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Innovations in Pediatrics

Scientific research is key for progress in medicine. Huge progress has been made from Amsterdam perspective last year as well, as was recognized internationally by papers appearing in Nature & affiliated journals (5), Lancet & subspecialty journals (4), JAMA & subspecialty journals (6), the New England Journal of Medicine (1), Annals of Neurology (2), Neurology (1), Brain (1), Gastroenterology (1), Cell Host & Microbe (1), European Respiratory Journal (1), JACI (3), Journal of Clinical Investigation (1), Blood (2) and Clinical oncology (1). A total of 31 papers published in international journals with an impact factor >10 in 2018 shows the success of combining two research institutes in Amsterdam.

The Amsterdam Kindersymposium will have his eight’s annual meeting, held again in the vibrant heart of the city at the Nieuwe DeLaMar Theatre. This environment has been used successfully in recent years and offers good opportunities to interact. Although the majority of the participants are young researchers, the meeting is also well attended by clinicians and clinician-researchers. That is of major importance for broadening our views on the implications of our research. The mix of research conducted in children from all subspecialties, whether they are original pediatric studies, or conducted from surgical disciplines or psychology/psychiatry disciples guarantees that everyone attending will learn new facts. And that makes this symposium so unique.

Another unique selling point of this symposium is that it is completely organized by young researchers themselves. From fundraising to abstract books, from inviting renown key note speakers to setting up the materials for the parallel sessions, all and more is organized by the Symposium Committee. And year by year, the organization is getting more professional, also indicated by the ever increasing numbers of participants. Also in 2019 we expect over 200 participants.

The poster presentations are the backbone of the symposium, while the plenary sessions will be held in view of “Innovations in Pediatrics”. The Committee has selected very interesting plenary sessions, and has invited approximately 70 abstracts to be presented which makes this day a very special one for many.

I wish you all a beautiful day in DeLaMar Theater at our Amsterdam Kindersymposium 2019.

Hans van Goudoever
Chair, Pediatrics, Amsterdam
A word of welcome from the Symposium Committee

We are very happy to welcome you to the 8th edition of the Amsterdam Kindersymposium (AKS) in the DeLaMar Theatre in Amsterdam. The Amsterdam Kindersymposium 2019 is focused on ‘Innovations in Pediatrics’.

We will hear exciting talks about robotics, e-health and will hear different perspectives on innovations in reproductive medicine.

We are very honored to have not one, but two keynote speakers this year: Prof. dr. Heidi Mertes who is a professor in Ethics at the University of Ghent and with her, Dr. Sebastiaan Mastenbroek, who is assistant professor of Human Reproductive Biology. Together, they will provide important background into the innovations and possibilities of reproductive medicine, which we will include with a plenary discussion on this topic. We are very much looking forward to hearing their expert opinion and your input as well!

Traditionally, the SLAM-sessions will give you the opportunity to explore the enormous diversity of research being done in our hospitals. In short and catchy presentations you can hear all about the work of many (young) colleagues. After two successful years, we will again see the best researchers of the SLAM-sessions compete for the best presentation awards in the ‘SLAM Battle Final’!

We hope that you will enjoy the AKS 2019 and that you leave today inspired by our speakers with a positive view of the future!

We would like to thank everybody who contributed to making this day a success and we hope to continue and expand this endeavour for future editions.

Enjoy!

The Amsterdam Kindersymposium Committee 2018-2019,

Saranne Ingelse, Esmee Kooijmans, Laura Tseng, Fatma El-Khouly, Francis Stoutjesdijk, Jorn Gerritsma, Sander Garrelfs, Diana van Stijn-Bringas Dimitriades, Nina Streefkerk
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# Slam session I – Morning (10:25 till 11:40h)

**Rode Foyer (-1st floor)**

Chair: Prof. Dr. Reinoud Gemke

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**Diner Foyer (2nd floor)**

Chair: Dr. Frans Plötz

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**Rode Foyer (-1st floor)**

Chair: Dr. Diederik Bosman

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

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PLENARY SESSIONS

INFORMATION ON ALL SPEAKERS
Moderators

Drs. A.C.M. van Bellegem

Which study/studies did you do (incl. time period in years)?
Biology 1994
Biomedical Health Science 1994-1996
Medicine 1995-2001
Pediatrics 2003-2009
Fellowship social pediatrics 2009-2012

At which university did you study?
University of Nijmegen

When did you obtain your PhD and what was the title of your thesis?
No thesis, no PhD

Since when are you working at your current institution?
I started working at the AMC in 2005.

What are you most proud of?
I am most proud of the establishment of the Medical Psychiatric Unit for children and adolescents. This department for children with combined somatic and psychiatric care needs has been operational since 2016, also thanks to the innovation money of the AMC.

Which aspects of your work do you like most?
I find it most inspiring and challenging to work in a multidisciplinary team where the wellbeing of the child and his/her family are put first.

What is an important innovation in the field you are working in?
There are several very interesting developments in the field of neuropsychiatry using, for example, the knowledge of the pathophysiology in experimental treatments. An example of this is Deep Brain Stimulation for patients with Anorexia Nervosa or research in the field of the gut-brain axis / microbiome.

What do you like to do after work hours?
Spend time with my 2 kids and friends, do sports: mostly dancing.

What are your future plans?
I think it is important that doctors work with a more holistic view of people and healthcare and that we will become more detached from dualistic thinking. I want to achieve that more combined somatic and psychiatric care facilities are created.

What is your favorite movie?
The documentary the Dancer (2016) is a documentary about Sergei Polunin, a very talented professional ballet dancer who became the youngest first soloist at the Royal Ballet. His fame made him self-destructive and he increasingly saw his talent as a heavy burden than a gift.
Drs. C. Hartdorff

Which study/studies did you do (incl. time period in years)?
- Medicine 1997-2003
- Pediatrics 2004-2011
- Fellowship Intensive care 2011-2016

At which university did you study?
Vrije Universiteit van Amsterdam

Since when are you working at your current institution?
I have been working as an pediatric intensivist since 2016, until the summer of 2018 at the Free University medical center, later the Amsterdam University medical center, location Meibergdreef.

What are you most proud of?
I am most proud of my colleagues working together as a team on the PICU

Which aspects of your work do you like most?
I strongly prefer working on the ward, in a team, for acute as well as more chronical care.

What is an important innovation in the field you are working in?
A couple of years ago, we implemented family-centered care on our ward, with optimization of information sharing with parents and collaborating with parents at all levels of health care. I strongly believe in family-centered care.

What do you like to do after work hours?
Running, yoga, tennis.

What are your future plans?
Keep on working as a pediatric intensivist.

What are you most excited about of this symposium?
To hear enthusiastic and motivated colleagues speak about their research, being up to date. And the collaboration with Annemarie.

What music album did you play most?
Leonard Cohen, Live in Dublin
Speakers

Dr. J. Kimpen, Chief Medical Officer, Philips

Jan Kimpen is the Philips Chief Medical Officer, a position he has held since January 2016. As the functional leader for clinical innovation, medical affairs and health economics, Jan and his team work collaboratively to advance clinical capabilities at Philips and to support organic and external growth opportunities.

Jan also leads the Medical Leadership Team, with responsibility for the company’s medical strategy. This includes advocacy, customer partnerships and responsibility for clinical trials and medical guidelines. He also leads health economics and market access for Philips, and is closely involved in M&A.

A frequent speaker on eHealth and digital innovation, Jan also represents Philips on the Global Health Security Agenda private sector roundtable and the WEF Global Health Security Advisory Board.

Jan joined the company from the University Medical Center Utrecht - one of the largest healthcare organizations in the Netherlands - where he served as professor and chairman of Pediatrics before being appointed as CEO in 2009.
Speakers

Dr. B. van den Voorn
Dr. Bibian van den Voorn is selected with her PhD on “The HPA axis in preterm birth: Short- and long-term correlates” as best thesis of 2017-2018. She has studied medicine from 2005-2012 and is currently working at the Erasmus Medical Center as a Post-doctoral researcher and medical doctor at the Obesity Center CGG. She is most proud of a study she performed from start to finish that resulted in a publication by herself, M de Waard, JB van Goudoever, J Rotteveel, AC Heijboer and MJJ Finken on “Breast-milk cortisol and cortisone concentrations follow the diurnal rhythm of maternal hypothalamus-pituitary-adrenal axis activity” in Nutrition, 2016. What she likes most about her work is being able to share creativity, ambitious and innovative ideas with an inspired team. Her future plans are to create an infrastructure that facilitates a platform via which (para) medical professionals and governmental organizations within one region can learn about each other’s expertise and could easily work together with an integrated, multidisciplinary approach for stress related diseases such as obesity.
Keynote speakers

Dr. S. Mastenbroek

Sebastiaan Mastenbroek is an Assistant Professor and Senior Clinical Embryologist at the Academic Medical Center of the University of Amsterdam, the Netherlands. An important focus of his research in past years has been Preimplantation Genetic Screening (PGS). In 2007, publication of his randomized controlled trial on PGS in the New England Journal of Medicine started a fiercely debated controversy on the use of PGS as it showed that the technique lowered rather than increased pregnancy rates after IVF. He then published research that provided technical as well as biological reasons for the inefficacy of the first generation of PGS methods. From a broader perspective he is interested in ovarian aging, early human development, implantation, assisted reproductive techniques and evidence based laboratory practice.
Keynote speakers

Professor Heidi Mertes
Professor Heidi Mertes currently holds a position as a professor in Ethics at Ghent University. She has studied Moral Sciences (1997-2001) and has obtained two PhD degrees; in 2009 a PhD in Moral Sciences entitled "The interaction between science and ethics in the debate concerning stem cell research", and in 2017 a PhD in Philosophy entitled "Egg banking in anticipation of age-related fertility decline. Using medical technology for better, not for worse". She is most proud of one of her publications with G. Pennings published in Reproductive BioMedicine in 2011. "Social egg freezing: for better, not for worse". The fact that the field of bioethics is not static, but constantly faced with new dilemmas and challenges, is what Heidi likes most about her work. In the future, she aims to continue building bridges between ethics and other domains such as health care, biotechnology, bio-informatics and bio-engineering. Her take home message is: Reproduction is never risk-free and no child is perfect, but serious and/or unnecessary risks for our offspring are to be avoided.
Motivational speaker

Dr. M. Haerkens

Dr. Marck Haerkens is founder and leader of "Wings of Care", an organization with expertise in aviation, aerospace and medicine. Wings of Care aims to improve team performance in critical processes. Marck studied medicine and did a residency in surgery with traumatology as sub-specialty at the Radboud University of Nijmegen and completed the military pilot training with the Royal Netherlands Air Force (Type ratings: Bo-105cb (recon) and AH-64D (attack) helicopters). In 2017, he obtained a PhD entitled "Human Factors and Team Performance". He is most proud of his publication with M Kox, J Lemson, S Houterman, JG van der Hoeven, P Pickkers "Crew Resource Management in the Intensive Care Unit: a prospective 3-year cohort study" in Acta Anaesthesiologica Scandinavia in 2015. An important innovation in his field of work is adapting and implementing the aviation-based Crew Resource Management (CRM) team concept for clinical teams performing critical/ high-risk tasks. His future plan is to integrate Human Factors awareness training as standard in all (para-) medical education curricula. After his presentation, he would like you to remember that "a team of professionals is not automatically a professional team". After work, he likes to enjoy time with his family, dog and friends and to operate go fast machines.
**Professor Dr. T. Belpaeme**

Professor Tony Belpaeme currently holds a position as a professor of Cognitive Systems and Robotics at Ghent University (Belgium) and Plymouth University (UK). His research interests include social systems, cognitive robotics and artificial intelligence in general. In 2002 he obtained a PhD on Factors influencing the origins of colour categories at Vrije Universiteit Brussel. He is most proud of a publication by L. Steels and himself entitled “Coordinating Perceptually Grounded Categories through Language. A Case Study for Colour” published 2005 in Behavioral and Brain Sciences. An important innovation in his field of work is that we now realize that robots should not only be able to operate in the physical world, but that being able to navigate the social world is equally important. He likes the fact that machines help us understand more about what makes us human and wants you to remember that robots are nothing to worry about. His future plans are enjoying academia as much as possible, spend time with interesting people and if it all fails, open an icecream shop. His favorite music album is Hunky Dory by David Bowie.
ABSTRACT BOOK

ABSTRACTS SELECTED FOR THE MASTERCLASS
Statin Therapy Initiated in Childhood: 20 Years of Follow-up of Patients with Familial Hypercholesterolemia

I.K. Luirink

Affiliations:

Keywords:

Rationale
Familial hypercholesterolemia (FH) is characterized by severely elevated low-density lipoprotein cholesterol (LDL-C) levels and premature cardiovascular disease. Short-term efficacy of statin therapy in children is well established but follow-up studies into adulthood to evaluate changes in cardiovascular disease risk are scarce. We therefore performed a 20-year follow-up study of statin therapy in children.

Methods
214 FH patients, previously randomized into a placebo-controlled trial evaluating the 2-year efficacy and safety of pravastatin, were invited for a follow-up visit, together with their 95 unaffected siblings. Participants completed a questionnaire, gave blood and underwent a carotid intima-media thickness (c-IMT) measurement. The cardiovascular disease incidence was compared to that of their 156 affected parents.

Results
Of the original cohort, 261 (84%) participants visited the hospital; data on cardiovascular events and cardiovascular mortality were available for 95% and 100%, respectively. Mean LDL-C levels in FH patients were decreased by 32% since baseline and 37 (20%) patients achieved treatment goals (<100 mg/dL). Mean c-IMT progression over the entire follow-up period was 0.0056 mm/year and 0.0057 mm/year (p=0.663) for FH patients and siblings, respectively. The cumulative incidence of cardiovascular morbidity and cardiovascular mortality at the age of 39 years was lower in the FH patients compared to their affected parents (0.6% versus 26.3%; p<0.001 and 0% versus 7.1%; p<0.001, respectively).

Conclusion
The present findings indicate that statin initiation during childhood in FH patients normalizes c-IMT progression and reduces cardiovascular disease risk in adulthood.
The influence of contextual (child abuse directed) information on the interpretation of radiographs of young children with a femoral fracture

M.H.J. Loos1, W.M. Allema2, R. Bakx3, R.D. Stoel5, R.R. van Rijn4, W.A. Karst6

Affiliations:
1 Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Paediatric Surgery, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
2 Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Paediatric Surgery, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
3 Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Paediatric Surgery, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
4 Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Radiology, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; Department of Forensic Medicine, Section on Forensic Pediatrics, Netherlands Forensic Institute, PO Box 24044, 2490 AA The Hague, The Netherlands.
5 Division Specialist Services and Expertise, Team Forensic Statistics, Netherlands Forensic Institute, PO Box 24044, 2490 AA The Hague, The Netherlands.
6 Department of Forensic Medicine, Section on Forensic Pediatrics, Netherlands Forensic Institute, PO Box 24044, 2490 AA The Hague, The Netherlands.

Keywords: Femur fracture, child abuse, contextual information, bias, non-accidental trauma

Rationale
Femoral fractures can result from accidental trauma, but non-accidental trauma (NAT) must be considered, especially in pre-ambulatory children. Identifying NAT is complicated and based on i.a. clinical history. Contextual information can influence health care professionals in their decision-making process regarding NAT. Our aim is to determine the influence of contextual information on the interpretation of radiographs as bias in diagnosing NAT in young children with a femoral fracture.

Methods
An electronic survey was designed with 9 radiographs from children (0-2 years) with a femoral shaft fracture. For each radiograph, two different stories of contextual information were designed (non-abuse vs. abuse context). One of the stories was randomly assigned to the participant, followed by a question on the interpretation of the fracture. The participants of the online survey were medical residents and staff members of different departments from several hospitals and institutions in the Netherlands.

Results
172 participants completed the survey. There was a significant effect of influence by contextual information (p 0.000); participants answered more towards child abuse as cause of the fracture when they were assigned to a story with an abuse context. Furthermore, there was no significant correlation between influence by contextual information and either years of experience, function or department.

Conclusion
Health care professionals are biased by contextual information when interpreting radiographs of femoral fractures of young children, regardless of their expertise level, function or department. It is important to prevent contextual bias as much as possible, with the recognition of its existence as a first step in this process.
The Impact of benzodiazepines and opioids on neurocognitive development in children

E.S.V. de Sonnaville, MD¹, M. Königs, PhD², H. Knoester, MD, PhD¹, H. van Ewijk, PhD⁴, K.J. Oostrom, PhD¹, J.B.M. van Woensel, MD, PhDⁱ, J. Oosterlaan, PhD²,³,⁴

Affiliations:
¹ Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Intensive Care, Amsterdam, The Netherlands,
² Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Emma Neuroscience Group, Amsterdam, The Netherlands,
³ Emma Children’s Hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, The Netherlands,
⁴ Vrije Universiteit, Clinical Neuropsychology section, Amsterdam, The Netherlands

Keywords: PICU, pediatric intensive care, neurocognitive development, IQ, memory, long-term, benzodiazepines, opioids, sedatives, analgesics, childFunction

Rationale
General anesthetics and sedatives are widely used at the Pediatric Intensive Care Unit (PICU). A number of animal studies have indicated that exposure of the immature brain to these agents may cause neurodegeneration. In adults, studies have shown an inverse association between cumulative doses of benzodiazepines and neurocognitive functioning. However, literature on children is scarce. The current study aims to explore the impact of benzodiazepines and opioids on neurocognitive development in children.

Methods
This study included children aged 6-12 years admitted to the PICU of the Academic Medical Centre Amsterdam during infancy or early childhood (max age 10 months) for respiratory insufficiency due to severe viral lower respiratory tract infections. All children required invasive ventilation and received midazolam as sedative and morphine as analgesic. Healthy peers acted as controls. We assessed full-scale IQ (FSIQ), verbal memory and verbal working memory. Children in the exposure and control group were matched for age, gender and socio-economic status.

Results
Currently, we have included 41 patients (24 males) and 41 controls (17 males). Mean (SD) age of patients and controls at follow-up was 8.6 (0.8) and 8.9 (1.0) years, respectively. Preliminary results indicate that, compared to healthy peers, children in the exposure group have a significantly lower FSIQ \( (p = 0.02) \); and a significantly poorer verbal memory, including both short \( (p = 0.04) \) and long term memory \( (p = 0.03) \).

Conclusion
Our preliminary results suggest that children with a history of mechanical ventilation and exposure to midazolam and morphine are at risk of decreased global neurocognitive functioning and verbal memory. We will further assess dose-response relationships in a broader range of outcome measures, including neurocognitive, behavioral and school functioning.
Neurocognitive development in perinatal HIV using combination antiretroviral therapy: a longitudinal study of the NOVICE cohort


Affiliations:
1 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Infectious Diseases, Amsterdam, the Netherlands.
2 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Clinical Research Office, Amsterdam, the Netherlands.
3 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Psychosocial Department, Amsterdam, the Netherlands.
* Both authors contributed equally.

Keywords: HIV neurocognitive development

Rationale
Neurocognitive impairment is a major concern for perinatally HIV (PHIV)-infected patients. It remains unknown how neurocognitive development during adolescence and young adulthood differs from that of healthy controls. We aimed to (1) evaluate if neurocognitive development in PHIV-infected patients on combination antiretroviral therapy (cART) is different from that of healthy peers, and (2) explore associations between HIV- and treatment-related variables and neurocognitive development.

Methods
We performed a longitudinal study comparing neurocognitive development in PHIV-infected patients and healthy age-, sex-, ethnicity- and socioeconomic status (SES)-matched controls. We assessed neurocognitive function at two different time points using standardized tests measuring intelligence (IQ), working memory, executive function, learning abilities and visual-motor function. We used linear mixed effects models to assess group-by-time interaction effects and to explore associations with HIV- and treatment related variables.

Results
21 PHIV-infected patients (mean age 18.0 years [SD 3.34]) and 23 controls (mean age 17.5 years [SD 2.75]) completed both assessments (26%, mean interval 4.6 years [SD 0.33]. Adjusted for adoption status, region of birth and IQ, we found no difference between groups in the development in the cognitive domains (group*time p>0.05). The difference in IQ score between PHIV-infected patients and controls decreased over time (adjusted: β 6.01, 95%CI 1.53–10.50, p=0.012). CDC classification, zenith HIV VL, nadir CD4+ T-cell and age of start cART did not impact the group-by-time interaction effect of IQ.

Conclusion
Our data suggest that despite an overall slightly less favorable IQ, neurocognition of PHIV-infected patients on long-term cART follows a normal developmental trajectory during adolescence and young adulthood.
Hypertension in childhood cancer survivors treated with potential nephrotoxic therapy: evaluation of prevalence and treatment risk factors

M.C.F. Pilon1, E.C.M. Kooijmans1,2, H.J.H. van der Pal2, A. Bökenkamp1, M.A. Veening2

Affiliations:
1 Emma’s Children's hospital, Amsterdam UMC, Vrije Universiteit Amsterdam, pediatric oncology, Amsterdam, the Netherlands.
2 Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands.

Keywords: hypertension, childhood cancer, childhood cancer survivors, late effects, nephrotoxic cancer treatment

Rationale
Hypertension is a known late effect in childhood cancer survivors (CCS) after nephrotoxic treatment. However, literature is inconclusive about the prevalence of and risk factors for hypertension in CCS. This nationwide cross-sectional cohort study aims to examine prevalence and risk factors of hypertension in CCS, treated with possible nephrotoxic cancer therapy.

Methods
All CCS (≥ 5 years post diagnosis), aged ≥ 18 years at time of study, treated between 1963–2002 with potential nephrotoxic chemotherapy (ifosfamide, cisplatin, carboplatin, high-dose (HD) cyclophosphamide), abdominal radiotherapy, total body irradiation (TBI), and/or nephrectomy, were eligible. Oncological data were retrieved from medical records. Renal function and blood pressure were measured at study visit. Logistic regression was used to determine the relationship between GFR and hypertension (defined as systolic blood pressure ≥140 and diastolic ≥90 mmHg). Multivariable regression analysis was performed to examine potential treatment risk factors. We adjusted for sex, BMI, and follow-up duration. P-value <0.05 was considered significant.

Results
Among 493 CCS, 47.7% was male. Median age at diagnosis was 5.0 years, median age at follow-up 32.0 years, and median follow-up time 25.0 years. Leukemia (31.3%), renal tumors (19.9%) and bone and soft tissue sarcomas (18.9%) were most prevalent diagnoses. The overall prevalence of hypertension was 18.0%. A lower GFR was associated with hypertension (OR 1.02, 95%CI 1.01-1.04). TBI (OR 2.82, 95%CI 1.16-6.84) and HD-ifosfamide (>16,000 mg/m²) (OR 2.49, 95%CI 1.21-5.14) were associated with hypertension. Abdominal irradiation was almost significant (OR 2.12, 95%CI 0.98-4.62, p=0.057).

Conclusion
In 18.0% of the CCS who received potential nephrotoxic treatment, hypertension was present. TBI and HD-ifosfamide were risk factors for hypertension, relevant for developing future treatment protocols and surveillance of CCS.
A Randomized Trial of Neonatal Platelet Transfusion Thresholds

Anna Curley*, Simon J. Stanworth*, Karen Willoughby, Susanna F. Fustolo-Gunnink, Vidheya Venkatesh, Cara Hudson, Alison Deary, Renate Hodge, Valerie Hopkins, Beatriz Lopez Santamaria, Ana Mora, Charlotte Llewelyn, Angela D’Amore, Rizwan Khan, Wes Onland, Enrico Lopriore, Karin Fijnvandraat, Helen New, Paul Clarke, Timothy Watts, on behalf of the PlaNeT2 and MATISSE collaborators

Affiliations:
Neonatal Intensive Care Unit, National Maternity Hospital, Dublin, Ireland (AC); Transfusion Medicine, NHS Blood and Transplant, Oxford, UK (SS); Department of Haematology, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK (SS); Radcliffe Department of Medicine, University of Oxford, and Oxford BRC Haematology Theme, UK (SS); Department of Obstetrics and Gynaecology, University of Cambridge, Cambridge, UK (KW); National Health Service Blood and Transplant, Clinical Trials Unit, Cambridge, UK (KW, CL, CH, AD, RH, VH, AM); Center for Clinical Transfusion Research, Sanquin Blood Supply, Leiden, the Netherlands (SG, KF); Department of Epidemiology, Leiden University Medical Center, Leiden, the Netherlands (SG); Department of Pediatric Hematology, Emma Children’s Hospital, Academic Medical Center, Amsterdam, the Netherlands (SG, KF); Neonatal Intensive Care Unit, Cloud Nine Hospital, Bangalore, India (VV); Neonatal Intensive Care Unit, Evelina London Children’s Hospital, Guy’s & St Thomas’ NHS Foundation Trust, London, UK (BLS, TW); University Maternity Hospital Limerick, Limerick, Ireland (RK); Department of Neonatology, Emma Children’s Hospital, Academic Medical Centre, Amsterdam, the Netherlands (WOO); Department of Neonatology, Leiden University Medical Center, Leiden, the Netherlands (EL); NHS Blood and Transplant, London, UK (HNI); Department of Hematology, Imperial College London, London, UK (HN); Neonatal Intensive Care Unit, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK (PC); Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, UK (PC). * - equal authorship

Keywords: neonatal thrombocytopenia, platelet transfusions

Rationale
Platelet transfusions are commonly used to prevent bleeding in non-bleeding thrombocytopenic preterm infants. Data are lacking to guide thresholds for prophylactic platelet transfusions in preterm neonates with severe thrombocytopenia.

Methods
In this multicenter randomized trial, infants born at <34 weeks’ gestation who developed severe thrombocytopenia were assigned to receive platelet transfusion at platelet count thresholds of 50x10^9/L or 25x10^9/L. Bleeding was documented prospectively using a validated bleeding assessment tool. The primary outcome was mortality or new major bleeding within 28 days of randomization.

Results
660 infants (median birthweight 740g and gestational age 26 weeks) were randomized. The percentage of infants who received at least one platelet transfusion was 90% (296/328) in the <50x10^9/L group, compared with 53% (177/331) in the <25x10^9/L group. A new major bleed or death occurred in 26% (85/324) in the <50x10^9/L group versus 19% (61/329) in the <25x10^9/L group (odds ratio 1.57, 95% CI 1.06-2.32). There was no significant difference between groups in rates of serious adverse events, excluding major bleeding (25% vs. 22%, respectively, OR 1.14, 95% CI 0.78–1.67).

Conclusion
Among preterm infants with severe thrombocytopenia, those randomized to receive platelet transfusions at a platelet count threshold <50x10^9/L had a significantly higher rate of mortality or major bleeding within 28 days of randomization than those in the <25x10^9/L group.
Maternal risk-based group B streptococcus screening strategy and sepsis calculator implementation

N.B. Achten1, J.W. Dorigo-Zetsma2, A.M.C. van Rossum3, R. Oostenbrink4, F.B. Plötz1

Affiliations:
1 Department of Pediatrics, Tergooi hospital, Blaricum, The Netherlands
2 Department of Medical Microbiology, Tergooi hospital, Blaricum, The Netherlands
3 Division of Infectious Diseases and Immunology, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands
4 Department of General Pediatrics, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands

Keywords: neonatal sepsis, sepsis calculator, GBS

Rationale
The sepsis calculator is used to guide antibiotic treatment for suspected early onset sepsis (EOS) in newborns. It utilizes maternal Group B Streptococcus (GBS) colonization status as a risk factor. We evaluated the use of risk-based GBS screening with the sepsis calculator and specifically whether this would affect sepsis calculator recommendations for empiric antibiotic therapy.

Methods
Newborns ≥35 weeks were prospectively screened for EOS risk factors. Newborns at risk for, or with signs of EOS were evaluated with the sepsis calculator, using maternal GBS status as clinically available at birth. After obtaining all GBS-results, including intrapartum test results, we reviewed if additional GBS status information would have yielded different results of the sepsis calculator, in particular the recommendation on start of empiric antibiotic therapy.

Results
Among 1877 newborns, 208 at-risk newborns were identified. GBS-status was ultimately obtained for 78% of at risk newborns, versus 14% at time of sepsis calculator appliance in clinic. Median EOS risk did not increase and sepsis calculator results remained unchanged in 97% of newborns after including all available GBS-results. We found no cases where empiric antibiotics were recommended due to adjusted GBS status. Positive maternal GBS status was mainly determined <48 hours before delivery, but this rarely revealed colonization that warranted intrapartum antibiotic prophylaxis.

Conclusion
A risk-based GBS screening strategy screening during pregnancy barely affects sepsis calculator results, in particular regarding the recommendation for empirical antibiotic therapy. Future research on sepsis calculator implementation should carefully consider local protocols and rapidity of intrapartum GBS screening.
Gut organoids, a promising model to study enterovirus infection and disease pathogenesis

I. Aknouch1,2, A. Sridhar1,2, K.J. Stittelaar3, K.C. Wolthers2*, D. Pajkrt1*

Affiliations:
1 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Infectious Diseases, Amsterdam, The Netherlands.
2 Department of Clinical Virology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.
3 Viroclinics Biosciences B.V., Rotterdam, The Netherlands.
* Both authors contributed equally.

Keywords: Enteroviruses, gut organoids, infection

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
In this study, we developed fetal gut derived gut organoids for virus infection. Crypt cells derived from 16 week old human fetal jejunum and ileum were proliferated and differentiated until they formed small intestinal organoids representing primary replication sites for EVs. We infected 16 week old intestinal organoids with two different enteroviruses, namely EV-A71 C1 and Coxsackie B3 virus GFP clone. The establishment of fetal gut derived intestinal organoids was visualized via the confocal microscopy.

Results
The fetal gut derived intestinal organoids expressed GFP, which allowed for tracking Coxsackie B3 infection. Additionally, we found that the organoids were susceptible to infection by EV71-C1 virus.

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.
Modular control in children with cerebral palsy during the development of walking

A. Bekius¹, J.N. Kerkman¹, C.S. Zandvoort¹, A. Daffertshofer¹, A.I. Buizer², J. Harlaar²,³, N. Dominici¹

Affiliations:
¹ Department of Human Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Institute of Brain and Behaviour Amsterdam, the Netherlands
² Department of Rehabilitation Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, the Netherlands
³ Department of Biomechanical Engineering, Delft University of Technology, the Netherlands

Keywords: Muscle synergies, modular control, cerebral palsy, walking.

Rationale
Cerebral palsy (CP) is a developmental motor disorder, caused by non-progressive lesions in an immature brain, which affects the development of walking. In typically developing (TD) children the number of muscle synergies involved in walking increases throughout the motor development from two during neonate stepping to four in toddlers when they start to walk independently. We investigated whether and how such modular organization of muscle activation differed in children with CP during development.

Methods
We recorded bilateral electromyography (EMG) (14-28 muscles) during treadmill and over-ground walking in 15 CP (uni- and bilateral) and 10 TD children (age range: 3-46 months). Patients were included based on high-risk of developing CP with abnormalities in brain magnetic resonance imaging. Muscle synergies were estimated using non-negative matrix factorization to EMG envelopes pooled across steps. We compared their number and pattern between CP and TD children.

Results
After the first independent steps, CP children required on average three muscle synergies to describe the bilateral muscle activation compared to four in TD children. Unilateral analysis revealed three muscle synergies for the affected compared to four for the non-affected side in the majority of unilateral CP children. During supported walking, severely affected CP children (GMFCS II/III) required two or three muscle synergies instead of four in age-matched TD children who walked independently.

Conclusion
The current results suggest that CP children use a simpler motor control strategy during walking compared to TD children, which seems to be side-specific in unilateral CP children.


Teenagers’ participation during family centered rounds

M. Bonnema¹, L. Groot¹, B. van Oort¹, J. Maaskant¹

Affiliations:
¹ Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, The Netherlands

Keywords: Family integrated care

Rationale
Participation of teenagers in healthcare may reduce anxiety and uncertainty, and make them feel in control. Family centered rounds (FCRs) may be excellent moments to put into practice the involvement of teenagers in their treatment and care. The aim of this study was to investigate the effect of active participation of teenagers during FCRs on information exchange and teamwork.

Methods
A survey was undertaken among teenagers by means of a questionnaire with twelve questions. The survey was executed before and after start of the implementation of teenagers’ participation in FCRs. In addition, qualitative data were collected from daily evaluations with teenagers, pediatric nurses and pediatricians for 6 months after start of the teenagers’ participation.

Results
We collected 58 and 45 questionnaires in the pre and post-intervention periods respectively. We found 10 out of the 12 items on the questionnaire improved. For example, we found significant improvements on the items “I understand what is going to happen” (p<0.05) and “I am well informed about the period after hospital admittance” (p<0.05). At first most teenagers are hesitant to participate in FCRs and they need encouragement by their parents. During the FCRs support by the nurses, e.g. by reciting their feelings, is important. Most teenagers show growing confidence and feel themselves member of the team.

“So you are all here to discuss on me and my illness? Well, listen I know best!”

Conclusion
Teenagers who participate in FCRs report better information exchange and teamwork. They appreciate their involvement in the FCRs, although they need support.
Prediction of mortality in severe acute malnutrition by faecal volatile organic compound analysis: a proof of concept study

D.A. van den Brink1,2, T. de Meij3, W.P. Voskuilj1,4,5

Affiliations:
1 Global Child Health Group, Emma Children’s Hospital, Amsterdam UMC, The Netherlands
2 Department of Pediatrics, Center for Liver, Digestive and Metabolic Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
3 Department of Pediatric Gastroenterology, Amsterdam UMC, Free University, The Netherlands
4 The Childhood Acute Illness & Nutrition Network (CHAIN), Nairobi, Kenya
5 Department of Pediatrics and Child Health, College of Medicine, University of Malawi, Blantyre, Malawi

Keywords: Malnutrition, VOCs, SAM, Microbiome, Biomarker, Machine-learning

Rationale
Undernutrition still has a severe impact on childhood mortality. In-patient mortality of children with severe acute malnutrition (SAM) remains high (>20%) even with strict adherence to WHO treatment protocols. Volatile organic compounds (VOC) provide a unique opportunity to investigate metabolic dysfunction and altered microbiota compositions in these children through a non-invasive procedure. Our aim is to determine if fecal VOC analysis could identify mortality or clinical deterioration in severely malnourished children.

Methods
VOCs were retrospectively analysed on faecal samples from 63 children (<5years) with complicated SAM, and 7 healthy controls; using field asymmetric ion mobility spectrometry (FAIMS). Using machine learning algorithms faecal VOC profile were analysed: SAM vs. controls; mortality < 5 days vs. survival; mortality < 3 days vs. survival; mortality < 3 days vs mortality on day 4 or 5.

Results
Mortality within 3 days could be separated from survival with high accuracy (AUC: 0.83; 95% CI: 0.67-1.0; P<0.0004). Mortality within 5 days could be separated from survival with fair accuracy [area under the receiver operating characteristic curve (AUC) or accuracy: 0.73; 95% CI: 0.59-0.87; P<0.002]. Mortality within 3 days could be separated from mortality on day 4 and 5 with fair accuracy (AUC: 0.77; 95% CI: 0.55-0.99; P<0.02).

Conclusion
Using machine-learning algorithms, mortality in children with complicated SAM can be predicted based on their VOC profiles. This opens up opportunities to further explore the clinical opportunities of faecal VOC analysis as a non-invasive biomarker.
High Frequency and Diversity of Parechovirus A in a Cohort of Malawian Children

L. Brouwer1, E. Karelehto1, A.X. Han2,3, X.V. Thomas1, A.H.L. Bruning1, J.C.J Calis4, M. Boele van Hensbroek4,5, B.M. Westerhuis1, D. Amarthalingam1, S.M. Koekkoek1, S.P. Rebers1, K.S. Phiri6, K.C. Wolthers1, D. Pajkrt4

Affiliations:
1 Department of Medical Microbiology, Laboratory of Clinical Virology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
2 Bioinformatics Institute, Agency for Science, Technology and Research (A*STAR), Singapore
3 Laboratory of Applied Evolutionary Biology, Department of Medical Microbiology, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
4 Department of Pediatric Intensive Care, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
5 Department of Pediatric Infectious Diseases, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
6 School of Public Health and Family Medicine, College of Medicine, University of Malawi, Blantyre, Malawi

Keywords: Parechovirus, Sub-Saharan Africa, Parechovirus Genotyping, Epidemiology, Prevalence, Children

Rationale
Human Parechoviruses (PeVs) are a known cause of CNS infection in young children, and are highly prevalent viruses worldwide. Over the last decades, several studies have been published on PeV epidemiology in Europe, Asia and North-America, while information on other continents is lacking. The aim of this study was to describe PeV circulation in a cohort of children in Malawi, Africa.

Methods
749 stool samples obtained from Malawian children aged 6 to 60 months were tested on PeV presence by real time PCR. We performed typing by phylogenetic analyses and Basic Local Alignment Search Theorem (BLAST).

Results
PeV was found in 57% of stool samples. Age was significantly associated with PeV positivity (p=0.01), with younger children being more often infected than older ones. PeV positivity was not significantly associated with any symptom groups (i.e. respiratory, gastro-intestinal and CNS symptoms and fever). We found 15 different PeV-types, of the currently 19 types identified. Importantly, we identified a new type, PeV-A20. PeV-A1, -A2 and -A3 were the most prevalent types (26.8%, 13.8% and 9.8% respectively).

Conclusion
The high prevalence of PeVs found in this study is remarkable. We found a vast genetic diversity of PeVs, with many recently identified types, and a new type, PeV-A20. Our data form an important contribution to the scarce data available on PeV epidemiology in Africa.
Respiratory insufficiency due to severe metabolic alkalosis in children presenting with Hypertrophic Pyloric Stenosis.

F.A.I.M. van den Bunder¹, L.W.E. van Heurn², J.P.M. Derikx³

Affiliations:
¹ Department of Paediatric Surgery, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands.

Key words: Pyloric stenosis, metabolic alkalosis, hypochloremia, hypokalemia, respiratory problems, apnea

Rationale
Infantile Hypertrophic Pyloric Stenosis (IHPS) is a common condition in young children. Due to the excessive loss of gastric fluids, IHPS could lead to severe dehydration and metabolic derangements. It is suggested metabolic alkalosis could have an effect on the central control of ventilation and respiratory drive and thus could lead to respiratory problems. The objective of this study is to determine the incidence of respiratory problems due to alkalosis in infants with IHPS and to examine a possible correlation between the alkalosis and respiratory problems.

Methods
Data were analyzed retrospectively from all patients with pyloric stenosis who underwent a pyloromyotomy at two tertiary pediatric surgical centers in Amsterdam between January 2007 and December 2017. We searched for respiratory complications in the hospital files and notes from admission until surgery and ranged the complications by a new developed classification based on parameters or intervention.

Results
In the study period 480 infants were diagnosed with IHPS, of whom 6 were excluded because of initial treatment in another hospital, brain disease and status after cardiopulmonary resuscitation. 401 were male and the median age was 33 days. Unfortunately we only have preliminary results. The final results and analyses are estimated to be available in December 2018/ January 2019.

Conclusion
No conclusion can be made so far, but we hypothesize a correlation between respiratory problems and severe metabolic alkalosis caused by IHPS.
Evaluation of the current post-transplantation Human Leukocyte Antigen antibody screening in pediatric renal transplant recipients

A. Demirok¹, C. Ranzijn², N. Lardy³, S. Florquin⁴, A. Bouts⁵

Affiliations:
¹ Amsterdam UMC, The Netherlands
² Department of Immunogenetics, Sanquin Diagnostic Services, Amsterdam, The Netherlands
³ Department of Immunogenetics, Sanquin Diagnostic Services, Amsterdam, The Netherlands
⁴ Pathology, Amsterdam UMC, Amsterdam, The Netherlands
⁵ Pediatric Nephrology Department, Emma Children's Hospital, Amsterdam UMC, Amsterdam, The Netherlands

Keywords: HLA-antibody, kidney transplantation, pediatric recipients

Rationale
The necessity of post-transplant monitoring for donor specific antibodies (DSA) is unclear. This study evaluates the clinical relevance of post-transplantation donor specific HLA antibodies in pediatric renal transplant recipients, aiming at better stratification of patients at risk of graft dysfunction, and better recommendations for post-transplant monitoring.

Methods
A cohort of 68 pediatric kidney recipients, involving 76 transplantations between 2004 and 2014, was studied retrospectively. All patients were screened for HLA antibodies at 1, 3, 6 and 12 months after transplantation, and yearly thereafter. Samples testing positive were further analyzed to detect DSA. A biopsy was performed on clinical indication. We studied the baseline characteristics of the patients with biopsy, with DSA, and with rejection. We assessed the effect of post-transplant DSA on clinical outcome, including antibody-mediated acute rejection and GFR decrease.

Results
In our cohort the prevalence of DSA was 19% (13/68 transplantations). Most patients with HLA antibodies after transplantation were DSA-positive (76%; 13/17). A clear association between DSA and subsequent rejection was found. At the end of the study period, a significant lower GFR was found in patients with biopsy, DSA or rejection.

Conclusion
Based on our observations we recommend routine post-transplantation screening for HLA and DSA. The presence of DSA justifies a renal biopsy even in the absence of clinical signs of rejection.
Stem cell derived brain organoids, a promising model to study enterovirus infection and disease pathogenesis

J. Depla1,2, A. Sridhar1,2, M. Evers3, K.C. Wolthers2*, D. Pajkrt1*

Affiliations:
1 Pediatric Infectious Diseases, Emma Children’s Hospital, Amsterdam UMC, the Netherlands.
2 Department of Clinical Virology, Amsterdam UMC, the Netherlands.
3 Department of Research and Development, uniQure, the Netherlands.
* Both authors contributed equally.

Keywords: Picornavirus, Brain organoids, CNS

Rationale
Picornaviruses commonly cause mild disease but can lead to severe CNS infection in children. Mainly due to lack of suitable model systems, their pathogenesis is poorly understood. New models to study picornavirus infection in the brain are needed to understand the underlying mechanisms. Brain organoids have proven increasingly to be useful to study human specific disease. Brain organoids are self-organizing 3D cultures derived from human stem cells that recapitulate the organ microenvironment. These brain organoids have the advantage of complex morphology over transformed cell lines and the advantage of its human origin over animal models.

Methods
From induced pluripotent stem cells, over the course of 40 days, brain organoids were formed. Organoids were characterized by immunostaining. Beta tubulin 3 (Tuj1) and paired box protein 6 (PAX6) were stained to respectively visualize neurons and neural progenitors. Besides the presence of neural cell types, the organoid morphology was studied. After characterization, brain organoids were transduced with an adeno associated virus expressing GFP. In the future, the organoids will be infected with HPeV3, EV71 and E68, members from picornavirus family known to cause CNS infection.

Results
We can establish the iPSC derived human brain organoid model. Organoids expressed GFP, which allowed for tracking infection in brain organoid.

Conclusion
We are able to establish brain organoids to study viral infection of the brain. This model will enable us to extend our knowledge on picornavirus infection leading to CNS damage.
Abstracts submitted to the Amsterdam Kindersymposium 2019

Matching psychosocial support needs of parents of a child with a chronic illness to a feasible intervention

M. Douma¹, L. Scholten¹, C. P. Bouman¹, H. A. van Oers¹, H. Maurice-Stam¹, L. Haverman¹, M. A. Grootenhuis¹,²

Affiliations:
¹ Psychosocial Department, Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, The Netherlands
² Prinses Maxima Center for Pediatric Oncology, Utrecht

Keywords: parents, chronic illness, support needs, psychosocial support, e-health, online intervention, coping skills

Rationale
Parents of children with a chronic illness (CI) are at risk for psychosocial problems such as depression. The aim of this study is to develop an online intervention for parents based on the Op Koers program by 1) exploring parental psychosocial support needs (important themes) and 2) practical preferences.

Methods
Parents were asked to complete an open access online questionnaire, and, for more in-depth information, invited to participate in a focus group or telephone interview. Descriptive statistics were used to describe background variables, support needs and information from the focus groups.

Results
In total, 272 parents (85% female, mean age 43.1 years, mean age children 10.7 years) completed the questionnaire. Three focus groups (15 parents) and seven telephone interviews were conducted. Results of the questionnaire showed that 51% of the parents have expressed the need for psychosocial support. Most important themes were: own emotional functioning, how to support their child, family functioning and practical support with authorities. The results from the questionnaire and focus groups showed that parents were somewhat reluctant to online support. However, they also report many logistical barriers, therefore the possibility to participate from home is preferable. After an explanation of how an online intervention works, parents in the focus groups report to be less reluctant.

Conclusion
Parents raising a child with CI need psychosocial support matched to their needs. Based on the outcomes of this study, we developed an online psychosocial group intervention: Op Koers Online for parents. An RCT to assess feasibility and effectiveness of the intervention is currently running.
Screening for Lysosomal Acid Lipase Deficiency: a retrospective data mining study and evaluation of screening criteria

L. Draijer¹, A. Bosch¹, A. Wiegman¹, B. Sjouke², M. Benninga¹, B. Koot¹

Affiliations:
¹ Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, Location Academic Medical Center, the Netherlands
² Department of Internal Medicine, Amsterdam UMC, Location Academic Medical Center, the Netherlands.

Keywords: Lysosomal Acid Lipase Deficiency, LAL-D, Wolman Disease, Cholesteryl Ester Storage Disease, children, screening, dyslipidemia

Rationale
Lysosomal Acid Lipase Deficiency (LAL-D) is a lysosomal storage disorder. In severe cases it can cause life-threatening organ failure due to lipid substrates accumulation, however mild phenotypes of this disorder are increasingly recognized. The aim of this study is to determine the number of missed LAL-D patients in a large pediatric hospital population.

Methods
In a retrospective data mining study the medical files of children who visited the outpatient clinic at a university hospital between 2000 and 2016 with high plasma low density lipoprotein cholesterol (LDL-C) levels were evaluated. Previously developed LAL-D screening criteria, with lipid and alanine aminotransferase (ALT) values adjusted for children, were used to analyze which children are suspect for LAL-D. For suspicion of LAL-D, at least 3 out of 5 screening criteria had to be met. Subsequently data on presentation and follow-up were collected to determine if the clinical picture was compatible with LAL-D.

Results
We identified 2037 children with high LDL-C levels. Of those, 36 children complied with ≥ 3 screening criteria. Thirty-one of those had an underlying disorder other than LAL-D that explained the abnormalities and in the 5 remaining children, ALT and lipid levels normalized spontaneously, thus excluding LAL-D.

Conclusion
This study shows that retrospective data mining is unlikely to yield a significant number of LAL-D cases in children. The screening algorithm adjusted for children seems useful and accurate in the selection of children for further testing, suggesting it can be applied prospectively, although further validation is warranted.
Laparoscopic versus open pediatric inguinal hernia repair: state of the art comparison and future perspectives from a systematic review and meta-analysis.

K.M.A. Dreuning1, S.C. Maat1, J.W.R. Twisk2, L.W.E. van Heurn1, J.P.M. Derikx1

Affiliations:
1. Department of Pediatric Surgery, Pediatric Surgical Centre of Amsterdam, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Amsterdam, The Netherlands.

Keywords: Child; Hernia, Inguinal; Laparoscopy

Rationale
Decisive level 1a evidence regarding the superiority of laparoscopic versus open pediatric inguinal hernia repair is lacking. An extensive meta-analysis on all relevant outcome measures is warranted.

Methods
A systematic literature search was performed querying PubMed, EMBASE, MEDLINE and the Cochrane Library databases. Randomized controlled trials (RCTs) comparing laparoscopic with open hernia repair in children (<18 years old) were considered eligible, without year or language restrictions. Heterogeneity was assessed and data were pooled using a random (heterogeneity >50%) effects model.

Results
Eight RCTs (n=733 children; age range: 4 months-16 years) were included in this meta-analysis. Laparoscopic and open hernia repair were performed in 375 and 358 children, respectively. Laparoscopic repair resulted in shorter bilateral operation time (WMD -5.41, 95% CI -6.34 to -4.48; p<.001; I²=0%), increased length of hospital stay (WMD 1.50, 95% CI -0.87 to 2.12; p<.001; I²= 0%), and a lower metachronous contralateral inguinal hernia rate (OR 0.10, 95% CI 0.02 to 0.58; p=.01; I²=0%). Overall complications, unilateral operation time and recurrence rate did not differ between laparoscopic and open repair, though large heterogeneity exists between the included studies. Indifferent findings tend to show a trend towards less postoperative pain and better cosmesis after laparoscopic repair.

Conclusion
No definitive conclusions can yet be drawn from the available literature. Execution of large, prospective randomized trials taking into account all relevant outcome measures, the use of different laparoscopic and anesthetic techniques, and costs, are inevitable to obtain homogenous results to decide on the superiority of one of either treatment strategy.

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Screening for child abuse at the Emergency Department in the Academic Hospital Paramaribo (Suriname)

L. Eeftinck Schattenkerk

Affiliations:

Keywords:

Rationale
Physical, emotional and sexual abuse of children is a major health problem in Suriname with a lifetime exposure of 86.8 – 95.8%. A more systematically approach for the detection of child abuse in the emergency department (ED) is urgently needed. Therefore the SPUTOVAMO-R, combined with a multidisciplinary meeting, is implemented at the ED. This study will analyze the prevalence of child abuse and evaluate the effectiveness of the screening.

Methods
All patients aged 0-16 visiting the ED of the AZP are screened using the SPUTOVAMO-R. In case of a positive screening test, the paediatrician should be consulted in order to assess the risk of child abuse. All positive tests are discussed during the two-weekly multidisciplinary meetings. Also, admitted patients without a screening test are discussed. Results are compared to available retrospective data from the same period in 2016.

Results
Out of 1227 eligible patients a total of 375 had a completed screening test. Of 64 positive screening test, 32 were consulted by a paediatrician. 50 Patients (4.1%) were eventually found to be abused of which 26 (52%) had a screening test. In the same period in 2016 a total of 28 cases of abuse were reported. Sexual abuse was mostly reported with 26 (52%) cases. The sensitivity, specificity, positive- and negative predictive value of the screening test were respectively 88.5%, 92.3%, 37.5% and 99.4%.

Conclusion
By screening at the ED of the Academic Hospital Paramaribo in combination with a multidisciplinary meeting the number of correct referrals almost doubled when compared with earlier data. The screening test itself showed fairly high sensitivity, specificity and negative predictive value. Though usage was still suboptimal screening could help detecting child abuse at this ED.
Risk factors of late-onset sepsis in preterm infants: a prospective multicenter case-control study

S. el Manouni el Hassani1,2, D.J.C. Berkhout1,2, H.J. Niemarkt1, S. Mann2, W.P. de Boode1, V. Cossey3, C.V. Hulzebos4, A.H. van Kaam4,5, B.W. Kramer9, R.A. van Lingen10, J.B. van Goudoever11,12, D.C. Vijlbrief13, M.M. van Weissenbruch7, M.A. Benninga1, N.K.H. de Boer14, T.G.J de Meij1

Affiliations:
1 Amsterdam UMC, Emma Children’s Hospital, Department of Pediatric Gastroenterology, University of Amsterdam, Amsterdam, the Netherlands
2 Amsterdam UMC, Emma Children’s Hospital, Department of Pediatric Gastroenterology, Vrije Universiteit, Amsterdam, the Netherlands
3 Máxima Medical Center, Neonatal Intensive Care Unit, Veldhoven, the Netherlands
4 Amalia Children’s Hospital, Radboud University Medical Center, Neonatal Intensive Care Unit, Radboud Institute for Health Sciences, Nijmegen, The Netherlands
5 University Hospitals Leuven, Neonatal Intensive Care Unit, Leuven, Belgium
6 Beatrix Children’s Hospital, University Medical Center, Neonatal Intensive Care Unit, Groningen, the Netherlands
7 Amsterdam UMC, Emma Children’s Hospital, Neonatal Intensive Care Unit, Vrije Universiteit, Amsterdam, the Netherlands
8 Amsterdam UMC, Emma Children’s Hospital, Neonatal Intensive Care Unit, University of Amsterdam, Amsterdam, the Netherlands
9 Maastricht University Medical Center, Department of Pediatrics, Maastricht, the Netherlands.
10 Amalia Children’s Centre, Isala, Neonatal Intensive Care Unit, Zwolle, the Netherlands.
11 Amsterdam UMC, Emma Children’s Hospital, Department of Pediatrics, University of Amsterdam, Amsterdam, the Netherlands
12 Amsterdam UMC, Emma Children’s Hospital, Department of Pediatrics, Vrije Universiteit, Amsterdam, the Netherlands
13 Wilhelmina Children’s Hospital, University Medical Center Utrecht, Neonatal Intensive Care Unit, Utrecht University, Utrecht, the Netherlands.
14 Amsterdam UMC, Department of Gastroenterology and Hepatology, Vrije Universiteit, Amsterdam, the Netherlands

Keywords: Risk factors; parenteral feeding; breast fed; late-onset sepsis; Coagulase Negative staphylococcus.

Rationale
Late-onset sepsis (LOS) in preterm infants is a leading cause of mortality and morbidity. Timely recognition and initiation of antibiotics are important factors for improved outcome. Identification of risk factors could allow for selection of infants at increased risk for LOS. Therefore, we aimed to identify risk factors for the development of LOS.

Methods
In this prospective multicenter case-control study, preterm infants, born ≤30 weeks of gestation, were included at nine neonatal intensive care units. Detailed demographical and clinical data were collected daily up to day 28 postnatally. Clinical and demographic risk factors were identified using univariate and multivariate regression analyses in a 1:1 matched case-control cohort.

Results
In total, 755 infants were included, including 194 LOS cases (41 Gram-negative, 152 Gram-positive, 1 fungus). In the case-control cohort, every additional day of parenteral feeding increased the risk for LOS (Odds Ratio [95% CI]; p-value; 1.29 [1.07-1.55]; 0.006), whereas antibiotics administration decreased this risk (0.08 [0.01-0.88], 0.039). These findings could largely be attributed to specific LOS causative pathogens, since these predictive factors could be identified for gram-positive, but not for gram-negative LOS cases. Specifically cephalosporins administration prior to clinical onset was inversely related with Coagulase-negative Staphylococci-LOS (CoNS-LOS) development. Formula feeding was an independent risk factor for development of CoNS-LOS (3.779 [1.257-11.363], 0.018).
**Conclusion** Length of parenteral feeding was associated with LOS, whereas breastmilk administration was protective against CoNS-LOS. A rapid advancement of enteral feeding, preferably with breastmilk, may proportionally reduce the number of parenteral feeding days, and consequently the risk for LOS.
Fecal amino acid profiles as novel biomarker for preclinical detection of severe NEC: A pilot study

S. el Manouni el Hassani1,2, E.A. Struys3, H.J., A.Bakkali3, E.W. Jansen3, A.H. van Kaam4,5, M.M van Weissenbruch5, H.J. Niemarkt6, M.A. Benninga1, N.K.H. de Boer7, T.G.J. de Meij2

Affiliations:
1. Department of Pediatric Gastroenterology, Amsterdam UMC, University of Amsterdam, Emma Children’s Hospital, Amsterdam, the Netherlands
2. Department of Pediatric Gastroenterology, Amsterdam UMC, Vrije Universiteit, Emma Children’s Hospital, Amsterdam, the Netherlands
3. Department of Clinical Chemistry, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands.
4. Neonatal Intensive Care Unit, Amsterdam UMC, University of Amsterdam, Emma Children’s Hospital, Amsterdam, the Netherlands
5. Neonatal Intensive Care Unit, Vrije Universiteit, Amsterdam, the Netherlands
6. Neonatal Intensive Care Unit, Máxima Medical Center, Veldhoven, the Netherlands
7. Department of Gastroenterology and Hepatology, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands

Keywords: fecal biomarkers, NEC, amino acids

Rationale
To date, no diagnostic test for preclinical detection of necrotizing enterocolitis (NEC) is available, while early diagnosis is considered key prognostic factor. Recently, fecal amino acid analysis has been shown to have potential as non-invasive biomarker for pediatric inflammatory bowel disease, reflecting altered metabolic, microbial and inflammatory state. Therefore, we aimed to assess the potential of fecal amino-acids as novel, non-invasive early diagnostic biomarker for (NEC) in preterm born infants.

Methods
Current study was nested in an ongoing prospective multicenter cohort study. Fecal samples obtained from infants born at a gestational age ≤30 weeks were collected daily, up to 28 days of life. Patients with severe NEC (Bells stage IIIA/B) were strictly matched (1:1) with non-NEC controls, based on gestational age, birth weight, feeding practice and center of birth. Amino acid profiles were analyzed from fecal samples collected one day prior to clinical diagnosis of NEC by means of dedicated amino acid analysis (AAA).

Results
In total, 11 NEC cases were included. We found that 6 of 42 measured fecal amino acids were significantly elevated in NEC cases compared to the controls, including alanine (ratio 1.8, p-value 0.034), isoleucine (ratio 2.5, p-value 0.019), leucine (ratio 2.5, p-value 0.019), phenylalanine (ratio 2.5, p-value 0.047), proline (ratio 2.3, p-value 0.10), and valine (ratio 2.8, p-value 0.013).

Conclusion
We demonstrated that AAA seems to have potential as non-invasive early diagnostic biomarker for NEC. Furthermore, these observations may increase understanding of pathophysiology of NEC. Results will be externally validated in a larger cohort.
Implementing the KLIK PROM tool in clinical care; the healthcare professional’s point of view.

A.W. Gathier1, H.A. van Oers1, L. Teela1, M.M. van Muilekom1, M.A. Grootenhuis2, L. Haverman1

Affiliations:
1 Amsterdam UMC, University of Amsterdam, Emma Children’s Hospital, Psychosocial Department, Amsterdam, the Netherlands
2 Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

Keywords: PROMs, quality of life, clinical care, implementation, evaluation, professionals

Rationale
KLIK (www.hetklikt.nu) is an evidenced-based Patient Reported Outcome Measures (PROMs) portal developed in the Emma Children’s Hospital and implemented in clinical care in >20 Dutch hospitals. Patients and/or parents complete questionnaires about symptoms, psychosocial functioning and/or quality of life. Answers are converted into an ePROfile and discussed with the patient during consultation. This study aims to get insight in the KLIK implementation from the professional’s point of view.

Methods
Prior to annual KLIK evaluation meetings with the multidisciplinary teams, an online questionnaire is sent to all team members. This questionnaire consists of questions regarding (A) support of the KLIK team, (B) experiences with the ePROfile, (C) experiences of patients, (D) usability of KLIK, (E) feedback of PROMs in the ePROfile, (F) satisfaction with the PROMs, (G) suggestions for improvement, (H) advantages and disadvantages. Descriptive analyses are used.

Results
100 professionals of 21 multidisciplinary teams participated (response-rate 58%). Preliminary results show that (A) 69% experience enough support of the KLIK team, (B) 71% think KLIK improves their consultation, (C) 53% think patients/parents are satisfied with KLIK, (D) 75% think KLIK is easy to use, (E) 81% are satisfied with the feedback in the ePROfile, (F) 57% are satisfied with the current PROMs, and (G,H), improvements and (dis)advantages of KLIK are mentioned.

Conclusion
Most professionals are satisfied with the usability of KLIK. Room for improvement involves more relevant PROMs (e.g. PROMIS) and overcoming mentioned barriers (e.g. integration with EPIC). In the future, we will evaluate KLIK from the patient’s and parent’s point of view.
White matter hyperintensities in HIV: a comparison between children and adults

J.G. van Genderen1, M. Van den Hof MD1, R.A. Van Zoest MD2, M.W.A. Caan PhD3,4, F.W.N.M. Wit MD, PhD5, P. Reiss MD, PhD6, D. Pajkrt MD, PhD1 on behalf of the NOVICE and AGEhIV cohort studies

Affiliations:
1 Department of Pediatric Infectious Diseases, Emma’s Children’s Hospital, Amsterdam UMC, University of Amsterdam
2 Amsterdam Institute for Global Health and Development (AIGHD)
3 Department of Radiology, Amsterdam UMC, University of Amsterdam
4 Department of Biomedical Engineering and Physics, Amsterdam UMC, University of Amsterdam
5 HIV Monitoring Foundation, Amsterdam, The Netherlands
6 Department of Global Health, Amsterdam UMC, University of Amsterdam

Keywords: HIV, White matter hyperintensities, children, adults

Rationale
Despite effective combination antiretroviral therapy (cART), white matter hyperintensities (WMHs) remain present in people with HIV. To gain more insight in WMHs at different ages, we compared their presence and location in ongoing cohorts of perinatally HIV-infected children and adults ageing with HIV.

Methods
Fluid-attenuated inversion recovery MRI scans obtained at cohort entry from 31 HIV-infected children and 74 HIV-infected adults were assessed for the number, volume and location (periventricular vs. deep) of WMHs. WMHs were labeled periventricular when adjacent to or within 10mm of lateral ventricles. WMH volume was adjusted for intracranial volume. To compare non-parametric variables we used the Mann-Whitney U or Fisher’s exact test for numeric or categorical data, respectively.

Results
The median age was 13.8y [IQR:11.4–15.9] vs. 53.4y [IQR:48.3–60.8] respectively in children and adults; 27/31 children (87%) and all adults were on cART with viral load <200copies/mL. We excluded four children from MRI analysis following poor scan quality. WMHs were seen in 16/27 (52%) children and all adults. Adults had a higher number (median[IQR]: 18[9.3–37.5] vs. 5[2.0–12.5], p<0.001) and higher total volume of WMHs (median[IQR]: 1182[425–2617] vs. 109[61.7–625] mm3, p<0.001). Neither deep WMHs prevalence (100%vs.96%) nor number of deep WMHs (median[IQR]: 3.0[2.0–11.3] vs. 11[3.0–27.8]) differed significantly between children and adults, respectively. Periventricular WMHs were significantly more prevalent in adults (100%) compared to children (56%)(p<0.001).

Conclusion
WMHs were more prevalent in adults. The difference in location of WMHs between adults and children suggests a different underlying pathogenesis.
Bleeding phenotype and baseline factor VIII activity in patients with non-severe hemophilia A – preliminary data of a retrospective cohort study

F.R. Kloosterman1*, A. Abdi1*, C.L. Eckhardt1, S.C. Gouw1 [...], D.P. Hart2, C.J. Fijnvandraat1 for the INSIGHT investigators

Affiliations:
1 Department of Pediatric Hematology, Immunology and Infectious Diseases, Emma Children’s Hospital, Amsterdam UMC, location AMC, Amsterdam, The Netherlands
2 Royal London Hospital, Barts and The London School of Medicine and Dentistry, London, United Kingdom

Keywords: Hemophilia, bleeding phenotype, factor VIII activity

Rationale
Severe hemophilia A (SHA) patients have an increased risk for inhibitor development during the first exposures to factor VIII (FVIII) concentrate. Novel treatment therapies, such as non-replacement therapy and gene therapy, have the potential to convert a severe phenotype into a mild phenotype. If previously untreated SHA patients would be treated with these therapies, it might postpone FVIII exposure, possibly deferring their risk for inhibitor development. Currently there is insufficient data on the natural course of non-severe hemophilia A (NSHA). Therefore, the aims of this study are to assess the timing of FVIII exposures and to calculate the Annualized Bleeding Rate (ABR) in NSHA.

Methods
We performed an analysis in the data of the INSIGHT case-control study that included NSHA inhibitor and non-inhibitor patients (FVIII baseline level 2-40 IU/dl). For inhibitor patients, data on FVIII exposure days (EDs) were collected until the onset of inhibitor development. In order to interpret these data to resemble the unselected complete cohort of the INSIGHT study, reweighting with the inverse of the sampling fraction was used. We assessed the age at the first exposures to FVIII until the 20th ED in different categories of baseline FVIII level. Furthermore, we will analyze the ABR for spontaneous major bleeds. Sub-analyses will be performed based on year of birth and secular time periods for treatment strategies.

Results
For the current study we included 379 patients. In patients with a FVIII level between 2-5 IU/dl, the median age at the 1st ED was: 17 years (IQR 6-39), the median age at the 5th ED was: 20 years (IQR 8-43), the median age at the 10th ED was: 21 years (IQR 9-46) and the median age at the 20th ED was: 30 years (IQR 12-51). In patients with a FVIII level between 5-15 IU/dl the median age at the 1st ED was: 24 years (IQR 9-43), the median age at the 5st ED was 28 years (IQR 11-47), the median age at the 10th ED was 29 years (IQR 12-50) and the median age at the 20th ED was 31 years (IQR 14-55). The ABR results will be presented during the conference, as verification of the spontaneous bleeds is currently being performed.

Conclusion
Our preliminary findings show that patients with a baseline FVIII level of 5-15 IU/dl had their first FVIII infusions at higher ages than patients with a baseline FVIII level of 2-5 IU/dl.
A preconceptional lifestyle intervention and cardiovascular health in the offspring: A follow-up of a randomised controlled trial

T. den Harink¹, A. van Deutekom², H. Groen³, A. Hoek³, T. Roseboom¹

Affiliations:
¹ Department of Clinical Epidemiology, Biostatistics and Bioinformatics/Department of Obstetrics and Gynaecology
² Department of Pediatric Cardiology, Emma Children’s Hospital, Amsterdam UMC, The Netherlands
³ Department of Obstetrics and Gynaecology, University Medical Center Groningen

Keywords: maternal obesity, lifestyle intervention, cardiovascular health, echocardiography

Rationale
Maternal obesity during pregnancy may negatively influence cardiac development in the offspring with adverse long-term cardiovascular outcomes. Knowledge about how maternal obesity affects offspring health is important for developing appropriate preventive measures, such as a maternal lifestyle intervention. In the present study we aim to assess the effects of a preconceptional lifestyle intervention in obese women on the cardiovascular health of the offspring. We hypothesize that children born from mothers that received a lifestyle intervention prior to pregnancy will have enhanced cardiac health.

Methods
This is a follow up of a randomised controlled trial that included women with obesity. A 6 months lifestyle intervention (aimed at 5% weight loss and/or a body mass index (BMI) of ≤29 kg/m²) prior to fertility care was given to the intervention group and a control group received fertility care as usual. We assessed cardiovascular health of the offspring by means of echocardiography.

Results
Preliminary results are presented of thirty-eight children, mean age 6.2 years (SD 0.87), 58% girls. Children of women who received the lifestyle intervention (n= 14) had a thinner interventricular septum (5.3 mm [SD 0.63] vs. 5.9 mm [SD 0.68], P=0.01) and an increased ejection fraction (60.6% [SD 3.8] vs. 56.6% [SD 4.6], P=0.02) compared to children of controls (n= 24). Both these results are considered indices of better cardiovascular function in clinical care.

Conclusion
Our results suggest for the first time that a maternal lifestyle intervention before pregnancy improves echocardiographic indices of cardiovascular function in children, signalling improved cardiovascular health.
Abstracts submitted to the Amsterdam Kindersymposium 2019

Executive functions in preterm and/or low birthweight children: a meta-analysis.

Carolien A. van Houdt1,2, Jaap Oosterlaan3,4, Aleid G. van Wassenaer-Leemhuis1, Anton H. van Kaam4,6, Cornelieke S.H. Aarnoudse-Moens1,2,3,5

Affiliations:
1 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Neonatology, Meibergdreef 9, Amsterdam, The Netherlands
2 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Emma Neuroscience Group, Meibergdreef 9, Amsterdam, The Netherlands
3 Amsterdam UMC, Vrije Universiteit Amsterdam, Clinical Neuropsychology section, de Boelelaan 1117, Amsterdam, The Netherlands
4 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Pediatrics, Meibergdreef 9, Amsterdam, The Netherlands
5 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Psychosocial Department, Meibergdreef 9, Amsterdam, The Netherlands
6 Amsterdam UMC, Vrije Universiteit Amsterdam, Neonatology, de Boelelaan 1117, Amsterdam, The Netherlands

Keywords: Executive function, preterm birth, working memory, inhibition, cognitive flexibility

Rationale
PT/LBW children are reported to have poor executive function (EF), which may crucially impact behavior and academic achievement. We conducted a meta-analysis of studies on EF in PT/LBW children to investigate the magnitude of EF deficits and its dependency on GA, sex, age at assessment and year of birth.

Methods
PubMed, PsychINFO and Web Of Science were searched for studies reporting on EF in PT/LBW children and term controls born ≥ 1990, assessed at mean age of ≥ four years. Studies were included if at least five studies reported on the same EF measures.

Results
Thirty-five studies (3360 PT/LBW, 2812 controls) were included. PT/LBW children performed 0.5 standardized mean difference (SMD) lower on working memory and cognitive flexibility and 0.4 SMD lower on inhibition. SMDs for working memory, cognitive flexibility and inhibition did not significantly differ from each other. Meta-regression showed that heterogeneity in SMDs for working memory and inhibition could not be explained by study differences in GA, sex, age at assessment or year of birth.

Conclusion
PT/LBW children born since the 1990’s perform half a SMD below term born peers on EF; a deficit which does not seem to improve with more recent advances in medical care nor with increasing age.
Epidural-Related Fever and Maternal and Neonatal Morbidity: A Systematic Review and Meta-Analysis

S.J. Jansen¹, E. Lopriore², C. Naaktgeboren³, M. Sueters⁴, J. Limpens⁵, E. van Leeuwen⁶, V. Bekker⁷

Affiliations:
1. Department of Neonatology, Leiden University Medical Center (LUMC), Leiden, The Netherlands
2. University Medical Center Utrecht (UMCU), Department of Data Management & Research Support, Julius Center for Health Science and Primary Care
3. Department of Obstetrics and Gynecology, Leiden University Medical Center (LUMC), Leiden, The Netherlands
4. Department of Obstetrics and Gynecology, Academic Medical Center (AMC), Amsterdam, The Netherlands
5. Academic Medical Center, Center for Infection and Immunity Amsterdam (CINIMA), Emma Children’s Hospital, Academic Medical Center (AMC), Amsterdam, The Netherlands
6. Medical Library, Academic Medical Center (AMC) - University of Amsterdam, Amsterdam, The Netherlands

Keywords: Epidural analgesia; fever; neonatal sepsis; antibiotics

Rationale
To investigate the association between epidural analgesia and intrapartum fever, maternal and neonatal sepsis and antibiotic treatment.

Methods
We searched Pubmed, Cochrane, MEDLINE and Embase for randomized controlled trials (RCT) and observational cohort studies from January 1946 through December 2017. A total of 502 studies were identified with 84 for full-text eligibility. Data was analyzed for RCT’s and observational cohort studies separately. Meta-analyses were performed using the random effects model of Mantel-Haenszel to produce summary risk ratios (RR) with 95% confidence intervals (CI).

Results
Nine RCTs and 14 observational cohort studies involving 578,127 parturients were included. RRs for maternal fever for the RCT and cohort analyses were 3.87 (95% CI, 2.86-5.23) and 5.40 (95% CI, 4.13-7.08), respectively. Although meta-analysis of data from observational studies showed an increased risk of maternal and neonatal antibiotic treatment after epidural analgesia (maternal antibiotic treatment: RR 3.71; 95% CI, 1.19-11.57; neonatal antibiotic treatment: RR 2.47; 95% CI, 1.11-5.52), no increased risk for maternal infection was found in either analysis. For both analyses, neonates born to women with epidural were not evaluated more often for a suspected sepsis. Neither analyses reported an increased rate of neonatal sepsis after epidural analgesia, although data were insufficient to be conclusive. Within the RCT analyses, women with epidural analgesia and their neonates were not treated more frequently with antibiotics.

Conclusion
Epidural analgesia increases the risk of intrapartum fever. Despite increased maternal and neonatal antibiotic treatment, no increased risk of maternal or neonatal sepsis was observed. Viewing epidural-related intrapartum fever as a risk factor may therefore lead to antibiotic overtreatment.
The potential coverage of polysaccharide vaccines for invasive GBS disease in neonates in the Netherlands (1987-2016)

M.N. van Kassel¹, D. Jamrozy², M.C. Brouwer³, M.W. Bijlsma¹³, A. van der Ende⁴, D. van de Beek⁴

Affiliations:
¹ Department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, The Netherlands
² Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, United Kingdom
³ Department of Pediatrics, Amsterdam UMC, The Netherlands
⁴ Department of Medical Microbiology, Netherlands Reference Laboratory for Bacterial Meningitis, Amsterdam UMC, The Netherlands

Keywords: GBS, streptococcus agalactiae, neonates, sepsis, meningitis, bacterial infections, vaccine, serotype

Rationale
Streptococcus agalactiae (GBS) is the most common cause of sepsis and meningitis in neonates. Despite intrapartum antibiotic prophylaxis incidence rates of neonatal invasive GBS disease are increasing in the Netherlands. Vaccination during pregnancy is a promising new strategy to protect newborns against GBS. Monovalent (serotype III), Trivalent (serotypes Ia, Ib, III) and pentavalent (serotypes Ia, Ib, II, III, V) vaccines against the GBS polysaccharide capsule have been tested in phase 2 studies and are safe and immunogenic. We present the potential coverage of these vaccines in the Netherlands.

Methods
We used nationwide surveillance data from the Netherlands Reference Laboratory for Bacterial Meningitis to identify all neonates (0-3 months old) with GBS meningitis or sepsis between 1987–2016. Serotyping with both latex agglutination test and whole genome sequencing (WGS) was performed.

Results
1399 GBS episodes were identified. 876 (63%) were cultured from blood, 177 (17%) from CSF and 346 (25%) from CSF and blood. Based on latex agglutination (n=1370[98%]), maximum coverage was 61%, 85% and 95% for the mono-, tri- and pentavalent vaccine respectively. Based on WGS (n=1341[96%]), maximum coverage was 61%, 87% and 97% for the mono-, tri- and pentavalent vaccine.

Conclusion
A vaccine against serotypes Ia, Ib, II, III, V would have covered 95-97% of all GBS isolates from Dutch neonates with GBS meningitis and sepsis over the last three decades.
The relative contributions of genetic and environmental factors on cortisol metabolism at pre-, mid- and post-pubertal ages

B.J. van Keulen 1, C.V. Dolan 2, R. Andrew 3, B. Walker 3, D.I. Boomsma 2, J. Rotteveel 1, M.J.J. Finken 1

Affiliations:
1 Department Pediatric Endocrinology, Emma Children’s Hospital, Amsterdam UMC, VU University Medical Center, The Netherlands
2 Department Biological Psychology, Vrije Universiteit, Amsterdam, The Netherlands
3 Endocrinology unit, Queen’s Medical Research Institute, Edinburgh, Scotland

Keywords: cortisol metabolism, heritability, puberty

Rationale
Inter-individual differences in the metabolism of cortisol have been postulated to emerge during puberty, and might be explained by a complex interplay of genetic and environmental factors. The aim of the current study was to estimate the relative contributions of genetic, shared, and unshared environmental factors on cortisol metabolism in a longitudinal cohort of twins assessed at pre-pubertal, mid-pubertal and post-pubertal ages.

Methods
Participants were enrolled from a population-based twin register. Early-morning urine was collected at pre-pubertal, mid-pubertal and post-pubertal ages. Cortisol metabolites were measured, and ratios were calculated, representing the activities of various enzymes involved in cortisol metabolism. Data were analyzed using a model-fitting approach to obtain the relative influences of additive genetic effects (A), dominance effects (D), shared (C) and unshared (E) environmental factors.

Results
94 monozygotic and 124 dizygotic twins were included. 213, 167 and 162 samples were analyzed at pre-pubertal, mid-pubertal and post-pubertal ages, respectively. For cortisol production rate, broad heritability was: 43%, 29% and 0%; shared environment was 0%, 0% and 23%; unshared environment was 60%, 71% and 77%, respectively. For 5β-reductase-activity, broad heritability was 40%, 61% and 26%; shared environment was 32%, 0% and 25%; unshared environment was 28%, 39% and 50%, respectively. For the majority of other indices, the contribution of unshared environmental factors also increased with age.

Conclusion
There were considerable differences in the relative contributions of genetic and environmental factors. With few exceptions, the contribution of unshared environmental factors was found to increase with age, implicating that individual circumstances seem to play a predominant role in later life.
Reference values and prediction equations for Volumetric Capnography indices in lung healthy mechanically ventilated children

R. Klein-Blommert¹, Ismail Arrahmani², Merel Weel³

Affiliations:
¹ Department of Pediatric intensive care, Emma Children’s Hospital, Amsterdam UMC, The Netherlands

Keywords: Mechanical ventilation, Volumetric Capnography

Rationale
Volumetric capnography provides the clinician more insight into physiological and ventilatory parameters like physiological and alveolar dead space (Vdphys, VDalv), alveolar ventilation (AV) and volume expired of carbon dioxide (VCO2). Reference values for Vcap are unknown especially for children. This study has examined whether there is a difference between the Vcap parameters in mechanically ventilated patient with or without a lung disease. Secondly, we aimed to construct an equation able to predict the Vcap parameters in lung healthy mechanically ventilated patients.

Methods
266 mechanically ventilated children were included. Oxygenation Index ≤ 2.5 defined absence of lung disease. Outcome variables included physiological and alveolar dead space VCO2 and alveolar ventilation. Univariate comparison of baseline characteristics, ventilation and physiological parameters and Vcap indices was performed using Student’s t-test. Correlations were calculated between several patient’s characteristics and Vcap indices. Multivariable linear regression analysis was performed to formulate the best fitted prediction equation for VCO2 and VDalv.

Results
VDalv and VCO2 were significantly (P value <0.001) different in lung healthy mechanically ventilated children compared to lung diseased mechanically ventilated children. A prediction equation for these indices was defined. VCO2 found to be dependent on tube size, tidal volume, inspiratory time and gender (adjusted R² = 0.88), whereas VDalv was dependent on tidal volume (adjusted R² = 0.52). Correlation analysis and visual evaluation of scatter plots indicated actual body weight to be the best variable to standardize Vcap indices.

Conclusion
Reference values and equations could be defined for VDalv and VCO2. More subsequent research is warranted to confirm the current findings and validate the presented prediction equations.
Reduction of acylcarnitines restores electrophysiological abnormalities in VLCAD deficient hiPSC-cardiomyocytes

Suzan J.G. Knottnerus1,2,*, Isabella Mengarelli3,*, Rob C.I. Wüst1, Vincent Portero3, Lodewijk IJlst1, Jeannette C. Bleeker1,2, Sacha Ferdinandusse1, Ronald J.A. Wanders1, Frits A. Wijburg4, Gepke Visser1,2, Kaomei Guan6, Arie O. Verkerk4,5, Riekelt H. Houtkooper1,*, Connie R. Bezzina3,*

Affiliations:
1 Laboratory Genetic Metabolic Diseases, Academic Medical Centre, Amsterdam, The Netherlands
2 Department of Paediatric Metabolic Diseases, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, The Netherlands
3 Department of Experimental Cardiology, Academic Medical Centre, Amsterdam, The Netherlands
4 Department of Paediatric Metabolic Diseases, Emma Children's Hospital, Academic Medical Centre, Amsterdam, The Netherlands
5 Department of Medical Biology, Academic Medical Centre, Amsterdam, The Netherlands
6 Institute of Pharmacology and Toxicology, Technische Universität Dresden, Dresden, Germany

Keywords: hipsc cardiomyocytes, vlcadd

Rationale
Patients with a deficiency in very long-chain acyl-CoA dehydrogenase (VLCAD), an enzyme that catalyzes the first step in the mitochondrial beta-oxidation, are at risk of developing cardiac symptoms including arrhythmias. Treatment options are scarce, partly because the exact underlying mechanism leading to arrhythmias in these patients is currently unknown. The electrophysiological derangement may be related to either (1) energy shortage because of defective fat utilization, or (2) the accumulation of fatty acid oxidation intermediates i.e. long-chain acyl-CoAs and/or notably long-chain acylcarnitines. To address this question, we have used a pharmacological approach involving either enhanced mitochondrial biogenesis or substrate reduction in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) derived from VLCAD deficient (VLCADD) patients.

Methods
We measured electrophysiological and biochemical parameters in cardiomyocytes from one control and two VLCADD patient-derived hiPSC lines: VLCAD1 (p.Val283Ala/p.Glu381del), and VLCAD2 (homozygous for c.104delC). We used two strategies to reduce the accumulation of acyl-CoAs and/or acylcarnitines by pre-incubating the cells 48h with (1) 50 µM resveratrol to increase mitochondrial biogenesis, or (2) 100 µM etomoxir – a powerful inhibitor of the rate controlling enzyme carnitinepalmitoyl transferase 1 (CPT1) - to reduce the fatty acid oxidation flux.

Results
When cultured under standard conditions, the cardiomyocytes from the two VLCADD hiPSC lines accumulated long-chain acylcarnitines. Action potentials, measured with patch clamp and Kir2.1 injection via dynamic clamp, were shorter and displayed lower amplitudes in VLCADD compared to control. Moreover, the susceptibility to delayed afterdepolarizations (DADs) was increased in cardiomyocytes from the two VLCADD lines. In VLCAD1, but not in VLCAD2, long-chain acylcarnitine accumulation was decreased by pre-incubation with resveratrol. Accordingly, action potentials were normalized and susceptibility to DADs generation was reduced in VLCAD1. Pre-incubation with etomoxir led to a reduction of acylcarnitine production in both patients, and reduced the amount of DADs in cardiomyocytes from both cell lines.

Conclusion
Cardiomyocytes from hiPSC-lines of VLCADD patients show accumulation of long-chain acyl-CoAs and/or long-chain acylcarnitines, shorter action potentials, and a higher susceptibility to DAD generation, an important cellular mechanism for arrhythmias. The reduction of acylcarnitine...
accumulation by resveratrol or etomoxir reduced DAD generation in the two patients’ cell lines, indicating that DADs in VLCADD hiPSC-CM are caused by acylcarnitine accumulation rather than energy shortage.
Resting-state Networks in Children with Traumatic Brain Injury

J.E. Botchway1,2,3, J. Oosterlaan4,5, L.W.E. van Heurn6, R. Bakx6, R.J. Vermeulen7,8, J.C. Goslings9,10, B.T. Poll-The7, M. van der Wees11, C.E. Catsman-Berrevoets12, P.J.W. Pouwels13,14 & M. Königs4

Affiliations:
1. Murdoch Children’s Research Institute, Melbourne, Australia.
2. Royal Children’s Hospital, Melbourne, Australia.
3. Department of Paediatrics and Melbourne School of Psychological Sciences, University of Melbourne, Melbourne, Australia.
4. Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Emma Neuroscience Group, Amsterdam, The Netherlands
5. Clinical Neuropsychology Section, VU University Amsterdam, Amsterdam, The Netherlands
6. Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Surgical Center, Amsterdam, The Netherlands
7. Emma Children’s Hospital, Amsterdam UMC, Pediatric Neurology, Amsterdam, The Netherlands
8. Department of Pediatric Neurology, Maastricht UMC+, Maastricht, The Netherlands
9. Trauma Unit, Academic Medical Center, Amsterdam, The Netherlands
10. Department of Surgery, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
12. Department of Pediatric Neurology, Erasmus University Hospital/ Sophia Children’s Hospital, Rotterdam, The Netherlands
13. Department of Radiology and Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands
14. Neuroscience Campus Amsterdam, Amsterdam, The Netherlands

Keywords: Pediatrics, Traumatic Brain Injury, Resting-state Functional Connectivity; Functional Outcome

Rationale
Children with traumatic brain injury (TBI) are at risk of persisting deficits in neurocognitive and behavioral functioning. This study aims to investigate the potential impact of pediatric TBI on resting-state functional connectivity and its role in functional outcome.

Methods
Children aged 8-14 years with mild TBI and risk factors for complicated TBI (mildRF+ TBI, n = 20) and children with moderate/severe TBI (n = 17) at 2.8 years post-injury will be compared to children with trauma control (TC) injury (n = 27). Functional outcome was measured using neurocognitive tests and parent/teacher questionnaires for behavioral functioning. Resting-state functional MRI data was obtained at 3T and is currently analysed using FSL ‘MELODIC’ for network identification and ‘Dual Regression’ for group comparisons.

Results
Regarding functional outcome, we found that children with mildRF+ TBI or moderate/severe TBI have impaired neurocognitive functioning (full-scale IQ, working memory, long-term memory) and behavioral functioning (internalizing and externalizing problems). Pre-processing of functional MRI data identified six well-known resting state networks in a representative subsample of the TC group (n = 5), i.e. the visual, somatomotor, dorsal attention, ventral attention, frontoparietal and default mode networks. Functional connectivity in these networks will be compared between study groups using permutation testing. The relation between network abnormalities and functional outcome will be assessed using regression techniques. These analyses are currently carried out and the results will be presented at the symposium.

Conclusion
The potential role of resting-state functional connectivity disturbance in the functional outcome of pediatric TBI will be discussed.
High prevalence of sleep problems in survivors of a childhood brain tumor with neurocognitive complaints: the association with psychosocial and neurocognitive functioning

J.A.M.C. van Kooten1,2, H. Maurice-Stam1, A.Y.N. Schouten1,4, D.G. van Vuurden1,2, B. Granzen5, C. Gidding6, M.A. de Ruiter3, R.R.L. van Litsenburg1,3, M.A. Grootenhuis1,3

Affiliations:
1. Department of Pediatric Oncology-Hematology, Cancer Center Amsterdam, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands
2. Princess Maxima Center for pediatric oncology, Utrecht, The Netherlands
3. Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Psychosocial Department, Amsterdam, The Netherlands
4. Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Department of Pediatric Oncology, Amsterdam, The Netherlands
5. Department of Pediatrics, Maastricht University Medical Center, Maastricht, The Netherlands
6. Department of Pediatric Oncology/Hematology, Radboud University Medical Center, Nijmegen, The Netherlands

Keywords: Sleep, pediatric, neurocognitive functioning

Rationale
Survivors of a childhood brain tumor (CBTS) are prone to sleep- and neurocognitive problems. Sleep problems are negatively related to neurocognitive functioning (NCF), but no information is available about CBTS. Therefore, the prevalence of and potential risk factors for sleep problems, and the relation between sleep and NCF in CBTS were evaluated.

Methods
Baseline data of a RCT on the effectiveness of neurofeedback are reported here. CBTS with parent-reported neurocognitive complaints, 8-18 years, ≥2 years after treatment were eligible. Parents completed the Sleep Disturbance Scale for Children (SDSC). NCF was assessed by parents and teachers with the Behavior Rating Inventory of Executive Functioning (BRIEF). Multiple linear regression analyses were used to examine sociodemographic and medical characteristics, emotional difficulties and hyperactivity/inattention (Strength and Difficulties Questionnaire) as potential risk factors for sleep problems, and to assess the association between sleep and NCF.

Results
CBTS (n=82, 7.0±3.6 years post-diagnosis, age 13.8±3.2 years) had a high prevalence of sleep problems (48.8%) and scored significantly worse than the norm on the subscales Disorders of Initiating and Maintaining Sleep, Disorders Of Excessive Somnolence, Sleep Wake Transition Disorders and the total scale (effect sizes 0.32-0.92). Emotional problems and/or hyperactivity/inattention were significantly associated with sleep. More sleep problems were associated with worse NCF reported by parents, but not by teachers.

Conclusion
CBTS with parent-reported neurocognitive complaints have a high prevalence of sleep problems, which are related to worse NCF. Emotional problems and hyperactivity/inattention are potential risk factors for sleep problems. It is worthwhile to investigate whether optimizing sleep, for instance by behavioral approach, might improve NCF.
The safety of a modified, low protein infant formula designed to prevent obesity in healthy infants born at term: A Randomized, Double-blind, Equivalence Trial

S.M.P. Kouwenhoven¹, N. Antl², M.J.J. Finken³, E.M. van der Beek¹, B. Koletzko⁴, J.B. van Goudoever¹ ¹

Affiliations:
¹ Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, VU University Medical Center, the Netherlands
² Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children’s Hospital, University of Munich Medical Centre, Munich, Germany
³ Nutricia Research, Utrecht, The Netherlands
⁴ Department of Pediatrics, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
⁵ Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, the Netherlands

Keywords: Infant nutrition, growth, body composition, protein intake, amino acids

Rationale
Evidence suggests that high protein intake in early life predisposes to later obesity. We assessed safety and efficacy of an infant formula with a modified amino acid profile and a lower protein content (mLP, 1.7 g protein/100 kcal) on growth and body composition compared to standard protein (SP, 2.1 g protein/100 kcal) infant formula up to 6 months of age.

Methods
In this double blinded equivalence randomized controlled trial, we enrolled healthy term-born infants aged ≤45 days. A breast-fed group served as reference. Anthropometry and body composition were determined at baseline, and at ages 17 weeks (including blood sampling) and 6 months. Primary outcome was daily weight gain from enrolment up until to age 17 weeks (equivalence margin of ±3.0 gram/day).

Results
178 formula-fed (n=90 mLP and n=88 SP) and 67 breast-fed infants were enrolled. Weight gain (g/day) from enrolment up until the age of 17 weeks was equivalent between the mLP and SP formula groups (mLP 27.9 vs SP 28.8 difference 0.86 [-2.68 - 0.95]). We found no differences between these groups in growth parameters, body composition or adverse events. Blood urea nitrogen (BUN) was significantly lower in the mLP formula group compared to the SP formula group (-1.6 [-2.03 – -1.12] P <0.001).

Conclusion
Infants fed modified lower protein formula showed equal growth and body composition as infants fed standard protein formula. This, in combination with a lower BUN concentration, indicates that protein metabolism is more efficient in infants fed modified lower protein formula.
Abstracts submitted to the Amsterdam Kindersymposium 2019

Foreign body ingestion in children 0-18 years – an evidence-based guideline


Affiliations:
1 Department of Pediatric Gastroenterology, Emma Children’s Hospital, Amsterdam UMC, The Netherlands
2 Department of Epidemiology, Dutch Association of Pediatrics, The Netherlands
3 Department of Pediatric Gastroenterology, Jeroen Bosch Ziekenhuis, The Netherlands
4 Department of Pediatrics, Juliana Children’s Hospital of the Haga Teaching Hospital, The Netherlands
5 Department of Otolaryngology/Head and Neck Surgery, Erasmus University Medical Center, Rotterdam, The Netherlands
6 Department of Radiology, Amsterdam UMC, The Netherlands
7 Department of General Practice, Erasmus University Medical Center, Rotterdam, The Netherlands
8 Child and Hospital Foundation, Utrecht, The Netherlands

Keywords: Guideline, Pediatrics, Foreign body ingestion, Magnets, Batteries, Sharp objects, Blunt objects, Endoscopy

Rationale
Children with foreign body ingestion are treated differently amongst health care practitioners. Therefore, this evidence-based guideline aims to provide a uniform policy concerning foreign body ingestion in children (0-18 years) in the Netherlands.

Methods
The guideline was developed by a multidisciplinary working group on behalf of the Dutch Association of Pediatrics. Relevant research questions were formulated, after which Medline, Embase and Cochrane databases were searched systematically. Evidence was graded by “Evidence-Based Richtlijn Ontwikkeling” (EBRO-)method or The Grading of Recommendations Assessment, Development and Evaluation (GRADE-) method. Recommendations were based on other considerations in addition to the evidence.

Results
Foreign bodies can be divided into blunt objects and coins, sharp objects, batteries, and magnets. Several complications can occur directly, but also weeks to months after ingestion. The absence of symptoms does never rule out foreign body ingestion. Therefore, a radiograph (AP) showing neck until abdomen, should always be made by all children presenting in 2nd-3rd line with suspected foreign body ingestion. Other diagnostics and treatment depends on foreign body type, localization, and symptoms. Sharp objects and button batteries located in the esophagus should be removed <2 hours, as well as all foreign bodies in the esophagus and stomach in symptomatic children. 2 or more magnets in esophagus and stomach should be removed as soon as possible, at the latest within 24 hours.

Conclusion
This guideline provides evidence-based recommendations to guide health care professionals in the diagnostics and treatment of children with foreign body ingestion.
Spectroscopic detection of brain propylene glycol in neonates: effects of different pharmaceutical formulations of phenobarbital

Petra J.W. Pouwels¹, Monique van de Lagemaat ², Laura A. van de Pol³, Bregje C.M. Witjes⁴, Inge A. Zonnenberg⁵

Affiliations:
¹ Department of Radiology and Nuclear Medicine, Amsterdam UMC, Amsterdam, The Netherlands
² Department of Pediatrics/Neonatology, Emma Children’s Hospital, Amsterdam UMC, Amsterdam, The Netherlands
³ Department of Child Neurology, Emma Children’s Hospital, Amsterdam UMC, Amsterdam, The Netherlands
⁴ Department of Pharmacy, ErasmusMC-Sophia Children’s Hospital, Rotterdam, The Netherlands

Keywords: propylene glycol, MRS, neonate

Rationale
First choice for treatment of neonatal convulsions is intravenous phenobarbital, which contains propylene glycol (PG). Although PG is generally considered safe, the dosage can exceed safety thresholds in neonates. We aimed to investigate a relationship between brain PG concentration and medication administered to neonates and to study if a correlation between spectroscopically detected PG and lactate was present.

Methods
This retrospective study included 41 neonates who underwent MRI/MR with short echo time single voxel MRS at 1.5T. Concentrations of PG were correlated with phenobarbital administered. Intravenously administered phenobarbital solutions contained 10, 25, or 50 mg/ml, all containing 350 mg/ml PG. The interval between medication and MRI/MRS was determined.

Results
Of the 41 included neonates, 18 had brain PG >1 mM (median 3.4 mM, maximum 9.5 mM). All 18 neonates with high brain PG and 14 neonates with low brain PG (<1 mM) received phenobarbital as only source of PG. Nine neonates did not receive any phenobarbital or other PG containing medication. Neonates with high brain PG more often received 10 mg/ml phenobarbital resulting in higher PG dose (high versus low brain PG (median (IQR): 1400 (595) versus 350 (595) mg/kg, respectively, P<0.01). In addition, the interval between last phenobarbital dose and MRI was shorter in the high brain PG group (high versus low brain PG: 16 (21) versus 95 (83) hours, respectively, P<0.001).

Conclusion
These MRS findings may increase awareness of potentially toxic PG concentrations in the neonatal brain due to intravenous phenobarbital administration and its dependence on the phenobarbital formulation used in neonatal clinical practice.
Detection of Pseudomonas aeruginosa infection in cystic fibrosis patients by eNose technology

A. Lammers¹, R. Kos¹, R. de Vries¹, P. Brinkman¹, J.W.F. Dagelet¹, N.W. Rutjes¹, C.J. Majoor¹, S.W.J. Terheggen-Lagro¹, E.J.M. Weersink¹, L.D Bos¹, P.J. Sterk¹, A.H. Maitland-van der Zee¹, A.H. Neerincx¹ and for the Amsterdam CF research group

Affiliations:
¹ Amsterdam UMC, University of Amsterdam, Dept. of Respiratory Medicine - Amsterdam (Netherlands)

Keywords: cystic fibrosis, pseudomonas aeruginosa, eNose, exhaled breath

Rationale
Sputum culture is the golden standard for detecting Pseudomonas aeruginosa (PA) in cystic fibrosis (CF) patients; however, this is a time-consuming method. Volatile organic compounds (VOCs) in exhaled breath, as obtained by gas-chromatography and mass-spectrometry, have already been associated with PA infection [Robroeks Pediatr Res 2010]. Exhaled breath metabolomics based on pattern recognition of VOCs by electronic noses (eNose) might allow PA detection at the point-of-care. The aim of this study was to determine the diagnostic accuracy of exhaled breath analysis by eNose for discrimination between CF patients with and without a PA infection.

Methods
This was a cross-sectional observational study in CF patients infected or non-infected with PA. As part of spirometry, exhaled breathprints were collected in duplicate by eNose (SpiroNose) based on 4 identical metal oxide sensor arrays with in total 7 different sensors [De Vries ERJ 2018]. Infection was defined as 1. PA positive culture at inclusion or 2. PA present in ≥50% of cultures over the past year (≥4 samples). Data-analysis involved signal processing, ambient correction and statistics based on linear discriminant analysis followed by receiver operating characteristic (ROC) analysis.

Results
Exhaled breath results of 18 paediatric and 33 adult CF patients infected (n=23) and non-infected (n=28) with PA were available. Sensor 3, 5 and 7 showed a significant difference (p<0.01) between the two groups, with a cross-validation value of 82.4% and ROC-AUC of 0.93 (95% CI 0.86-1.00).

Conclusion
Breath analysis by eNose is able to discriminate between CF patients with and without PA infection. When independently validated (in progress), these results are supportive of using eNose technology for fast and non-invasive detection of PA at point-of-care.
Evaluation of an outpatient sport-related concussion research clinic

S. Langdon, M. Konigs, E. Goedhart, J. Oosterlaan

Affiliations:
Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, The Netherlands
Polikliniek voor Sportgerelateerde Hersenschuddingen, Koninklijke Nederlandse Voetbal Bond (KNVB), Zeist, The Netherlands

Keywords: Sport related concussion, symptoms

Rationale
A sport-related concussion (SRC) is a traumatic brain injury induced by biochemical forces acting on the brain. It is a heterogeneous injury in terms of etiology and pathophysiology, and consequently, involving variable presentations of symptoms between athletes. Current clinical guidelines however still provide a unitary approach to manage SRC. The heterogeneity in the presentation of SRC symptoms suggests that subtypes of SRC may exist, which may relate to clinical outcome and its trajectory, and may require differential, targeted clinical management and treatment. The outpatient clinic at the KNVB aims to improve SRC treatment by identifying it subtypes and match targeted management and treatment.

Methods
Amateur and elite athletes received questionnaires prior to their intake, assessing demographics, medical history, trauma specifics, premorbid risk factors and symptoms. At clinic appointments, athletes were examined by a multi-disciplinary team of health care professionals, including sport-medical doctors, physiotherapists and neuroscientists assessing neurological functioning, balance and postural stability, physical functioning, neurocognitive functioning and eye movements. Follow-up questionnaires were obtained after 3 and 6 weeks and follow-up measurements took place after 6 weeks.

Results
Mean post-injury time at intake was 5 months, 60.7% of SRC injury was obtained during soccer and 27.7% was hit on the back of the head. The majority of athletes did not experience on-field signs, such as unconsciousness (64.3%) and post-traumatic amnesia (retrograde: 75%; anterograde: 60.7%). At the day of injury 89.3% experienced headache, 78.6% dizziness, 50.0% nausea and 0% vomiting. At intake, fatigue (46.5%), difficulty concentrating (28.6%), trouble falling asleep (28.6%), “not feeling well” (17.9%) and headache (14.3%) were the most common highest rated symptoms. Symptom severity was significantly decreased ($F(2,28) = 10.958, p < .001$) and percentage of feeling well was significantly increased ($F(2,28) = 10.948, p < .001$) at follow up. Information processing speed and stability were significantly improved at follow up ($F(1,17) = 18.318, p = .001$; $F(1,17) = 9.253, p = .007$). Alerting attention, interference processing, verbal memory (encoding) and visuomotor functioning were significantly improved at follow-up ($F(1,17) = 7.060, p = .017$; $F(1,17) = 11.226, p = .004$; $F(1,15) = 8.317, p = .012$). Postural stability and single leg balance were also significantly improved at follow-up measurements ($F(1,20) = 4.472, p = .047$; $F(1,20) = 6.838, p = .017$).

Conclusion
These preliminary data suggest that athletes may improve subjective and objective outcomes following a SRC by providing them individualized management and treatment programs. Future research should aim to examine which SRC subtypes exist, investigate the recovery trajectory of these differential subtypes and develop, match and investigate the efficacy of targeted clinical management and treatment.
Effect of electrode position on transcutaneous electromyography of the diaphragm.

R. van Leuten¹, R. Bekhuis¹, C. de Waal¹, F. de Jongh¹,², G. Hutten¹, A. van Kaam¹,²

Affiliations:
¹ Department of neonatology, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
² Department of neonatology, Emma Children’s Hospital, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands
³ Faculty of Engineering Technology, University of Twente, Enschede, The Netherlands

Keywords: Peak activity, monitoring, neonatal intensive care unit

Rationale
Monitoring electrical activity of the diaphragm with transcutaneous electromyography (dEMG) is feasible in preterm infants. The dEMG signal provides respiratory rate (RR), heart rate (HR), and neural breathing effort. The recommended electrode positioning is the right and left mid-clavicular line at the costo-abdominal margin. However, monitoring in daily clinical practice requires multiple different electrode positions to avoid skin lesions. Aim of the study was to describe the impact of different electrode positions on the derived dEMG parameters compared with the recommended position.

Methods
dEMG was simultaneously recorded for one hour by two pairs of electrodes in spontaneously breathing preterm infants. One pair was placed at the recommended position. The other position was randomly assigned: lateral, medial, superior, inferior to the recommended position or dorsal on the back. Peak and tonic activity, amplitude and variability were derived from the dEMG signal and compared between the two positions.

Results
Thirty infants (gestational age 30.1 ± 3.0 weeks, birth weight 1460 ± 645 grams) were included. HR and RR derived from dEMG did not significantly differ between recommended and alternative positions. Amplitude of the dEMG signal was lower at all different positions. The lateral position recorded the strongest signal (19.7% lower peak activity compared with recommended position). The variability of the signal was comparable for all positions (coefficient of variation 22.5 – 29.6% for peak activity).

Conclusion
This study suggests that different positions of dEMG electrodes can be used to monitor vital signs and detect diaphragmatic activity. Although dEMG amplitude decreases, monitoring of HR and RR remain reliable.
Feedback options for using PROMs in daily pediatric clinical practice using KLIK

L. Haverman¹, H.A. van Oers², M.M. van Muilekom¹, M.A. Grootenhuis²

Affiliations:
¹ Amsterdam UMC, University of Amsterdam, Emma Children’s Hospital, Psychosocial Department, Amsterdam, The Netherlands
² Princess Maxima Center for Pediatric Oncology, Utrecht, The Netherlands

Keywords: Patient Reported Outcomes, Interpretation, Clinical practice, Pediatrics

Rationale
This abstract describes the different ways Patient Reported Outcome Measures (PROMs) are being fed back to healthcare providers (HCPs) and the aids provided using the KLIK PROMs portal (www.hetklikt.nu).

Methods
Patients (children/parents/adult patients) complete online PROMs at home about their Health-Related Quality of Life (HRQOL), symptoms and/or psychosocial functioning before an outpatient consultation. PROMs are converted into a KLIK ePROfile and discussed during the consultation.

Results
The first PROM used in KLIK was a generic HRQOL questionnaire. Currently, KLIK includes a variety of different PROMs (>300). The ePROfile consists of a broad spectrum of feedback options; 1) literal representation of individual items (e.g., by using traffic light colors), 2) summary scores, and 3) four graphic representations (longitudinal trend line, norm line, clinical cut-off, and pictures). Aids that help HCPs interpret the ePROfile are the KLIK training, a decision tree and a summary of information about the ePROfile.

Conclusion
This paper was written following an invitation by Johns Hopkins University to participate in a paper series focusing on the best PROM portals in the world used as part of standard clinical care. The strength of KLIK is its flexibility; KLIK can be applied for many patient groups (e.g., diabetes, rheumatology) and every PROM (with good psychometric qualities) can be built in. In addition, KLIK is evidence-based, and the only PROM portal mainly focusing on pediatrics. However, implementing PROMs in clinical care encompasses different challenges and is therefore an ongoing process of improvement and adaptation.
High mortality in children with early-detected congenital central hypothyroidism

J.C. Naafs1, N. Zwaveling-Soonawala1, P.H. Verkerk2, A.S.P. van Trotsenburg1

Affiliations:
1 Department of Pediatric Endocrinology, Emma Children’s Hospital, Amsterdam UMC - location AMC, The Netherlands
2 Department of Child Health, Netherlands Organisation for Applied Scientific Research (TNO), 2301 DA Leiden, The Netherlands

Keywords: Congenital hypothyroidism (CH) of central origin, panhypopituitarism, infant and childhood mortality, newborn screening

Rationale
Approximately 60%-80% of patients with congenital central hypothyroidism (CH-C) have multiple pituitary hormone deficiencies (MPHD), making CH-C a potentially life-threatening disease. However, data on mortality in children with CH-C are lacking. Mortality rates were calculated in an 18-year cohort of children with early-detected and treated CH-C.

Methods
Overall mortality rate, infant mortality rate (IMR) and under-5 mortality rate were calculated in all children with CH-C detected by neonatal screening between 1 January 1995 and 1 January 2013. Medical charts were reviewed to establish if causes of death were related to endocrine disease.

Results
The cohort consisted of 139 CH-C patients, of which 138 could be traced (82 with MPHD, 56 with isolated CH-C). Total observation time was 1414 years with a median follow-up duration of 10.2 years. The overall mortality rate was 10.9% (15/138). IMR and under-5 mortality rate were 65.2/1000 (9/138) and 101.4/1000 (14/138), respectively, compared with an IMR of 4.7/1000 and under-5 mortality rate of 5.4/1000 live-born children in the Netherlands during the same time period (p<0.0001). Main causes of death were severe congenital malformations in six patients, asphyxia in two patients and congenital or early neonatal infection in two patients. Pituitary hormone deficiency was noted as cause of death in only one infant.

Conclusion
We report an increased mortality rate in pediatric patients with early-detected CH-C that does not seem to be related to endocrine disease. This suggests that mortality due to pituitary insufficiency is low in patients with early-detected and early-treated CH-C.
Standardized versus Individualized Parenteral Nutrition Mixtures in the Pediatric Home Parenteral Nutrition Population

S.C.J. Nagelkerke¹, C.F. Jonkers-Schuitema¹, M.A. Benninga¹, B.A.E. de Koning², M.M. Tabbers¹

Affiliations:
¹ Amsterdam UMC, University of Amsterdam, Emma Children’s Hospital, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Amsterdam, The Netherlands
² Erasmus Medical Center, Erasmus University Rotterdam, Sophia Children’s Hospital, Department of Pediatric Gastroenterology, Rotterdam, the Netherlands

Keywords: Pediatric Intestinal Failure, Home Parenteral Nutrition, Standardized Mixtures, Growth, Electrolytes

Rationale
Current guidelines concerning pediatric Parenteral Nutrition (PN) conclude that standardized PN mixtures are not suitable for children with chronic Intestinal Failure on Home PN. However, no studies have been undertaken to endorse this conclusion. Possible advantages of standardized PN could be a reduction in costs and a longer shelf life.

Methods
Retrospective cohort study in Dutch children on Home PN between June 2017 and July 2017. The group receiving individualized PN was compared to the group receiving standardized PN. Growth was assessed by calculating the difference of Weight-for-age (WFA) and Height-for-age (HFA) SD scores between date of inclusion and 6, 12 and 24 months prior to inclusion. Primary outcome was growth over 2 years, secondary outcomes were electrolyte disturbances and biochemical abnormalities.

Results
50 patients (50% female) were included, of whom 16 (32%) received standardized PN mixtures. For children receiving standardized PN mixtures, median weight gain in 2 years was significantly higher compared to the individualized PN mixtures group of children who lost weight (+0.38 SD score vs 0.55 SD score, p: .003)). No significant differences were demonstrated in electrolyte disturbances or biochemical abnormalities. Age (11 vs 5 years), gestational age (GA) (36.2 vs 39.2 weeks) and PN duration (97 vs 39 months) were significantly higher in the group receiving standard PN (p: ≤0.0001; 0.027; 0.013 respectively).

Conclusion
Standardized PN mixtures are at least non-inferior to individualized PN mixtures in terms of biochemical abnormalities in a home PN cohort. In the older child with standardized PN mixtures, weight gain was higher.
Psychosocial Functioning in Parents of MPS III Patients

Stephanie Nijmeijer¹, Thirsa Conijn¹, Hedy van Oers², Frits Wijburg³, Lotte Haverman⁴

Affiliations:
¹ Amsterdam UMC, University of Amsterdam, Pediatric Metabolic Diseases, Emma Children’s Hospital and Amsterdam Lysosome Center “Sphinx”, Meibergdreef 9, Amsterdam, Netherlands.
² Amsterdam UMC, University of Amsterdam, Psychosocial Department, Emma Children’s Hospital, Meibergdreef 9, Amsterdam, Netherlands

Keywords: MPS III; psychosocial functioning; parental distress; anxiety; depression; posttraumatic stress symptoms.

Rationale
Mucopolysaccharidosis type III (MPS III or Sanfilippo syndrome) is a lysosomal storage disease resulting in progressive neurocognitive decline during childhood and early demise. Its diagnosis may have a great impact on parents, potentially leading to psychosocial problems such as anxiety, depression, parental distress, and posttraumatic stress.

Methods
Twenty-six mothers and 19 fathers of 34 Dutch MPS III patients completed the ‘Hospital Anxiety and Depression Scale’ (HADS), the ‘Distress Thermometer for Parents’ (DT-P) and the ‘Self Rating Scale for Posttraumatic Stress Disorders’ (SRS-PTSD). Independent-samples T-tests and Chi-Square tests were used to assess differences between parents of MPS III patients and reference groups regarding anxiety and depression (HADS), distress (DT-P), and posttraumatic stress (SRS-PTSD).

Results
Mothers met the criteria for clinically relevant anxiety (50%) and depression (34.6%) more frequently compared to reference mothers (p=.001). Fathers more often met the criteria for clinically relevant depression (36.8%) compared to reference fathers (p=.022). Clinically relevant distress was highly prevalent in mothers (84.6%) and fathers (68.4%) of MPS III patients compared to reference parents (p<.01). Finally, the prevalence of PTSD was strikingly higher in both mothers (26.9%) and fathers (15%) than reported in the general Dutch population (respectively p<.001 and p<.05).

Conclusion
We report a clinically relevant impact of parenting an MPS III patient on psychosocial functioning, which is demonstrated by high levels of anxiety, depression, distress and a remarkably high prevalence of PTSD. Structural monitoring of the psychosocial functioning of MPS III parents is therefore essential and may be beneficial for the whole family.
The safety and efficacy of pharmacological treatment for gastroesophageal reflux disease in children: a systematic review

A.C. Ouwendijk¹, M. van Lennep², M.A. Benninga³, M.M. Tabbers⁴, M.M.J. Singendonk⁵

Affiliations:
¹ Department of Pediatric Gastroenterology and Nutrition, Emma Children’s Hospital, Amsterdam UMC, location AMC, The Netherlands

Keywords: N.A.

Rationale
Gastroesophageal reflux disease (GERD) is defined as GER causing troublesome symptoms and/or complications. GERD treatment usually focuses on reducing acid burden. In children however, safety and efficacy of acid-suppressive agents is debated. Our aim was to systematically assess the safety and efficacy of pharmacological GERD treatment in children.

Methods
PubMed, Embase and Medline were searched for randomized controlled trials and systematic reviews on pharmacological GERD treatment in children 0-18 years old. Quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation system. Outcomes of interest were predefined according to latest international guidelines, and included: esophagitis, complications of GERD, GERD related signs and symptoms, quality of life, crying and distress, visible vomiting/regurgitation, heartburn and side-effects.

Results
Twenty-six studies were included with data from 1795 children. Quality of evidence was low to very low. Based on respectively eight and three studies, neither PPI nor H2RA treatment significantly improved GERD symptoms (i.e. vomiting, crying) when compared to placebo or other treatment. Antacids give significant better symptom reduction in vomiting (RR: 0.28 (95% CI 0.26 – 0.89) compared to placebo, but not when compared to PPI or H2RA. Two studies assessed endoscopic healing and found H2RA to reduce endoscopic healing compared to placebo. In three comparative studies, H2RA was not significant better in endoscopic healing compared to other treatment (antacid n=2 studies, sucralfate n=1study).

Conclusion
Evidence to support the efficacy and safety of pharmacological GERD treatment in infants and children is limited and of low quality.
Does online cognitive behavioral therapy for insomnia “i-Sleep youth” improve sleep of adolescents after childhood cancer? Design of the MICADO-study: a randomized-controlled trial

Shosha H. M. Peersmann, Martha A. Grootenhuis, Annemieke van Straten, Gertjan J. L. Kaspers, Raphaëlle R. L. van Litsenburg

Affiliations:
1. Princess Maxima center for Pediatric Oncology, Utrecht, The Netherlands
2. Department of Pediatric oncology, Emma Children’s Hospital, Amsterdam University Medical Center, Vrije Universiteit, The Netherlands
3. Department of Clinical, Neuro, and Developmental Psychology, Section Clinical Psychology, Faculty of Behavioural and Movement science, Vrije Universiteit Amsterdam, The Netherlands

Keywords: Insomnia, Online CBT, Adolescents, Childhood Cancer

Rationale
Insomnia is a prevalent (26-29%) and disabling sleeping disorder after childhood cancer, negatively impacting quality of life (QoL), fatigue, pain and general functioning. Adolescents with childhood cancer might be at risk for insomnia. The first-line treatment is cognitive behavioral therapy for insomnia (CBT-I). However, access to this care is limited due to limited capacity. The online CBT-I “i-Sleep” might facilitate access. i-Sleep is shown effective in adult (breast cancer) patients, but it is unknown if it is feasible and effective in pediatric oncology patients.

Methods
We aim to evaluate the effectiveness of “i-Sleep youth” in a national randomized-controlled clinical trial comparing online CBT-I to a waiting-list condition at posttest and 6 months (n=70). After 6 months the waiting-list (n=35) is offered i-Sleep. At 12 months only the intervention condition (n=35) is assessed to evaluate if treatment effects sustained. i-Sleep consist of five online guided sessions in 5-8 weeks. Adolescents (age 12-25y), childhood cancer diagnosis before age <19 years, max. 7 years since diagnosis, ≥6 months since last treatment and selected during a national screening within pediatric oncology, will be eligible for MICADO. Primary outcomes are sleep efficiency (actigraphic) and insomnia severity (self-report) and secondary include: fatigue, QoL, chronic distress, depressive– and anxiety symptoms and intervention feasibility.

Results
Starting October 2018, we aim to include patients in the upcoming 2.5 years and finish data collection and analyses in 2022.

Conclusion
If online CBT-i is feasible and effective, screening and guidelines for insomnia after childhood cancer can be installed for adolescents pediatric oncology patients.
Fever in Children At-Risk for the Brugada Syndrome

P.J. Peltenburg, S.A. Vink, N.A. Blom, S.A.B. Clur

Affiliations:
1 Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, The Netherlands

Keywords: Fever, Brugada Syndrome, Children

Rationale
Brugada syndrome (BrS) is a rare rhythm disorder. Associated variants in the SCN5A gene are in some cases identified. Fever is a known trigger for arrhythmic events, especially in children. Children with a positive family history for BrS, independent of the genetic profile, are at-risk for BrS and are currently advised to record an fever-ECG. We aimed to evaluate this policy by identifying risk factors for symptoms and Brugada pattern during fever (f-type 1).

Methods
Children at-risk for BrS or diagnosed with BrS with ≥1 available fever-ECG were included and data was retrospectively retrieved and analysed. The children with ≥1 fever-ECG with f-type 1 were compared to those without this pattern during follow-up.

Results
In total 68 children were included, of whom 20 had ≥1 f-type 1 during follow-up. Compared to children without f-type 1 they differed significantly in genetic background. Eighteen (90.0%) of the children with f-type 1 were carrier of a SCN5A variant, in one child this variant was of unknown significance. All but one at-risk children without associated genetic variant in the family did not have f-type 1 during follow-up. All symptomatic children had ≥1 f-type 1 and were carrier of a SCN5A pathogenic variant. In 5 symptomatic children (71.4%) symptoms occurred during fever.

Conclusion
Children at-risk for BrS with Brugada type 1 pattern during fever were mostly carriers of a SCN5A variant. All symptomatic children carried a SCN5A variant. This suggests a higher risk of symptoms and f-type 1 in at-risk children carrying a SCN5A variant.
Rationale
The evaluation of bleeding symptoms in children may be challenging. As the existing bleeding assessment tools (BATs) for children (ISTH-BAT and Pediatric Bleeding Questionnaire (PBQ)) have their limitations, this study aims to develop a refined pediatric BAT with higher sensitivity and flexibility.

Methods
In this observational study, children presenting with signs and symptoms of bleeding, and/or a positive family history of a bleeding disorder were included. A new developed comprehensive bleeding questionnaire (iCHEC for Identifying Children with HEreditary Coagulation disorders), including the ISTH-BAT and PBQ, was completed by the subjects and a uniform diagnostic work-up was performed afterwards. Total bleeding scores (TBS) are compared between children with and without a hemorrhagic disorder. A TBS cutoff ≥ 3 for ISTH-BAT and ≥ 2 of the PBQ is considered as positive test outcome.

Results
Preliminary results for 60 subjects are presented. Most were female (n=36, 60%); median age was 5.0 years (IQR 2-13). Eight (13%) were diagnosed with a bleeding disorder. Neither TBS of the ISTH-BAT nor PBQ demonstrated a statistically significant difference between both groups. Both, ISTH-BAT and PBQ, had a low positive predictive value (21% and 15%) and a high negative predictive value (92% and 90%). Sensitivity (ISTH-BAT: 63%, PBQ: 75%) and specificity (ISTH-BAT: 63%, PBQ: 37%) were low.

Conclusion
These results confirm that the ISTH-BAT and PBQ might lack discriminative power in children. This underlies the clinical need of a refined BAT in children.
The validation of a clinical screening instrument for tumor predisposition syndromes in children with cancer (TUPS): a prospective, observational, multi-center study

**Rationale**
Up to 10% of the children with cancer has a tumor predisposition syndrome (TPS). Identification of a TPS in a child with cancer is of clinical relevance. Half of the TPSs are not recognized prior to or during the treatment of their cancer. To increase effectivity and decrease costs we developed a screening instrument, ensuring evaluation for a TPS in all children with cancer. Only children more likely of having a TPS will be referred to the clinical geneticist for full genetic counseling.

**Methods**
The TuPS study is a prospective, observational, multi-center study including all children in the Netherlands newly diagnosed with cancer. The screening instrument consists of a score form, 2D and 3D pictures and a digital assessment of these by two independent clinical geneticists. If a TPS is suspected by at least one of the clinical geneticists (positive assessment), the patient will be invited for full genetic consultation. The primary outcome measurement is the sensitivity of the instrument.

**Results**
Interim analysis of the first 150 patients show a positive assessment rate of 62% (93/150) (27% single positive, 36% double positive). The reason for a positive assessment was mainly based on the type of cancer, family history and 2D pictures, although the pictures are seemingly not a decisive factor. Fourteen children were referred as part of a negative control group. Seventy-five patients have been evaluated by full genetic consultation thus far. Further genetic testing has been carried out in 38 of these patients. In two patients a TPS was diagnosed. In two other patients a germline mutation of non-conclusive significance has been found.

**Conclusion**
Preliminary results indicate the screening instrument to be an easy-to-use tool in the care of children with cancer, ensuring evaluation of a TPS. Numbers are still too small to determine the sensitivity of the instrument.
Multiple tumors due to mosaic genome-wide paternal uniparental disomy

Floor A.M. Postema1,2, Jet Bliek3, Carel van Noesel4, Laura J.C.M. van Zutven5, Jan C. Oosterwijk6, Saskia M. J. Hopman7, Johannes H. M. Merks3, Raoul C. Hennekam1

Affiliations:
1. Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC – location AMC, Amsterdam, The Netherlands
2. Princess Máxima Center for Pediatric oncology, Utrecht, The Netherlands
3. Department of Clinical Genetics, Amsterdam UMC – location AMC, Amsterdam, The Netherlands
4. Department of Pathology, Amsterdam UMC – location AMC, Amsterdam, The Netherlands
5. Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands
6. Department of Genetics, University Medical Center Groningen, Groningen, The Netherlands.
7. Department of Genetics, University Medical Center Utrecht, Utrecht, The Netherlands.

Keywords: tumors, syndrome, uniparental disomy, beckwith-wiedemann syndrome

Rationale
Mosaic genome-wide paternal uniparental disomy is an infrequently described disorder in which affected individuals have signs and symptoms that may resemble Beckwith-Wiedemann syndrome. In addition they develop multiple benign and malignant tumors throughout life. Routine molecular diagnostics may not detect the (characteristic) low level of mosaicism and the diagnosis is likely frequently missed. Genetic counseling and a life-long alertness for the development of tumors is indicated. We describe the long diagnostic process of a patient who had already a tumor at birth, developed multiple tumors in childhood and adulthood, and we offer clues to recognize the entity.

Methods

Results

Conclusion
Concurrence of sleep problems and distress: prevalence and determinants in parents of children with cancer.

Niki Rensen1,5, Lindsay M.H. Steur1, Sasja A. Schepers2,5, Johannes H.M. Merks3,5, Annette C. Moll4, Martha A. Grootenhuis2,5, Gertjan J.L. Kaspers1,5, Raphaële R.L. van Litsenburg1,5

Affiliations:
1 Amsterdam UMC, Emma Children’s Hospital, Vrije Universiteit Amsterdam, Pediatric oncology-hematology, Cancer Center Amsterdam, De Boelelaan 1117, Amsterdam, Netherlands
2 Amsterdam UMC, Emma Children’s Hospital, Univ of Amsterdam, Psychosocial department, Meibergdreef 9, Amsterdam, Netherlands
3 Amsterdam UMC, Emma Children’s Hospital, Univ of Amsterdam, Pediatric oncology-hematology, Meibergdreef 9, Amsterdam, Netherlands
4 Amsterdam UMC, Vrije Universiteit, Ophthalmology, De Boelelaan 1117, Amsterdam, Netherlands
5 Princess Máxima Center for pediatric oncology, Heidelberglaan 25, Utrecht, Netherlands

Keywords: child, cancer, parents, sleep, psychological stress

Rationale
Parents of children with cancer often report sleep problems or distress. Concurrence of these issues is unknown, but might indicate parental need. This study evaluates prevalence and determinants of this symptom clustering.

Methods
Parents completed questionnaires on sociodemographics, sleep (MOS Sleep Scale), distress and daily problems (DT-P). Clinical sleep problems were defined as score >1SD above the norm and clinical distress as overall score above the established cut-off of 4. Four parent categories were identified: 1) neither clinical sleep problems nor clinical distress; 2) low distress but sleep problems; 3) no sleep problems but distress; 4) both sleep problems and distress. Predictive determinants (sociodemographic, medical, psychosocial) for each parent category were assessed with multilevel multinomial logistic regression. Effects were displayed as Odds ratio’s (OR) and 95% confidence intervals.

Results
Parents (202 mothers, 150 fathers) of 231 children with different cancers participated. Mean time since diagnosis was 3.3±1.4 years (90% off-treatment). 50% reported neither sleep problems nor distress, 28% reported both in the clinical range, 9% had only sleep problems and 13% only distress. Compared to parents without sleep problems or distress, parents who reported both were more likely to report parenting problems (OR 4.4, [2.2-9.1]), chronic illness (OR 2.8, [1.2-6.5]), lack of social support (OR 3.7, [1.5-9.1]), pre-existent sleep problems (OR 6.2, [2.0-18.6]) and be female (OR 1.8, [1.1-4.2]).

Conclusion
It is important to identify parents with specific difficulties. Future research must show which interventions are most effective in this group: mainly targeted at sleep improvement or with prominent roles for stress management or trauma processing.
Long-term follow-up of gut-directed hypnotherapy self-exercises at home using CD versus individual therapy by qualified therapists in children with irritable bowel syndrome or functional abdominal pain (syndrome)

R. Rexwinkel1, A.M. Vlieger2, J. Bovendeert1, J.M.T.M. Rutten1, C. Frankenhuis1, M.A. Benninga1

Affiliations:
1 Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Gastroenterology, Amsterdam, The Netherlands.
2 Department of Pediatrics, St. Antonius Hospital, Nieuwegein, the Netherlands.

Keywords: Irritable bowel syndrome, Functional abdominal pain (syndrome), Hypnotherapy, Children

Rationale
We previously showed that home-based gut-directed hypnotherapy treatment with CD is non-inferior to individual hypnotherapy (iHT) by a therapist in the treatment of children with irritable bowel syndrome (IBS) or functional abdominal pain (syndrome) (FAP(S)). Aim of this follow-up study was to investigate the long-term effects of iHT and CD-hypnosis-exercises at home.

Methods
150 out of 250 participants from our previous randomized controlled trial (RCT) were invited to complete: 1) an online standardized abdominal pain dairy, on which pain frequency and intensity were scored, and 2) an online questionnaire including adequate relief, quality of life (QoL), anxiety/depression scores, somatization, pain beliefs, school and/or work absenteeism and health care utilization.

Results
To date, 70 CD-patients and 74 iHT-patients have completed this study. After a mean duration of 5.8 years follow-up, 80.0% in the CD-group vs 83.8% in the iHT-group reported adequate relief of abdominal complaints. More than 50% reduction in pain intensity and pain frequency was seen in 67.2% in the CD-group vs 66.7% in the iHT-group, respectively. Also, anxiety/depression scores, somatization, pain beliefs, healthcare utilization and school/work absenteeism improved significantly in both study groups. No differences were found in QoL.

Conclusion
Both home-based CD-self-exercises and iHT given by a qualified therapist show persisting positive results in the treatment of children with IBS or FAP(S) after more than 5 years of follow-up. These results support the rationale for implementation of this easy to use, widely available and cost-effective home-treatment in daily practice.
Neurodevelopmental outcomes of children with a congenital malformation of gastro-intestinal tract: a systematic review and meta-analysis

D. Roorda¹, M. Königs², L. Eeftinck Schattenkerk¹, L.W.E. van Heurn¹, J.Oosterlaan²

Affiliations:
¹ Department of Pediatric Surgery, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Pediatric Surgical Centre Amsterdam, Amsterdam, The Netherlands
² Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Emma Neuroscience group, Amsterdam, The Netherlands

Keywords: Neurodevelopment; Cognitive; Motor; Language; Congenital Malformations; Gastro-intestinal

Rationale
There is growing evidence that patients with a congenital malformation of the gastro-intestinal tract are at risk for neurodevelopmental impairment. This study aims to provide a comprehensive overview of current evidence on neurodevelopmental outcomes of patients with a congenital malformation of the gastro-intestinal tract.

Methods
A systematic review and meta-analysis was performed by searching Pubmed, Embase and Web of Sciences. (Last search: july 2018). Search terms included terms related to (1) congenital malformations of the gastro-intestinal tract, (2) infancy to adolescence and (3) neurodevelopmental outcomes. Standardized mean differences in neurodevelopmental outcomes were pooled using random-effects meta-analysis. Heterogeneity among studies in effect size was studied using multivariate random-effects meta-regression and subgroup comparison.

Results
A total of 40 studies representing 1882 patients met inclusion criteria. Across all types of malformations except mid gut malformations, and all age-groups, significant evidence for small-to-moderately-sized neurodevelopmental impairment was found. There was evidence for small-sized impairment in cognitive development (d=-0.393, P<0.001) small to moderately-sized impairment in motor development (d=-0.483, P <0.001) and moderately-sized impairment in language development (d=-0.597 P<0.001). Impairment in cognitive development in childhood/adolescence was larger than in infancy/toddlerhood (Q=3.92; p=0.05). None of the meta-analytic effects was moderated by gestational age or birthweight.

Conclusion
In this meta-analysis, robust evidence was found that patients with congenital malformations of the gastrointestinal tract have a risk of small to moderately impaired neurodevelopmental outcomes compared to healthy peers. These findings support the need for standardized neurodevelopmental screening of patients with a congenital malformation of the gastro-intestinal tract in follow-up.
Histopathological characteristics of the transition zone of patients with Hirschsprung disease

D. Roorda1, L. Beltman2, J.P. van der Voorn2, J.J.T.H. Roelofs4, J.P.M. Derikx1, L.W.E. van Heurn1

Affiliations:
1 Department of Pediatric Surgery, Emma Children’s Hospital, Amsterdam UMC, Amsterdam, The Netherlands
2 Maastricht University, Maastricht, The Netherlands
3 Department of Pathology, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
4 Department of Pathology, Amsterdam UMC, Universiteit van Amsterdam, Amsterdam, The Netherlands

Keywords: Histopathology; hirschsprung disease; transition zone

Rationale
Hirschsprung disease is characterized by the absence of ganglion cells in the submucosal and myenteric plexus of the intestine due to a defect in the migration of neurocrest cells. Between distal the aganglionic segment and the proximal normally innervated bowel, there is a transition zone. Anastomosing the transition zone is associated with persistent obstructive symptoms and occurs in about 6% of all Hirschsprung patients. Better insight in the histopathological characteristics of the transition zone may help to improve per-operative estimation of the transition zone delineation in order to prevent a transition zone pull-through.

Methods
The pathology reports of 164 patients treated for Hirschsprung disease in Amsterdam between 2000 and 2017 were retrospectively reviewed, assessing the prevalence of a transition zone pull-through and the histopathologic characteristics of the transition zone. Of patients with transverse sections of the resection specimen, these sections were re-evaluated, in order to describe circumferential delineation of the transition zone. Additionally, the resection specimens of 10 new patients treated in 2018 were sampled by making closely spaced transverse sections from the distal aganglionic segment to the proximal normal ganglionic segment in order to assess circumferential delineation of different histopathologic aspects of the transition zone. These sections were compared to autopsy specimens from children deceased from extra-intestinal causes.

Results
Results are awaited and will be presented at the conference.

Conclusion
Conclusions are awaited and will be presented at the conference.
Botulinum toxin injections for treatment of persistent obstructive defecation problems in patients with Hirschsprung disease: a systematic review

D. Roorda1, Z.A. Abeln1, J.P.M. Derikx1, L.W.E. van Heurn1

Affiliations:
1. Department of Pediatric Surgery, Emma Children’s Hospital, Amsterdam UMC, The Netherlands

Keywords: Hirschsprung; obstructive defecation problems; botulinum toxin

Rationale
About 30% of children with Hirschsprung disease experience persistent obstructive defecation problems after a pull-through procedure. One of the current treatment strategies for patients with persistent obstructive symptoms is Botulinum toxin injections in the internal anal sphincter. This systematic review aims to provide an outline of current evidence on effects of Botulinum toxin injections on obstructive problems in patients with Hirschsprung disease.

Methods
A systematic review was performed. Pubmed, Embase and the Cochrane Library were searched, using entry terms related to (1) Hirschsprung disease, (2) botulinum toxin injection and (3) obstructive symptoms. Data on patient characteristics, characteristics of procedures and clinical outcome was extracted.

Results
In this systematic review 14 studies representing 235 patients with Hirschsprung disease were included. Clinical improvement after botulinum toxin injections in short term was reported in 80% of the patients (7 studies, n=164 patients) with a mean length of follow-up of 2 weeks. Mean duration of clinical improvement was 5.25 months and patients needed a mean of 2.6 injections. Good initial response and rectosigmoid disease were associated with clinical improvement in long-term (length of follow-up ranging from 6-126 months), whereas dose and type of botulinum toxin were not.

Conclusion
Current evidence suggests a good response to botulinum toxin in most patients, although mainly in short-term and with temporary effect. The evidence is limited by large heterogeneity in definitions of outcomes, indication for botulinum toxin injections, length of follow-up and differences in procedures. We recommend botulinum toxin injections only when a sphincter problem is suspected as cause of obstructive symptoms.
Early-life antibiotics use increases the risk of asthma and eczema: a discordant twin study

Elise M.A. Slob1,2*, Chantal J.A.R. Kats1,2*, Susanne J.H. Vijverberg1, Mariëlle W. Pijnenburg2, Toos C.E.M. van Beijsterveldt1, Gerard H. Koppelman4, Dorret I. Boomsma3, Anke H. Maitland – van der Zee5,6*

Affiliations:
1 Dept. of Respiratory Medicine, Amsterdam Public Health research institute, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands;
2 Dept. of Pediatrics, Pediatric Pulmonology & Allergology, Erasmus Medical Center- Sophia Children’s Hospital, Rotterdam, The Netherlands;
3 Netherlands Twin Register, Department of Biological Psychology, Amsterdam Public Health research institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands;
4 Dept. of Pediatric Pulmonology & Allergology, University Medical Center Groningen, Groningen, The Netherlands;
5 Dept. of Paediatric Pulmonology, Amsterdam Public Health research institute, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands.
6 shared first co-author

Keywords: antibiotics, asthma, eczema, paediatrics, twin study

Rationale
Epidemiological studies have shown that early-life exposure of antibiotics in children increases risk of asthma and eczema. However, causal relationships were difficult to assess in these studies (1,2). We aim to investigate evidence for causality in the relationship between early-life antibiotic use and development of asthma and eczema in a Dutch twin cohort.

Methods
We investigated 7,386 children (age: 3-10 years) from the Netherlands Twin Register prospectively followed by questionnaires (3). Outcome was defined as parental-reported asthma at age 3, 5, 7 or 10 years. Early-life antibiotic exposure was defined as parental-reported use of antibiotics between 0-2 years. Individuals derived from twin pairs were included in unmatched case-control analyses, using generalized estimating equation models. Conditional logistic regressions were performed in twin pairs using a co-twin control analysis. This design includes disease discordant twin pairs. Affected twins were matched to their healthy co-twin. It takes advantage of the fact that MZ and DZ twin pairs share different degrees of genetic relatedness and share their environment, while exposure to antibiotics can differ within twin pairs (4).

Results
Early-life antibiotic use was associated with an increased risk of asthma (OR: 1.28, 95% CI: 1.18-1.45; n=7,386) and eczema (OR: 1.17, 95% CI: 1.08-1.27; n=7,038) in affected twins with unrelated controls. After controlling for shared environmental factors by analysing disease discordant MZ and DZ twin pairs (healthy co-twin as control), the risk of developing asthma was significantly increased (OR: 1.84, 95% CI: 1.05-3.22, n=536), but non-significant for eczema (1.21, 95%CI: 0.81-1.80; n=946). After controlling for both shared environmental and genetic factors in disease discordant MZ pairs, increased risk remained, but not statistically significant for developing asthma (OR: 3.33, 95% CI: 0.92-12.11; n=138) and eczema (OR: 2.00, 95% CI: 0.90-4.45; n=306). Lack of statistical power may be a reason for reaching this borderline significant finding. We could not correct for prescription of antibiotics caused by viral infections, which may be a confounder.

Conclusion
Our results suggest that the association between early-life antibiotic use and asthma or eczema is not confounded by environmental or genetic factors, and might be causal. The risks and benefits of using antibiotic therapy in young children should be considered before the start of therapy.
A precision medicine trial to study heterogeneity in paediatric asthma: design of the PUFFIN trial

Elise M.A. Slob¹, Susanne J.H. Vijverberg³, Mariëlle W. Pijnenburg², Gerard H. Koppelman³, Anke-Hilse Maitland – van der Zee¹

Affiliations:  
¹ Dept. of Respiratory Medicine, Academic Medical Center, Amsterdam, The Netherlands;  
² Dept. of Pediatrics, Pediatric Pulmonology & Allergology, Erasmus Medical Center, Rotterdam, The Netherlands;  
³ Dept. of Pediatric Pulmonology & Allergology, University Medical Center Groningen, Groningen, The Netherlands.

Keywords: paediatrics, asthma, long-acting beta2-agonists, randomized controlled trial, pharmacogenetics

Rationale  
There is large heterogeneity in treatment response to asthma medication and a one-size fits all approach based on current guidelines might not fit all children with asthma. It is expected that children with one or more variant alleles (Arg16Arg and Arg16Gly) within the beta2 adrenergic receptor (ADRB2) gene coding for the beta2-receptor have a higher risk to poorly respond to long-acting beta2-agonists (LABA) comparing to the Gly16Gly wildtype [1,2]. We aim to study whether ADRB2 genotype-guided treatment will lead to improvement in asthma control in children with uncontrolled asthma on inhaled corticosteroids compared with usual care.

Methods  
A multicentre, double-blind, precision medicine, randomized trial will be carried out within 15 Dutch hospitals. 310 asthmatic children (6-17 years of age) not well controlled on a low dose of inhaled corticosteroids (ICS) will be included and randomized over a genotype-guided and a non-genotype-guided(control) arm. In the genotype-guided arm children with Arg16Arg and Arg16Gly will be treated with double dosages of ICS and with the Gly16Gly wildtype with add on LABA. In the control arm children will be randomized over both treatment options. Lung function measurements, questionnaires focussing on asthma control (ACT/c-ACT) and quality of life, will be obtained in three visits within 6 months. The primary outcome will be improvement in asthma control based on repeated measurement analysis of c-ACT or ACT scores in the first three months of the trial. Additional cost effectiveness studies will be performed [3].

Results  
N.A.

Conclusion  
Currently, pharmacogenetics is not used in paediatric asthma. This trial may pave the way to implement promising results for genotype-guided treatment in paediatric asthma in clinical practice.
Subjective but not objective increase in sleep problems during dexamethasone treatment in pediatric acute lymphoblastic leukemia

L.M.H. Steur¹, M.A. Grootenhuis⁵, N.K.A. van Eijkelenburg⁷, I.M. van der Sluis², N. Dors³,⁴, C. van den Bos¹,⁵, W.J.E. Tissing³,⁴, G.J.L. Kaspers¹,²,⁷, R.R.L. van Litsenburg¹,²

Affiliations:
¹Amsterdam UMC, Emma Children’s Hospital, Vrije Universiteit, Pediatric oncology-hematology, Cancer Center Amsterdam, Amsterdam, The Netherlands
²Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
³Erasmus Medical Center, Sophia Children’s Hospital, Department of pediatric oncology, Rotterdam, the Netherlands
⁴Radboud University Medical Center, Amalia Children’s Hospital, Department of pediatric oncology, Nijmegen, the Netherlands
⁵Amsterdam UMC, Emma Children’s Hospital, Univ of Amsterdam, Department of pediatric oncology, Amsterdam, The Netherlands
⁶Beatrix Children’s Hospital University Medical Center Groningen, Department of pediatric oncology, Groningen, the Netherlands
⁷Dutch Childhood Oncology Group, Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands

Keywords: Sleep, pediatric acute lymphoblastic leukemia, questionnaire, actigraphy

Rationale
Sleep problems are common in childhood cancer and glucocorticoid treatment seems to be a risk factor. Current evidence is limited by small sample sizes and heterogeneous treatment groups. Additionally, most studies have not combined objective and subjective assessments. This study evaluates the effect of dexamethasone treatment on objective and subjective sleep in children with acute lymphoblastic leukemia (ALL).

Methods
This study is a national prospective study on sleep in children treated for ALL. At one year post-diagnosis, children treated with cyclic dexamethasone (DEX) were assessed twice: on-DEX and off-DEX. Each measurement consisted of: objective 7-day sleep assessment with a wrist-worn accelerometer and subjective sleep assessment with the parent-reported Children’s Sleep Habits Questionnaire (CSHQ). CSHQ Z-scores were calculated based on age specific Dutch norms. Differences on-DEX and off-DEX were evaluated using multilevel analysis. The effect of age, sex, pre-existent sleep problems, comorbidity, and pain was evaluated.

Results
CSHQ scores were available in 68 patients, actigraphy in 47. Mean age was 5.9±2.5 years, 42% were girls. The prevalence of sleep problems was 55% on-DEX and 48% off-DEX. The mean CSHQ Z-score was 0.47 standard deviation higher on-DEX compared to off-DEX (p=0.009, 95% CI 0.12-0.82). There were no significant differences in any of the objective sleep outcomes.

Conclusion
The prevalence of sleep problems is high during ALL maintenance with cyclic corticosteroid treatment. On-DEX parent-reported sleep problems increase significantly compared to off-DEX, but actigraph outcomes remain similar. These results suggest that DEX treatment leads to more parent perceived sleep problems and stresses the importance of supporting families in how to cope with DEX effects.
The development of a game to facilitate pediatric patient participation in hospital care, research and intervention development

L. Teela1, L.E. Verhagen1, M.P. Gruppen2, M.A. Grootenhuis3, L. Haverman1

Affiliations:
1 Amsterdam UMC, University of Amsterdam, Emma Children’s Hospital, Psychosocial Department, Amsterdam, The Netherlands
2 Amsterdam UMC, University of Amsterdam, Emma Children’s Hospital, Pediatrics, Amsterdam, The Netherlands
3 Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands

Keywords: Participation, Patient engagement, Co-creation, Adolescents, Hospital care, Research, Intervention development

Rationale
Participation of patients in hospital care is essential, because patients can be seen as experts. Although this is increasingly acknowledged, professionals still find it hard to realize this, especially within pediatric patients. Therefore, the goal of this project is to develop a game for adolescents, called 'All Voices Count' ('Alle Stemmen Tellen'), which can be used by professionals to incorporate patient participation in hospital care, research and intervention development.

Methods
The game was developed in 3 steps; 1) focus groups with fifteen adolescents (age range 12-18y) with a chronic disease resulted in 10 major themes for adolescents regarding hospital care (e.g. my hospital and like me) and preferences for a group game that contains a winning element. 2) A first version of the game was developed based on the topics. Fourteen adolescents (age range 12-18y) gave their opinion about the draft version; the game helps adolescents to give their opinion more easily and the images on the cards should be more recognizable for adolescents. 3) Adjustments were made to the game. A pilot workshop with four adolescents (age range 13-16y) was held: the game is easy to play and a word accompanying the image would be supportive.

Results
A final version of the game was developed, including a training for professionals and a game manual. All Voices Count can now be provided to researchers and health care professionals.

Conclusion
With this game we provide professionals a tool to include the input from pediatric patients in the decision-making process of hospital care.
Indeterminate pulmonary nodules at diagnosis in rhabdomyosarcoma: are we undertreating patients? A report from the European paediatric Soft tissue sarcoma Study Group.

B. Vaarwerk1,2, G. Bisogno3, K. McHugh4, H.J. Brisse5, C. Morosi6, N. Corradini7, M. Jenney8, D. Orbach5, J.C. Chisholm9, A. Ferrari6, I. Zanetti3, G.L. De Salvo10, R.R. van Rijn1, J.H.M. Merks1,2

Affiliations:
1 Department of Pediatric Oncology (B.V., J.H.M.M.), Pediatric Radiology (R.R.v.R.), Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, the Netherlands.
2 Princess Máxima Center for pediatric oncology (B.V., J.H.M.M.), Utrecht, The Netherlands.
3 Pediatric Hematology and Oncology Division (I.Z., G.B), Department of Woman’s and Child’s Health, Padova University Hospital, Padova, Italy.
4 Department of Radiology (K.M.), Great Ormond Street Hospital for Children, London, United Kingdom.
5 SIREDO Oncology Center, PSL University (D.O.), Imaging department (H.J.B.), Institut Curie, Paris, France.
6 Fondazione IRCCS Istituto Nazionale Tumori Milano (A.F., C.M.), Milan, Italy.
7 Institut d’Hématologie et d’Oncologie Pédiatrique (N.C.), Centre Léon Bérard, Lyon, France.
8 Department of Pediatric Oncology (M.J.), Children’s Hospital for Wales, Heath Park, Cardiff, United Kingdom.
9 Children and Young People’s Department (J.C), Royal Marsden Hospital, Sutton, United Kingdom.
10 Clinical Research Unit (G.L.D.S.), Istituto Oncologico Veneto IOV - IRCCS, Padova, Italy.

Keywords: Pediatric Oncology, indeterminate pulmonary nodules, pulmonary metastases, rhabdomyosarcoma

Rationale
Staging for pulmonary metastases in pediatric rhabdomyosarcoma (RMS) is usually done by chest CT. However, improved resolution of chest CTs have introduced new diagnostic dilemmas; small nodules also became detectable, which are generally too small to biopsy. Therefore, the decision to treat patients according to non-metastatic or metastatic guidelines is often based on CT characteristics only. We evaluated the impact of indeterminate pulmonary nodules (defined as ≤4 nodules <5 mm or 1 nodule of 5-10 mm) on survival in patients with RMS.

Methods
Patients with supposed non-metastatic RMS enrolled in the EpSSG-RMS 2005 study in large pediatric oncology centers were included. Local radiologists were asked to review the chest CTs at diagnosis for the presence of pulmonary nodules. In the EpSSG-RMS 2005 study, patients with indeterminate pulmonary nodules were treated identically to patients without pulmonary nodules, enabling us to compare event-free survival (EFS) and overall survival (OS) between groups by log-rank test.

Results
In total, 316 patients were included; 67 patients showed indeterminate pulmonary nodules (21%), and 249 patients showed no pulmonary nodules at diagnosis (79%). Median follow-up for survivors (n=258) was 75 months; 5-year EFS and OS rates [95% CI] were 77% [65-86%] and 82% [70-90%] for patients with indeterminate nodules and 73% [67-78%] and 81% [75-85%] for patients without nodules at diagnosis (p=0.7, p=0.8).

Conclusion
Our study demonstrated that indeterminate pulmonary nodules at diagnosis do not affect outcome in patients with non-metastatic RMS. There is no need to intensify treatment for this group in future protocols.
Personal and environmental factors associated with spoken language comprehension in children with Cerebral Palsy: a systematic review

E. Vaillant¹, J. Geytenbeek¹, I. Jansma², K.J. Oostrom³, R.J. Vermeulen⁴, A.I. Buizer¹

Affiliations:
¹ Amsterdam UMC: Rehabilitation Department, location VUmc Amsterdam, The Netherlands
² VU Amsterdam, Amsterdam, The Netherlands
³ Amsterdam UMC: Psychosocial Department, Emma Children’s Hospital, Location AMC, Academic Medical Center, Amsterdam, The Netherlands
⁴ Maastricht UMC+, Maastricht, the Netherlands

Keywords: Cerebral Palsy, spoken language comprehension, influencing factors

Rationale
Children with CP form a heterogeneous group with large differences in motor functioning, communication and speech. Communication problems are common in children with CP. Because of the challenges associated with communication for children with CP, discrepancies between receptive (comprehension of spoken language) and expressive (speech, use of alternative communication) may exist. Comprehension of spoken language has shown to play a pivotal role in communication and social interactions. Therefore, better understanding of personal and environmental influencing factors on development of spoken language comprehension in children with CP can help us to identify factors that facilitate or impede language learning. The aim of this study is to identify which personal and environmental factors influence the language comprehension development of children with CP and to present the research protocol for the longitudinal CP-CaLL project.

Methods
Longitudinal research project investigating the spoken language comprehension of children with CP, age 1;6 – 11, and influencing factors. Systematic search in electronic literature databases to identify which personal and environmental factors influence the language comprehension development of children with CP.

Results
The CP-CaLL project started August 2017 and first results can be shown in February 2019 at Amsterdam Kindersymposium. In the systematic review 21 studies were included in qualitative and quantitative synthesis. Personal and environmental factors have variable outcomes when associated with spoken language comprehension.

Conclusion
Research about the personal and environmental factors influencing spoken language comprehension in children with CP is limited. More research, and specifically longitudinal research, has to be conducted.
primary focal segmental glomerulosclerosis (FSGS) is an important cause of end-stage renal disease in paediatric patients. The post-transplant recurrence risk of FSGS is high (30-70%), and is associated with an increased risk of early graft loss. Currently, no clear guidelines on preventive and/or therapeutic treatment for FSGS recurrence exist. We, therefore, conducted a survey to gain insight into existing differences in treatment protocols between centres.

Methods

We performed a web-based survey among all members of the European Society of Paediatric Nephrology.

Results

A total of 59 (15%) ESPN members from 31 countries responded. In total, 807 FSGS patients were reported. In 241 (30%) cases FSGS recurred after transplantation. Nephrectomy of the native kidney before and/or during transplantation was performed always (37%), never (39%) or on clinical indication (17%). About half (49%) starts preventive treatment before transplantation, using plasmapheresis (PD)/(double) filtration (n=10), Rituximab (n=4), combination therapy (n=9), cyclosporine (n=2) or unknown (n=4). Initial immunosuppressive therapy for patients without proven mutation consists of a combination of steroids, tacrolimus/cyclosporine, and mycophenolate mofetil in 73% of the responders. For the treatment of FSGS recurrence after transplantation, 66% used a combination of PD or immunoadsorption with Rituximab. No response to treatment was observed by 54% of the responders.

Conclusion

This survey showed that FSGS recurrence after transplantation is common (30%), but varies greatly among centres. Complete remission in >50% of the patients is achieved by 41% of the centres. Additionally, we showed great variability in preventive and therapeutic treatment regimens. Future research should focus on treatment and predisposing factors, including biopsy findings and genetic mutation analysis.
Health Related Quality of Life in Childhood Functional Constipation: a systematic review and meta-analysis

M.H. Vriesman¹, S. Rajindrajith², I.J.N. Koppen⁴, F.S. van Etten-Jamaludin³, N.M. Devanarayana⁵, M.M. Tabbers¹, M.A. Benninga¹

Affiliations:
¹ Department of Pediatric Gastroenterology and Nutrition, Emma Children’s Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
² Departments of Pediatrics, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka
³ Medical Library, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands
⁴ Department of Physiology, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka

Keywords: quality of life, functional constipation, children

Rationale
To systematically review the literature on health related quality of life (HRQoL) in children with functional constipation and to identify disease-related factors associated with HRQoL.

Methods
Pubmed, Embase, and PsycINFO were searched for studies that prospectively assessed HRQoL in children with functional constipation according to the Rome II, III or IV criteria. A meta-analysis was performed using the sample-size weighted pooled mean and standard deviation HRQoL scores. HRQoL scores were compared between self-reported and proxy-reported data, community and hospital based studies and between children with and without symptoms of fecal incontinence.

Results
A total of 19/2658 studies were included, of which 12 studies reported sufficient data to be included in the meta-analysis. All 12 studies used the Pediatric Quality of Life Inventory (PedsQL) instrument. HRQoL scores of children with functional constipation were found to be impaired compared to healthy reference samples. No significant difference was found between self-reported (child) and proxy-reported (parental) total HRQoL scores (69.8 vs. 70.6, p=0.206), however parents reported emotional and physical HRQoL to be significantly lower as compared to their children (67.6 vs. 61.8, p<0.000 and 75.9 vs. 70.9, p<0.000 respectively). Hospital-based studies reported lower HRQoL scores as compared to community-based studies (71.9 vs. 76.2, p=0.004). Two studies reported on HRQoL scores of children with and without symptoms of fecal incontinence, but no significant differences were found (78.3 vs. 79.4, p=0.408).

Conclusion
HRQoL in children with functional constipation is compromised and needs to be addressed in clinical practice. Future research should incorporate HRQoL as an important outcome to evaluate treatment success.
Abstracts submitted to the Amsterdam Kindersymposium 2019

Clinical factors associated with late-onset inhibitor development in non-severe hemophilia A patients – preliminary data of a case-control study

A. Abdi¹, C. Vuong¹, C.L. Eckhardt¹, M. Coppens², S.C. Gouw¹, K. Fijnvandraat¹

Affiliations:
¹ Department of Pediatric Hematology, Immunology and Infectious Diseases, Emma Children's Hospital, Amsterdam UMC, location AMC, The Netherlands
² Department of Vascular Medicine, Amsterdam Cardiovascular Sciences, Amsterdam UMC, location AMC, The Netherlands

Keywords: non-severe hemophilia A; factor VIII; inhibitor development; case-control study

Rationale
The development of factor VIII (FVIII) inhibitors is a severe complication in non-severe hemophilia A (NSHA) treatment. Although NSHA patients have a lifelong risk to develop inhibitors, knowledge on risk factors is limited to patients with an early onset of inhibitors. We aimed to identify patient and treatment related factors associated with late-onset inhibitor development in NSHA.

Methods
We performed a case-control study in the INSIGHT cohort, by selecting cases who developed inhibitors after 50 FVIII exposure days (EDs). Each case was matched to 1-4 inhibitor-negative controls for: date of birth, number of EDs and center/country. We collected data of first and last EDs until inhibitor development in cases and up to the same ED number in controls. We performed conditional logistic regression (adjusted for predefined confounders) to identify associations between patient and treatment related determinants and inhibitor development.

Results
Out of 2709 NSHA patients (FVIII baseline level 2-40 International Units (IU)/dL), we included 31 cases and 84 controls. Arg2150His was the most prevalent hemophilia genotype (cases, 19%; controls, 7%). At first treatment, cases were older (35 years, IQR 12-49) than controls (18 years, IQR 8.5-37). In last 10 EDs, cases received a higher mean FVIII dose (35 IU/kg, IQR 20-45) in a shorter time period (30 days, IQR 9-384) than controls (25 IU/kg, IQR 18-35; 202 days, IQR 23-620). We will perform multivariable analyses and present the results at the symposium.

Conclusion
Our preliminary findings suggest that patient and treatment related factors may be associated with late-onset inhibitor development in NSHA.
Ultrasound of the bowel in Healthy Children

E.A. van Wassenaer¹, F.A.E. de Voogd², R.R. van Rijn MD³, M.A. Benninga MD¹, B.G.P. Koot⁴

Affiliations:
¹ Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, The Netherlands
² Department of Gastroenterology and Hepatology Amsterdam UMC, Univ of Amsterdam, The Netherlands
³ Department of Pediatric Radiology, Amsterdam UMC, Univ of Amsterdam, The Netherlands

Keywords: Ultrasound, Bowel, Bowel wall thickness, Children, Reference value

Rationale
Ultrasound (US) is a non-invasive, easy accessible and fast imaging modality to assess the bowel of children. It can be used to detect abnormalities of the bowel wall, e.g. in Inflammatory Bowel Disease or Cystic Fibrosis. However, little is known about reference values in healthy children. The aim of this systematic review was to assess reference values for bowel wall measurements in healthy children.

Methods
We conducted a systematic review in Pubmed, Embase, Cochrane Library, and Cinahl. Inclusion criteria were studies examining the bowel in children and exclusion criteria were not using regular transabdominal US, only describing the appendix and unavailability of full text. Articles were first checked for duplication, then screened on title/abstract and subsequently on full text. A selection of items of the QUADAS was used to grade quality. The selection was performed by two authors. In case of conflicts a third author could be asked.

Results
Seven of 167 studies were included. Reasons for exclusion were wrong population, wrong outcome and full text unavailability. Average bowel wall thickness (BWT) was 0.8 mm in the jejunum, 1.0 in ileum, 1.2 in cecum, ascending and transverse colon and 1.3 in descending colon. BWT increased significantly with age in all colonic segments. The maximum BWT in all segments was 1.9 mm. In several studies mesenteric lymph nodes were reported.

Conclusion
BWT increases with age. The bowel wall in healthy children does not exceed 2 mm and mesenteric lymph nodes are a common finding. These results can be used when screening for pathology in children.
The neuropsychological spectrum of classical galactosemia patients

M.M. Welsink-Karssies¹, G.J. Geurtsen², M.E. Hermans³, K.J. Oostrom⁴, A.M. Bosch⁵

Affiliations:
¹ Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, The Netherlands
² Department of Medical Psychology, Amsterdam UMC, Amsterdam, The Netherlands
³ Department of Medical Psychology, Amsterdam UMC, Amsterdam, The Netherlands
⁴ Psychosocial Department, Emma Children’s Hospital, Amsterdam UMC, The Netherlands
⁵ Department of Pediatrics, Emma Children’s Hospital, Amsterdam UMC, The Netherlands

Keywords: Classical Galactosemia, GALT deficiency, Cognition, Intelligence, Neuropsychological assessment, Social functioning

Rationale
Despite early diagnosis and treatment, Classical Galactosemia (CG) patients frequently develop long-term complications, such as cognitive impairment. Previous research demonstrated a substantially lower mean Full Scale Intelligence Quotient (FSIQ) in CG patients compared to the general population, with a remarkably large variability. Until now, the full neuropsychological spectrum including intelligence quotient, functioning on specific cognitive domains and social functioning, has not been studied systematically.

Methods
To gain insight in the neuropsychological spectrum of CG patients, we investigated intelligence quotient, functioning on specific cognitive domains and social functioning with standardized neuropsychological measures in children and adults visiting the AMC CG expertise outpatient clinic.

Results
From the 70 CG patients visiting the expertise clinic, a total of 51 patients (73%) aged between two and 47 years, underwent a standardized neuropsychological assessment. FSIQ ranged from 45 to 103 (mean 77 ± 14). Twenty-three percent of the patients had a FSIQ below 70 (< -2SD), indicating intellectual deficiency. In our cohort, 18% of the patients reported difficulties in social functioning (against 16% in the normal population). Results on functioning on specific domains will follow.

Conclusion
In this study, we evaluated the neuropsychological profile of a large cohort of CG patients. The FSIQ was highly variable but severely decreased. Social functioning in CG patients was comparable to the general population. Because of the variety in cognitive abilities, all patients should be assessed from childhood on to ensure early diagnosis of cognitive impairment and timely intervention and support if needed.
Current clinical practice of pediatric image-guided radiation therapy in Europe

C. Windmeijer¹, A. Bel¹, R. De Jong¹, B. Balgobind³, PROS-Consortium Group¹, C. Rasch¹, I. Van Dijk¹

Affiliations:
¹ Department of Radiation Oncology, Amsterdam UMC - location AMC, The Netherlands
² Department of Radiation Oncology, Various centers, Europe

Keywords: Pediatric IGRT, childhood cancer, margin, radiotherapy

Rationale
Advanced treatment strategies such as Image-Guided Radiotherapy (IGRT) enable high precision tumor treatment while sparing healthy tissues. Particularly in pediatric radiotherapy the value of IGRT is widely acknowledged, but there is no consensus on the ‘best practice’. In this scoping study we addressed the following question: Do dedicated European RT centers agree on the application of IGRT for the treatment of childhood cancer, as measured by our in-house developed survey?

Methods
The survey focuses on radiotherapy preparation, planning and delivery and was developed by a multidisciplinary team of clinicians and physicists. The survey was executed in the web-based electronic data capturing system Castor.

Results
Clinical practice in pre-treatment imaging, patient positioning, and treatment delivery technique was similar in the 33 (60%) responding institutes. Variations were found in the use of in-room IGRT, although this was highly dependent on treatment site. The definition of planning target volume (PTV) safety-margin sizes and the use of treatment protocols varied considerably between institutes and indications.

Conclusion
In this study, we have given an overview of the current state of pediatric IGRT practice in a large sample of dedicated European pediatric RT centers. Our results show moderate agreement in clinical pediatric IGRT application. The outcomes of the survey could lead to a starting point for the establishment of international guidelines. At the same time, new insight from the overarching project will form the basis of a consensus towards optimal care.
Parental factors in pediatric functional abdominal pain disorders: a cross-sectional cohort study

J. Zeevenhooven*1, J. Rutten*1, M. van Dijk2, B. Peeters1, M. Benninga1

Affiliations:
1 Department of Pediatric Gastroenterology and Nutrition, Emma Children’s Hospital / Amsterdam University Medical Centers, location AMC, Amsterdam, The Netherlands
2 Psychosocial Department, Emma Children’s Hospital / Amsterdam University Medical Centers, location AMC, Amsterdam, The Netherlands

Keywords: Irritable bowel syndrome (IBS), functional abdominal pain - not otherwise specified (FAP-NOS), children, parents, parental factors, physical problems, child-rearing practices

Rationale
Parental factors are suggested to play a role in pediatric irritable bowel syndrome (IBS) and functional abdominal pain – not otherwise specified (FAP-NOS) and may influence treatment. Since studies on parental factors mainly focus on mothers, this study aims to compare physical health, psychological distress, personality dimensions and parenting behavior of both parents of children with IBS or FAP-NOS to parents of controls.

Methods
Parents of 91 children with IBS or FAP-NOS were included in this explorative cross-sectional cohort study. Parents of 74 age-matched healthy children were used as controls. Questionnaires were used to measure demographics, physical health, psychological distress and symptoms, personality dimensions and child-rearing practices.

Results
59 mothers and 52 fathers of 61 children with IBS/FAP-NOS (response rate 61.0%) and 56 mothers and 49 fathers of 59 controls completed the study (response rate 70.9%). Mothers of children with IBS/FAP-NOS reported more physical problems. Psychological distress and symptoms, personality dimensions and child-rearing practices did not differ between mothers of both groups. Fathers of children with IBS/FAP-NOS had significantly lower scores on the child-rearing practice subscale of ignoring of unwanted behavior. In the IBS/FAP-NOS group, fathers were more depressed and less agreeable than mothers. No differences on all assessed outcomes were found between parents of children with IBS and children with FAP-NOS.

Conclusion
Mothers of children with IBS/FAP-NOS and healthy peers differ with respect to physical health. Fathers in both groups differ with respect to child-rearing style. Clinicians should be aware of these differences when treating children with these disorders.
PRESENTING AUTHORS

WHO IS WHO
## Presenting authors AKS 2019 ‘Who-is-who’

<table>
<thead>
<tr>
<th>Name</th>
<th>Department</th>
<th>Hospital</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achten, Niek</td>
<td>Department of Pediatrics</td>
<td>Tergooi Blaricum</td>
<td><a href="mailto:niek.achten@gmail.com">niek.achten@gmail.com</a></td>
</tr>
<tr>
<td>Aknouch, Ikrame</td>
<td>Department of Pediatric Infectious Diseases</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:i.aknouch@amc.uva.nl">i.aknouch@amc.uva.nl</a></td>
</tr>
<tr>
<td>Bekius, Annike</td>
<td>Department of Human Movement Sciences</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:a.bekius@vu.nl">a.bekius@vu.nl</a></td>
</tr>
<tr>
<td>Bonnema, Marloes</td>
<td>Department of Pediatrics</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:m.e.bonnema@hotmail.com">m.e.bonnema@hotmail.com</a></td>
</tr>
<tr>
<td>Brink van den, Debbie</td>
<td>Global Child Health Group</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:d.a.vandenbrink@amc.uva.nl">d.a.vandenbrink@amc.uva.nl</a></td>
</tr>
<tr>
<td>Brouwer, Lieke</td>
<td>Department of Medical Microbiology</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:lieke.brouwer@amc.uva.nl">lieke.brouwer@amc.uva.nl</a></td>
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<tr>
<td>Bunder van den, Fenne</td>
<td>Department of Pediatric Surgery</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:f.a.vandenbunder@amc.uva.nl">f.a.vandenbunder@amc.uva.nl</a></td>
</tr>
<tr>
<td>Demirok, Aysenur</td>
<td>Department of Immunogenetics, Sanquin</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:a.demirok@amc.uva.nl">a.demirok@amc.uva.nl</a></td>
</tr>
<tr>
<td>Depla, Josse</td>
<td>Department of Pediatric Infectious Diseases</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:j.depla@uniqure.com">j.depla@uniqure.com</a></td>
</tr>
<tr>
<td>Douma, Miriam</td>
<td>Psychosocial Department</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:m.douma@amc.uva.nl">m.douma@amc.uva.nl</a></td>
</tr>
<tr>
<td>Draijer, Laura</td>
<td>Department of pediatrics</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:lg.draijer@amc.nl">lg.draijer@amc.nl</a></td>
</tr>
<tr>
<td>Eeftinck Schattenkerk, Laurens</td>
<td>Department of Pediatric Surgery</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:laurens-es@hotmail.com">laurens-es@hotmail.com</a></td>
</tr>
<tr>
<td>El Manouni El Hassani, Sofia</td>
<td>Department of Pediatric Gastroenterology, Hepatology and Nutrition</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:s.elmanounielhassani@vumc.nl">s.elmanounielhassani@vumc.nl</a></td>
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<td>Fustolo-Gunnink, Suzanne</td>
<td>Sanquin Blood Supply Foundation</td>
<td>Sanquin</td>
<td><a href="mailto:s.f.gunnink@amc.uva.nl">s.f.gunnink@amc.uva.nl</a></td>
</tr>
<tr>
<td>Gathier, Anouk</td>
<td>Psychosocial Department</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:a.w.gathier@amc.uva.nl">a.w.gathier@amc.uva.nl</a></td>
</tr>
<tr>
<td>Genderen van, Jason</td>
<td>Department of Pediatric Infectious Diseases</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:j.g.vangenderen@amc.uva.nl">j.g.vangenderen@amc.uva.nl</a></td>
</tr>
<tr>
<td>Groot de, Corien</td>
<td>Department of Pediatric Hematology</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:c.leckhardt@amc.nl">c.leckhardt@amc.nl</a></td>
</tr>
<tr>
<td>Haar ter, Marleen</td>
<td>Department of Pediatric Infectious Diseases</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:a.m.terhaar@amc.nl">a.m.terhaar@amc.nl</a></td>
</tr>
<tr>
<td>Harink den, Tamara</td>
<td>Department of Clinical Epidemiology, Biostatistics and Bioinformatics/ Department of Obstetrics and Gynaecology</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:t.denharink@amc.uva.nl">t.denharink@amc.uva.nl</a></td>
</tr>
<tr>
<td>Houdt van, Carolien</td>
<td>Department of Neonatology</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:c.a.vanhoudt@amc.uva.nl">c.a.vanhoudt@amc.uva.nl</a></td>
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<td>Jansen, Sophie</td>
<td>Department of Neonatology</td>
<td>LUMC</td>
<td><a href="mailto:sophjansen@gmail.com">sophjansen@gmail.com</a></td>
</tr>
<tr>
<td>Kassel van, Merel</td>
<td>Department of Neurology</td>
<td>Amsterdam</td>
<td><a href="mailto:m.n.vankassel@amc.uva.nl">m.n.vankassel@amc.uva.nl</a></td>
</tr>
<tr>
<td>Keulen van, Britt</td>
<td>Department of Pediatric Endocrinology</td>
<td>Amsterdam</td>
<td><a href="mailto:b.vankeulen@vumc.nl">b.vankeulen@vumc.nl</a></td>
</tr>
<tr>
<td>Klein-Blommert, Rozalinde</td>
<td>Departments of Pediatric Intensive Care</td>
<td>Amsterdam</td>
<td><a href="mailto:r.klein-blommert@vumc.nl">r.klein-blommert@vumc.nl</a></td>
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<tr>
<td>Knottnerus, Suzan</td>
<td>Laboratory Genetic Metabolic Diseases</td>
<td>Amsterdam</td>
<td><a href="mailto:s.j.knottnerus@amc.uva.nl">s.j.knottnerus@amc.uva.nl</a></td>
</tr>
<tr>
<td>Königs, Marsh</td>
<td>Department of Pediatrics, Neuroscience Group</td>
<td>Amsterdam</td>
<td><a href="mailto:m.konigs@amc.nl">m.konigs@amc.nl</a></td>
</tr>
<tr>
<td>Kooten van, Joanneke</td>
<td>Department of Pediatric Oncology- Hematology</td>
<td>Amsterdam</td>
<td><a href="mailto:j.vankooten1@vumc.nl">j.vankooten1@vumc.nl</a></td>
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<td>Kouwenhoven, Stefanie</td>
<td>Department of Neonatology</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:s.kouwenhoven@vumc.nl">s.kouwenhoven@vumc.nl</a></td>
</tr>
<tr>
<td>Krom, Hilde</td>
<td>Department of Pediatric Gastroenterology, Hepatology and Nutrition</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:h.krom@amc.uva.nl">h.krom@amc.uva.nl</a></td>
</tr>
<tr>
<td>Lagemaat van de, M</td>
<td>Department of Radiology and Nuclear Medicine</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:m.vandelagemaat@vumc.nl">m.vandelagemaat@vumc.nl</a></td>
</tr>
<tr>
<td>Lammers, Marije</td>
<td>Department of Pulmonology</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:a.lammers@amc.uva.nl">a.lammers@amc.uva.nl</a></td>
</tr>
<tr>
<td>Langdon, Shari</td>
<td>Department of Pediatrics</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:s.langdon@amc.uva.nl">s.langdon@amc.uva.nl</a></td>
</tr>
<tr>
<td>Leuteren van, Ruud</td>
<td>Department of Neonatology</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:r.w.vanleuteren@amc.nl">r.w.vanleuteren@amc.nl</a></td>
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<tr>
<td>Loos, Marie-Louise</td>
<td>Department of pediatric surgery</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:m.h.loos@amc.nl">m.h.loos@amc.nl</a></td>
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<td>Department</td>
<td>Institution</td>
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<tr>
<td>Luirink, Ilse</td>
<td>Department of Vascular Medicine</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:i.luirink@amc.uva.nl">i.luirink@amc.uva.nl</a></td>
</tr>
<tr>
<td>Muilekom van, Maud</td>
<td>Psychosocial Department</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:m.m.vanmuilekom@amc.nl">m.m.vanmuilekom@amc.nl</a></td>
</tr>
<tr>
<td>Naafs, Jolanda</td>
<td>Department of Pediatric Endocrinology</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:j.c.naafs@amc.uva.nl">j.c.naafs@amc.uva.nl</a></td>
</tr>
<tr>
<td>Nagelkerke, Sjoerd</td>
<td>Department of Pediatric Gastroenterology, Hepatology and Nutrition</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:s.c.nagelkerke@amc.nl">s.c.nagelkerke@amc.nl</a></td>
</tr>
<tr>
<td>Nijmeijer, Stephanie</td>
<td>Department of Pediatric Metabolic Diseases</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:s.c.nijmeijer@amc.uva.nl">s.c.nijmeijer@amc.uva.nl</a></td>
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<tr>
<td>Ouwendijk, Amy</td>
<td>Department of Pediatric Gastroenterology, Hepatology and Nutrition</td>
<td>Amsterdam UMC</td>
<td><a href="mailto:a.c.ouwendijk@amc.uva.nl">a.c.ouwendijk@amc.uva.nl</a></td>
</tr>
<tr>
<td>Peersmann, Shosha</td>
<td>Department of Pediatric Oncology</td>
<td>UMCU</td>
<td><a href="mailto:s.peersmann@vumc.nl">s.peersmann@vumc.nl</a></td>
</tr>
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</table>
Peltenburg, Puck  
Department of Pediatrics  
Amsterdam UMC  
p.j.peltenburg@uva.amc.nl

Peters, Bram  
Department of Pediatric Hematology  
Amsterdam UMC  
brmpeters@gmail.com

Pilon, Maxime  
Department of Pediatric Oncology  
Amsterdam UMC  
m.pilon2@vumc.nl

Postema, Floor  
Department of Pediatric Oncology  
UMCU  
f.a.m.postema@amc.uva.nl

Rensen, Niki  
Department of pediatric oncology-hematology  
Amsterdam UMC  
n.rensen@vumc.nl

Rexwinkel, Robyn  
Department of Pediatric Gastroenterology and Nutrition  
Amsterdam UMC  
r.rexwinkel@amc.uva.nl

Roorda, Daniëlle  
Department of Pediatric Surgery  
Amsterdam UMC  
d.roorda@amc.uva.nl
Slob, Elisa
Department of Pulmonology
Amsterdam UMC
e.m.slob@amc.nl

Sonnville de, Eleonora
Department of Pediatric Intensive Care
Amsterdam UMC
e.s.desonnville@amc.nl

Steur, Lindsay
Department of pediatric oncology
Amsterdam UMC
l.steur@vumc.nl

Teela, Lorynn
Psychosocial Department
Amsterdam UMC
l.teela@amc.uva.nl

Vaarwerk, Bas
Department of Pediatric Oncology
UMCU
b.vaarwerk@amc.nl

Vaillant, Emma
Rehabilitation Department
Amsterdam UMC
e.vaillant@vumc.nl

Veltkamp, Floor
Department of Pediatric Nephrology
Amsterdam UMC
f.veltkamp@amc.uva.nl
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<th>Name</th>
<th>Department</th>
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<tr>
<td>Veen van, Marit</td>
<td>Department of Neonatology</td>
<td>Amsterdam</td>
<td><a href="mailto:s.vanveen@amc.uva.nl">s.vanveen@amc.uva.nl</a></td>
</tr>
<tr>
<td>Vriesman, Mana</td>
<td>Department of Pediatric Gastroenterology and Nutrition</td>
<td>Amsterdam</td>
<td><a href="mailto:m.h.vriesman@amc.uva.nl">m.h.vriesman@amc.uva.nl</a></td>
</tr>
<tr>
<td>Vuong, Caroline</td>
<td>Department of Pediatric Hematology</td>
<td>Amsterdam</td>
<td><a href="mailto:a.abdi@amc.nl">a.abdi@amc.nl</a></td>
</tr>
<tr>
<td>Wassenaer van, Elsa</td>
<td>Department of Pediatrics</td>
<td>Amsterdam</td>
<td><a href="mailto:e.a.vanwassenaer@amc.nl">e.a.vanwassenaer@amc.nl</a></td>
</tr>
<tr>
<td>Welsink-Karssies, Mendy</td>
<td>Department of Pediatric Metabolic Diseases</td>
<td>Amsterdam</td>
<td><a href="mailto:m.m.karssies@amc.nl">m.m.karssies@amc.nl</a></td>
</tr>
<tr>
<td>Windmeijer, Coen</td>
<td>Department of Radiotherapy</td>
<td>Amsterdam</td>
<td><a href="mailto:c.a.windmeijer@amc.uva.nl">c.a.windmeijer@amc.uva.nl</a></td>
</tr>
<tr>
<td>Zeevenhooven, Judith</td>
<td>Department of Pediatric Gastroenterology</td>
<td>Amsterdam</td>
<td><a href="mailto:j.zeevenhooven@amc.uva.nl">j.zeevenhooven@amc.uva.nl</a></td>
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