmacological and non-pharmacological treatment regimes, symptoms may persist in a significant amount of IBS patients. These refractory patients might benefit from new treatment approaches focusing on other components of the underlying pathophysiology, such as the intestinal microbiota. Fecal microbiota transplantation (FMT) may be an effective treatment in adolescents with refractory IBS through manipulation of the intestinal microbiota.

Methods To assess efficacy, this randomized, placebo-controlled single-center pilot study, evaluates whether repetitive FMT is effective for reducing IBS complaints. A total of 30 adolescents (16–21 years) with refractory IBS will be included, according to the Rome IV criteria. Patients will be randomly allocated (1:1) to receive two allogeneic (healthy donor) or two autologous (own) fecal infusions at baseline and after 6 weeks. The primary outcome will be the proportion of patients with at least > 50% reduction of their abdominal pain intensity and frequency 12 weeks after the first FMT. Secondary outcomes include intra-individual changes in fecal gut microbiota composition, changes in quality of life, in depression and anxiety, in school or work absenteeism and in adequate relief, measured directly after FMTs and after 6 and 12 months of follow up. The study is approved by the Medical Research Ethics Committees AMC (MEC-AMC) in the Netherlands. Clinical trials registration number is NCT03074227.

Discussion This is the first RCT to investigate the effectiveness of repetitive FMT's in adolescent patients with refractory IBS.

Intrasphincteric Botulinum toxin injections for post-operative obstructive defecation problems in Hirschsprungs disease: predictors of response

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Rationale Hirschsprung disease (HD) is associated with obstructive symptoms and Hirschsprung-associated enterocolitis (HAEC) after surgery. Botulinum toxin injections (BTI) can help improve faecal passage by relaxing the internal anal sphincter. This study aims to describe the effects of BTI in treating post-operative obstructive symptoms and HAEC and to identify factors that are associated with receiving BTI and with favourable response to the first BTI.

Methods All patients that were treated for HDin our centre between 2003 and 2017 were included in a retrospective cohortstudy. Data on patient and clinical characteristics were retrieved from the medical records. Amount of received BTI, duration of improvement and proportion of injections and patients with favourable response were calculated. Adverse effects were described. Logistic regression was used to test associations between potential predictors and (a) the necessity of BT injections and (b) favourable response to the first injection.

Results Forty-one out of 131 patients received BTI (32%), with a median of two injections (range 1–11). A total of 115 injections were administered, of which 69 led to clinical improvement (60%). 25/41 patients (60%) had a favourable response after first injection. Duration of clinical improvement was on average 4.3 months after injections. Adverse effects were anal pain and temporary incontinence. No factors could be identified that were significantly associated with receiving BT injections or with a favourable response to the first injection.

Discussion Our findings show that BT injections effectively treat obstructive defecation problems in the majority of patients with Hirschsprung Disease, with limited adverse effects. There were no specific subgroups of patients with better odds at favourable response. We therefore recommend to not be reticent to use BTI in patients with post-operative obstructive symptoms.

Heterogeneity of astrocytes in Vanishing White Matter Disease: central in white matter lesion repair?

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Rationale Vanishing White Matter (VWM) is one of the most common leukodystrophies and is characterized by cavitating degeneration of the brain white matter. While oligodendrocytes and astrocytes are selectively affected, astrocyte dysfunction is implicated as the primary driver of VWM pathogenesis. Both disease severity and repair potential show striking regional variation in VWM, with the cerebral and cerebellar white matter consistently being severely affected with no potential for repair, while the brainstem is less severely affected with acute lesion formation and recovery over time. Recent findings show that astrocyte abnormality co-varies with the regional variation in lesions. In this current study, we are assessing the contribution of astrocyte heterogeneity to regional variation in intrinsic repair potential in VWM.

Methods Ex vivo organotypic brain slice cultures were generated from cerebral, cerebellar and pontine tissue of mice carrying VWM mutations and from cerebral white matter of human VWM tissue. After 14 days in culture, mouse slices were treated with lysolecithin (0.5 mg/ml) to induce acute global demyelination, and were kept in culture for an additional 14 days. In all slices, (re)myelination and reactive astrogliosis were assessed by immunofluorescence.

Results Our preliminary data show that lysolecithin treatment of wild-type mouse brain slices induces demyelination, followed by intrinsic remyelination ex vivo. In addition, human VWM brain slices survived up to three weeks in culture and recapitulate VWM disease characteristics, including dysmorphic astrocytes, lack of astrogliosis in response to injury due to slicing of the tissue, and paucity of myelin.

Discussion In conclusion, organotypic brain slice cultures can be used to study intrinsic repair of tissue and recapitulate disease entities of VWM. Our additional studies will provide insight into how astrocyte diversity might contribute to selective vulnerability and repair of the white matter.

Targeted analysis of volatile organic compounds for detection of Pseudomonas aeruginosa in cystic fibrosis patients by exhaled breath analysis

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Rationale In cystic fibrosis (CF), Pseudomonas aeruginosa (PA) is an important respiratory pathogen. Routine microbiology surveillance is time-consuming, expensive, and requires expectorated sputum in CF patients. Volatile organic compounds (VOCs) in exhaled breath, obtained by gas-chromatography mass-spectrometry (GCMS), are associated with PA colonization, but suffer from high within-patient variability [van der Schee, Chest, 2015]. Targeted analysis (using VOCs that were identified to be associated with PA in earlier studies) might lead to a profile that can be used for PA detection. We aim to 1) identify VOCs that 2) can recognize PA positive CF patients.

Methods This study consisted of 1) a literature review for a priori VOC targeting, and 2) a cross-sectional analysis of a prospective CF-cohort study. PA positive was defined as A) PA culture at visit, B) chronic PA infection; PA free defined as C) no PA culture in the past year. VOCs from exhaled breath were identified via electron ionization quadrupole MS and the NIST-library. Data-analysis involved: nonparametric tests, regression modelling, determination of the odds ratio with a 95% confidence interval (CI), construction of a receiver operating characteristic (ROC) curve with area under the curve (AUC).

Results 56 (from 241) VOCs were included based on ≥2 consistent associations in literature, 13 were detected by our GCMS. Exhaled breath of 25 paediatric and 28 adult CF patients, PA positive (n=16) and free (n=28) was available. 3 VOCs were statistically significant ($p<0.05$) between PA positive and free children; none were for adults. A 5-VOCs and single step regression model showed a ROC-AUC of 88% (CI 71–100%) and 87% (CI 72–100%) for adults and children, respectively.

Conclusion Targeted VOC analysis based on published data can discriminate children with and without PA positive culture. These data merit further validation of breath analysis as alternative for pathogen detection.

Positive effects of an online cognitive behavioral group intervention on anxiety and depression in parents of children with a chronic illness: a randomized controlled trial

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Rationale Parents of children with a chronic illness are at risk for psychosocial problems such as anxiety and depression. The aim of this study is to evaluate the efficacy of an online cognitive-behavioral group intervention on psychosocial functioning in parents of children with a chronic illness.

Methods Parents (n=81) participated in a multicenter randomized controlled trial comparing an intervention to a wait-list control group. The intervention, called Op Koers Online, consists of six weekly sessions, in a secured chatroom, with groups of 3–5 parents guided by two psychologists. Parents learned how to use adaptive coping strategies taught with techniques from cognitive behavioral therapy (CBT) and acceptance and commitment therapy (ACT). Assessments (online questionnaires) took place at baseline (T0), 6-months (T1) and 12-months (T2) follow-up. Outcomes were psychosocial functioning and disease-related coping skills. Mixed-model analyses were performed to test the difference in change in outcomes between intervention and control group.

Results Compared to the control group, the intervention had a significant positive effect ($p < .05$) on changes in psychosocial functioning (anxiety and depression) T1 vs T0 $\beta = -.47$ to $-.51$ and T2 vs T0 $\beta = -.39$ to $-.46$ and disease-related coping skills (open communication, relaxation, social support and predictive control) T1 vs T0 $\beta = .43$ to $.88$ and T2 vs T0 $\beta = .42$ to $.53$.

Conclusion This RCT supports the efficacy of a protocol-based online CBT/ACT group intervention for parents of children with a chronic illness. Parental psychosocial functioning and use of adaptive coping skills improves after the intervention. The next step is to implement Op Koers Online in other hospitals in the Netherlands.

NARSYN trial: intranasal administration of palivizumab against RSV infection

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Rationale Respiratory syncytial virus (RSV) is the leading cause of morbidity and mortality due to lower respiratory tract infections in infants worldwide. The only available form of protection is palivizumab, which is limited to high-risk infants due to prohibitive costs. To reduce costs, a lower dose of monoclonal antibodies may be administered mucosally. We hypothesize that intranasal administration of palivizumab provides local protection against RSV infection in late pre-term infants.

Methods In our double-blind randomized clinical trial (NARSYN), we plan to recruit 408 late pre-term infants during three subsequent RSV seasons (October-March). Included are infants born between 32–35 weeks who are maximum six months old at the beginning of the RSV season with an older sibling. Excluded are children with Down syndrome or with an indication for regular palivizumab administration. Parents are asked to administer one drop of Narsyn daily during the entire RSV season, to record respiratory symptoms and to take a nasopharyngeal swab if present. All nasopharyngeal swabs will be tested for RSV at the end of the study.

Results We have currently included 80 study participants during 1.5 RSV season. We are working together with 20 recruiting centers. We have received 69 nasopharyngeal swabs from 45 study participants.

Discussion Challenges that await the NARSYN trial are difficulties in including sufficient study participants within the intended study period, parental adherence to the study medication and reliance on parents for taking nasopharyngeal swabs. To overcome this, we actively counsel parents during our weekly follow-up phone calls and bimonthly home visits. Furthermore, we keep expanding to other hospitals in order to achieve the necessary sample size.

Transplantation outcomes in patients with Primary Hyperoxaluria Type I

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Rationale Primary hyperoxaluria type 1 (PH1) is a rare inborn error of glyoxylate metabolism characterized by an increased endogenous oxalate production. This leads to renal stone formation, nephrocalcinosis and ultimately renal failure. Liver transplantation is the only curative treatment at hand. There is an ongoing debate on the best transplantation strategy. In most cases, a combined liver- kidney transplantation (CLKT) is performed. Other transplantation centers prefer a sequential procedure (SLKT) and an isolated kidney transplantation (KTx) may be an option for pyridoxine responsive patients. Our aim was to compare the different transplantation strategies for both allograft and patient survival.

Methods We retrospectively collected data from the OxalEurope registry. Patients with PH1 who underwent a transplantation were selected. Data from ten European countries were obtained.

Results 323 transplantations were performed in 244 patients, between 1974 and 2019. The type of first transplant was mostly CLKT (n = 120), followed by KTx (n = 88) and SLKT (n = 24). Long-term outcomes were known for 199 cases, with a median follow-up of 5.6 years. Five-year patient survival rates were similar for CLKT (79%), SLKT (87%) and KTx (74%). Five-year kidney graft survival was 64% in CLKT and 79% in SLKT ($p = 0.285$), both superior as compared to KTx (28%, $p < 0.001$). In pyridoxine responsive patients, kidney graft survival did not differ between CLKT and KTx ($p = 0.781$).

Discussion Our study demonstrates that liver- kidney transplantation remains the transplantation modality of first choice in pyridoxine unresponsive PH1 patients, with no apparent advantage of SLKT over CLKT. In pyridoxine responsive PH1 patients a solitary KTx seems to be a viable option.

Region-resolved quantitative proteomic mapping of the human Vanishing White Matter brain

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Rationale Vanishing white matter (VWM) is one of the most prevalent childhood white matter disorder. It is caused by mutations in any of the five genes encoding the subunits of eukaryotic translation initiation factor 2B (eIF2B), a ubiquitously expressed enzyme crucial for mRNA to protein translation. To this day there remains a lack of in-depth knowledge about what happens in the human VWM brain. This is exacerbated by the fact that brain white matter is exclusively affected whereas gray matter appears relatively spared. Importantly, not all white matter structures are affected equally, adding a spatial component to the disease in which different brain regions develop pathology at different times as disease progresses.

Methods Here, we performed mass spectrometry-based proteomics analysis in four regions of human control and VWM-affected brains to find changes in protein expression profiles that may explain regional vulnerability in VWM pathology.
Four anatomical regions (i.e. cortex, frontal white matter, cerebellar white matter and pons) of human control (n=4) and VWM-affected brain (n=4) were isolated using laser capture microdissection. Protein expression profile of each brain region was then determined using high-resolution mass spectrometry-based proteomics.

Results We quantified over 3900 proteins in control and VWM brain tissues, revealing changes in protein expression profiles between VWM and control as well as across the different brain regions. These data also show that gray matter areas such as the cortex, rather than being spared by VWM, displays a distinct proteome profile from healthy controls and other brain regions, which could suggest the presence of gray matter pathology that has been overlooked so far in VWM.

Discussion This regional-resolved proteomics analysis provides a framework which can improve our current understanding on the pathology underlying the regional vulnerability in VWM and could provide us with possible new targets to abate VWM pathology.

The beneficial effect of native whey protein on intestinal integrity and innate defense in the immature intestine of preterm and near-term piglets

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Rationale Intestinal immaturity predisposes infants to nutritional challenges, which might lead to clinical complications like feeding intolerance and necrotizing enterocolitis (NEC). Feeding preterm infants with infant milk formula (IMF) is associated with an increased risk to develop NEC compared to human milk. Heat treatments are part of the IMF production to ensure microbial safety, but heating is linked to protein denaturation and loss of bioactivity. Aim of the current study was to determine if native whey protein concentrate (N-WPC) has beneficial effects over denatured WPC (D-WPC) on intestinal maturation in a piglet model hypersensitive to enteral nutrition.

Methods 34 preterm piglets (90% gestation) and 18 near-term piglets (96% gestation) were delivered by cesarean section and divided in two groups: 1) N-WPC received formula based on mildly pasteurized WPC (i.e. WPC heated 73°C, 30 sec), which maintains proteins in their native form and 2) D-WPC received formula with WPC that was mildly pasteurized and additional heat treated (i.e. 80°C, 6 min), resulting in protein denaturation. Piglets received minimal enteral nutrition for 5 days with parenteral nutrition support. At sacrifice, the gut was scored for NEC-like lesions, and tissue was collected for histology, enzyme activity, RNA and protein analysis.

Results Both macroscopic and microscopic scoring showed less lesions in the colon of piglets fed N-WPC compared to piglets fed D-WPC. Inflammatory markers (IL1-β, I-L8, TNFα and T cells) were also lower in the N-WPC group. Intestinal alkaline phosphatase showed increased activity in the colon of piglets fed N-WPC which potential dampened the colonic inflammatory response, thereby improving the intestinal barrier.

Discussion Overall, data indicates that a formula based on N-WPC has beneficial effects on gut inflammation and maturation in preterm and near-term piglets and might therefore also support intestinal maturation in preterm and (near)term infants.

The use of the KLIK PROM portal in clinical care; the patients' and parents' point of view

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Rationale Within the KLIK Patient Reported Outcome Measures (PROM) portal (www.hetklikt.nu) patients and/or parents complete PROMs online at home, prior to the outpatient consultation. Answers are converted into a KLIK ePROfile. The healthcare professional (HCP) discusses the KLIK ePROfile during the consultation, to monitor well-being over time, detect psychosocial problems or symptoms early and provide tailored advice and interventions. Since 2011, >16.000 patients are registered and >60 patient groups (e.g. dermatology, diabetes) use KLIK in >20 Dutch hospitals. To improve KLIK, this study aims to gain more insight into the experiences with KLIK from the patients' and parents' point of view.

Methods A mixed-method design was used: 1) Focus groups were held with adolescents (12–18y) and parents (of children 0–18y) from the Emma Children's Hospital and registered at the KLIK website to ask about the positive and negative experiences with KLIK. 2) A self-composed evaluation questionnaire was sent out to adolescents/parents, to quantitatively assess the study aim.

Results 1) In total, 8 adolescents and 17 parents participated. Adolescents mentioned that KLIK has an attractive lay-out and is easy to use. However, not all PROMs were relevant for every patient. Parents valued that KLIK helps them in preparing the consultation and to talk about psychosocial functioning which leads to a more efficient consultation, but reported that not every HCP discusses the KLIK ePROfile. 2) The evaluation questionnaire was completed by 125 parents and adolescents are still recruited. Results will be presented at the conference.

Discussion Based on the feedback provided by adolescents/parents, adjustments will be made to improve the user-friendliness of KLIK. For example, using PROMIS item banks to reduce the burden and to ask more relevant questions, and by motivating HCPs to discuss the KLIK ePROfile. This enables further optimization and implementation of the KLIK PROM portal.

Exploring the burden of Ntwetwe virus – a novel orthobunyavirus associated with CNS infections – in Ugandan children

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Rationale Ntwetwe virus is a novel orthobunyavirus, recently discovered from the cerebrospinal fluid of a three-year-old Ugandan girl with a fatal CNS infection. Orthobunyaviruses are arthropod-borne viruses, prevalent worldwide and can cause different types of disease, ranging from mild febrile illness to fatal CNS infections. Expectedly, human exposure to Ntwetwe virus may be common because of its presumed vector (Anopheles mosquito) and the high seroprevalence to its closest relative (Tataguine virus) in sub-Saharan Africa. Due to its recent discovery, attempts to further study this virus have not yet been performed. The objective of this study is to determine the prevalence of Ntwetwe virus infections in children in the region of first identification, describe clinical characteristics of infection and determine whether and which mosquitoes transmit Ntwetwe virus. This will provide us with the first insight into the burden of Ntwetwe virus infections which is important for clinicians, policy makers and future research.

Methods We conducted a human case-control study on children presenting with mild febrile and severe neurologic symptoms to Kiboga hospital between August 2019 and January 2020. Infection by Ntwetwe virus was determined by a quantitative real-time polymerase chain reaction of blood and cerebral spinal fluid samples in the Uganda Virus Research Institute. The prevalence of acute Ntwetwe virus infections for both case groups was compared to healthy controls. Clinical and anthropological risk factors for infection were determined and mosquitos were captured at two time points by field teams from the UVRI, over a period of 2 weeks in the same area, during the dry and rainy season.

Results Fifteen cases (14 mild and one severe) and five controls were included by mid October 2019. Further inclusion and testing is ongoing.

Discussion Results of this study will – for the first time – be presented at the Amsterdam Kinder Symposium.

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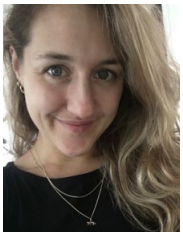
Linssen	Rosalie	Pediatric Intensive Care Unit	Amsterdam UMC	r.s.linssen@amsterdamumc.nl	
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