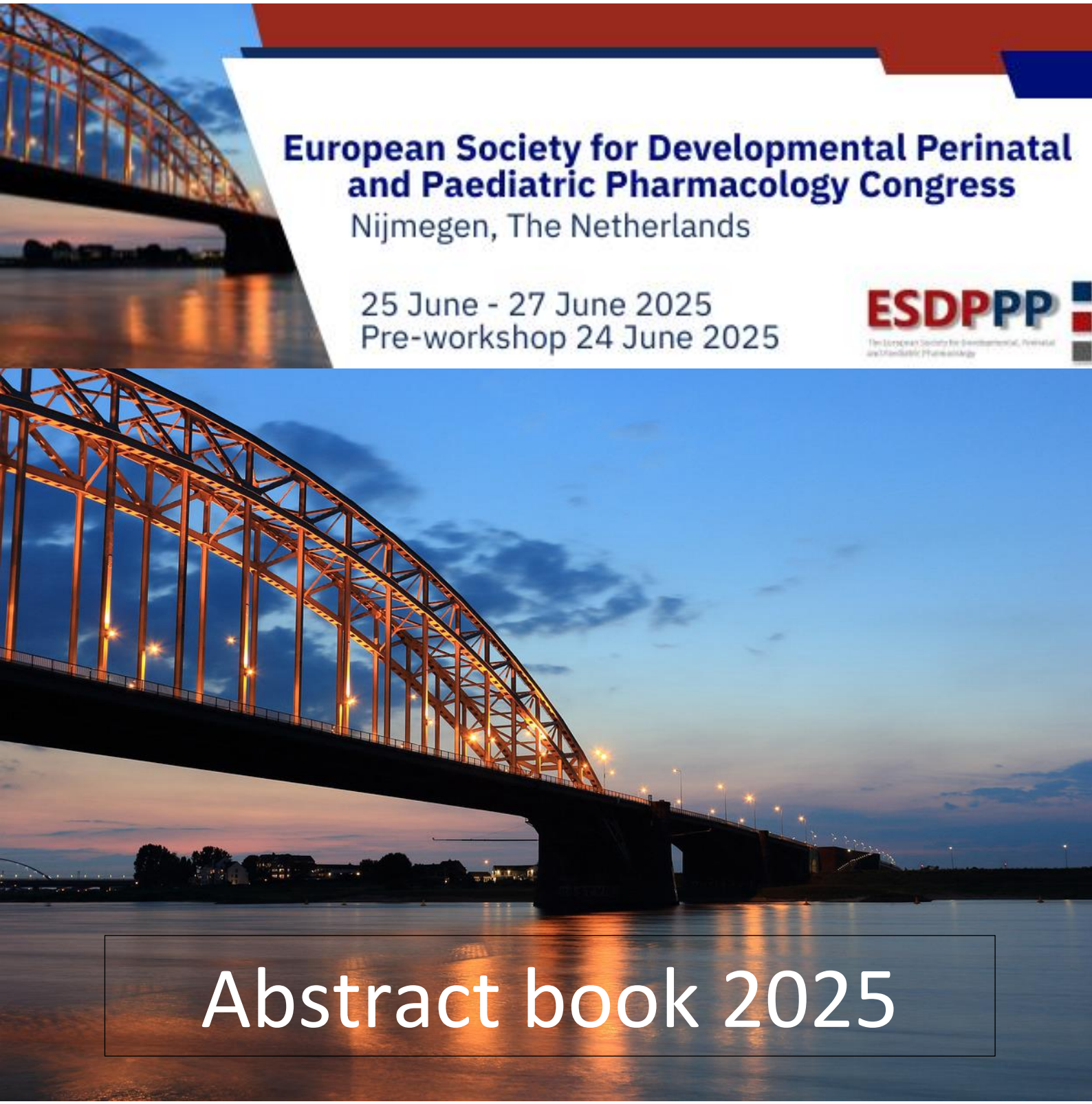

Abstract book 2025

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Table of contents*

The continuing problem of medicine shortages increases medication safety risks in children

A pooled population PK analysis investigating once-daily standard dosing of dolutegravir in HIV/TB co-infected children weighing 3 kg or more

SMAART: a clinical quality intervention tool embedded in electronic medical records to identify and challenge children with low-risk penicillin and cephalosporin allergies

Continuous glucose monitoring as reference for personalized monitoring for diabetic and healthy people of any age

Optimising paediatric HIV treatment: recent developments and future directions

Poster presentations

1. Lamotrigine use in lactating women: passage into breast milk and infant exposure **Authors:** den Besten-Bertholee D.[1], Wegner I.[2], Touw D.J.[3], ter Horst P.G.J.[1], Mian P.[3]

2. Identifying high-risk medication during pregnancy for adverse pregnancy outcomes in Electronic Patient Files (EPF) using disproportional analysis

3. Medication screening in pregnant women for cord blood donation in extremely preterm neonates

4. Spontaneous adverse drug reaction reporting of congenital malformations, a Danish national register study

5. Pediatric medication from off-label to on-intelligent-evidence

6. Angiotensin II/angiotensin I ratio as pharmacodynamic parameter in healthy adults and children with heart failure treated with enalapril: insights from an adult population pharmacokinetic-pharmacodynamic model and the LENA studies

7. A pharmacovigilance study on the association between proton-pump inhibitors and inappropriate neonatal use based on the FAERS database

8. AMI FABRY – A triple relief for pain, gut, and mood in Fabry Disease using amitriptylin

9. Drug interactions in critically ill neonates undergoing therapeutic hypothermia: a single centre study

10. Leveraging existing evidence on off-label prescribed drugs to support effective and safe pharmacotherapy: pediatrics as an example

11. A review on the role of extrapolation as basis for paediatric marketing authorisation applications of medicines in the EU

12. Preventing life-threatening symptoms of Noonan syndrome: Is it feasible to treat intra-uterine with trametinib?

13. On-label paediatric drug product information in Switzerland – the neglected child

14. Evaluation of nine population pharmacokinetic models for model-based vancomycin concentration monitoring in a local population of neonates

15. MEDeHelp –development of an emergency mobile application for Europe

16. Paracetamol concentrations and time-course of ductus arteriosus diameter in extreme preterm neonates: a population pharmacokinetic-pharmacodynamic analysis

17. The REPAIR-NEO study protocol to test a workflow on drug development in neonates undergoing therapeutic hypothermia

18. Quantifying milk and maternal postpartum changes to improve drug safety in breastfeeding

19. Developing evidence-based dosing recommendations for intravenous ciprofloxacin in critically ill children: a population pharmacokinetic study using total and unbound concentrations

20. In vivo cytochrome P450 1A2 activity in adolescents with and without obesity

21. Assessing the predictive performance of a population pharmacokinetic model for paracetamol and its metabolites in an external dataset of neonates, infants, and children receiving paracetamol as analgesic after cardiac surgery

22. Population pharmacokinetics of morphine in children under 3 years after cardiothoracic surgery: External validation and extrapolation of published models

23. Use of virtual populations to investigate 'weekend-off' efavirenz dosing in adults and adolescents with different CYP2B6 526 G>T genotypes

24. optimizing high-dose methotrexate dosing for the treatment of infant acute lymphoblastic leukemia

25. Establishing evidence-based, model-informed dose recommendations for amoxicillin in pregnancy

26. Optimizing paediatric opioid conversion and methadone tapering: physiologically-based pharmacokinetic modelling in critically ill children

27. Physiologically based pharmacokinetic ,odeling of Ivacaftor/Tezacaftor/Elexacaftor in children with cystic fibrosis: evaluating hepatic and intestinal CYP3A4 ontogeny

28. Evidence-based dose recommendations for preterm and term neonates: the neodose project

29. Optimization of microdialysis experiments to study antibiotic disposition in children: lessons learnt

30. Weight-based dosing of monoclonal antibodies in paediatrics: a systematic study of population pharmacokinetics studies to evaluate its impact on exposure of infliximab across the paediatric age range

31. Plasma protein binding: can we use piglets to study unbound drug disposition in children?

32. Osmolality of oral liquid medications intended for neonates and infants: a laboratory-based study - is not displayed

33. Hyperosmolar preparations and necrotizing enterocolitis: can a single overdose tip the balance? a case report - is not displayed

34. Ontogeny of hepatic and intestinal CYP3A activity across the pediatric age range quantified using population physiologically-based pharmacokinetic modelling

35. Drug utilisation at a German neonatal intensive care unit – Are evidence-based (off-label) dosing recommendations available?

36. Coproporphyrin I as biomarker in a pediatric population: Age-related differences and genetic influences

37. Extravasation of vesicant and irritant drugs in pediatric patients-

a literature review Authors: Tadayon A.[1], Eksborg S.[2,3], Lindemalm S.[3,4], Garnemark C.A.[3,4], Akkawi El Edelbi R.[2,3]

38. The reality of prescribing selected medications in the pediatric population: a single centre experience

39. Personalized Immunomodulatory Drug Repurposing in Patients with Mucopolysaccharidosis

40. "Meet the Pain" is an educational multidisciplinary project to improve the pain assessment skills of neonatal intensive care unit nurses

41. To re-dose or not? A decision-making flowchart after vomiting in the paediatric population

42. Causality, severity and avoidability of adverse drug reactions in children over an 11-year period

43. Trends in paediatric hypnotic prescriptions in France, 2016-2023

44. Patterns of paediatric methylphenidate users: a national time series analysis from 2016 to 2023

45. Model-based blood pressure prediction for personalized medicine for people at any age

46. Maternal drug use and infant exposure during breastfeeding

47. Effect of SARS-CoV-2 on psychotropic drug use in children: a population-based longitudinal study

48. Predictive performance, and model refinement, of physiologically based pharmacokinetic (PBPK) models for CYP3A inhibitors clarithromycin and fluconazole in a virtual paediatric population

49. Integrated, multimodal collaboration to support paediatric pharmacology and drug development: the conect4children (c4c) project and c4c stichting

50. Comparison of maternal and fetal exposure to escitalopram, sertraline, and paroxetine during pregnancy combining human ex vivo placental perfusion data and physiologically-based pharmacokinetic modeling

51. Comparative analysis of breast milk and infant formulas: microbiome and health implications

52. Sedative antipsychotic use by children and adolescents in the Netherlands: dosages, duration and prescribers

53. Impact of discontinuing open-label doxapram use in neonates on informed consent rates in the DOXA-Trial

54. The CANDi project’s first step: prioritization of off-label drug-indications warranting further assessment

55. Trends in hospitalizations for accidental poisoning in children in France, 2016-2023

56. Estimated glomerular filtration rates in neonates undergoing therapeutic hypothermia

57. Use of medication for gastroesophageal reflux during pregnancy and adverse birth outcomes

Abstracts faculty: Tuesday 24 June 2025

Pharmacokinetics

Paediatric drug formulations

Workshop: Pharmacology for clinicians

Abstracts faculty: Wednesday 25 June 2025

Drug discovery, paediatric gastrointestinal disease as example

Advancing patient-centric pediatric care using omics-derived biomarkers for predicting pharmacokinetic variability

Animal Models for In Vivo Lactation Studies

Relative impact of CYP2D6 genotype phenotype on exposure of SSRIs during pregnancy: extrapolation approach using RWD and PBPK modelling

Abstracts faculty: Thursday 26 June 2025

Extrapolation in paediatrics

Providing evidence on use and safety of medications in pregnancy when randomized clinical trials are not feasible

Drug safety in Neonates

A joint presentation about the LENA project: From formulation to market authorization

Benefit-risk in pregnancy and lactation, the regulator's view

Abstracts faculty: Friday 27 June 2025

Antithrombotic therapy in pregnancy

Pregnancy Formulary

The case of empagliflozin

* Click on the designated session to view the abstracts

Scientific programme

Tuesday 24 June 2025 – Pre-conference workshop

Auditorium

08:30 Registration

Chairs: Marjolein van Borselen and Emmely Wagener

09:00 **Welcome**
Prof. Saskia de Wildt, Radboud University Medical Center (NL)

09:15 **Pharmacokinetics**
Prof. Pieter de Cock, Ghent University Hospital (BE)

09:45 **Paediatric Pharmacology**
Prof. Anne Smits, UZ Leuven (BE)

10:15 **Obstetric Pharmacology**
Dr. Rick Greupink, Radboud University Medical Center (NL)

10:45 Coffee Break

Chairs: Marjolein van Borselen and Emmely Wagener

11:00 **Paediatric drug formulations**
Dr. Viviane Klingmann, Heinrich Heine University Düsseldorf (DE)

11:30 **Pharmacovigilance/safety**
Dr. Roberto De Lisa, European Medicines Agency (NL)

12:00 Lunch

12:45 **Workshops - breakout rooms**

Workshop Paediatrics – *breakout room 1*	**Workshop Obstetrics - *breakout room 2***	**Workshop pharmacology for clinicians - *breakout room 3***
How to design a paediatric trial	How to study drugs in pregnancy	Clinical workshop
Prof. Anne Smits	*Dr. Rick Greupink*	*Dr. Robert Flint*
Dr. Viviane Klingmann	*Prof. David Burger*	*Dr. Violette Gijsen*
Dr. Roberto De Lisa	*Dr. Marleen van Gelder*	*Prof. Pieter de Cock*

14:15 Coffee Break

14:30 **Workshops – breakout rooms**

Workshop Paediatrics – *breakout room 1*	**Workshop Obstetrics - *breakout room 2***	**Workshop pharmacology for clinicians - *breakout room 3***
Prof. Anne Smits	*Dr. Rick Greupink*	*Dr. Robert Flint*
Dr. Viviane Klingmann	*Prof. David Burger*	*Dr. Violette Gijsen*
Dr. Roberto De Lisa	*Dr. Marleen van Gelder*	*Prof. Pieter de Cock*

	Coffee Break /Feedback workshops 1/2
16:00	*Dr. Robert Flint, Erasmus MC (NL)*
17:30	**Closure – departure to informal dinner Hotel Rebyl**
19:00	**Diner Hotel Rebyl**

Wednesday 25 June 2025 – Congress day 1

Auditorium

08:30 Registration

Finding the 'drug'
Chairs: Prof. Stephanie Laer and Dr. Robert Flint

09:00 **Welcome**
Conference Chair – Prof. Saskia de Wildt, Radboud University Medical Center (NL)

09:15 **Keynote: Innovative Therapy for Metabolic Diseases**
Prof. Sabine Fuchs, UMC Utrecht (NL)

10:00 **RNA Therapy for Inherited Diseases: towards the prevention of blindness**
Prof. Rob Collin, Radboud University Medical Center (NL)

10:20 **Drug discovery, paediatric gastrointestinal disease as example**
Prof. Sven van IJzendoorn, University Medical Center Groningen (NL)

10:40 Coffee Break

11:00 **From lab to the dose – Getting the dose right**
Chairs: Prof. Julia Anna Bielicki and Dr. Marleen van Gelder
Abstract presentations:

- 3D printing of hydrocortisone tablets: a solution for pediatric dose customization
  MSc Amanda Holst
- Targeted slc and abc proteome quantification in human placenta cell lines
  Nicole Chang
- Mapping the Localization of Placental Transporters Using Extracellular Vesicles Derived from Ex Vivo Tissue Perfusions
  Assistant Professor Jacqueline Tiley

11:30 **Developmental Pharmacology**
Prof. Bhagwat Prasad, Washington State University (USA)

11:55 **Animal Models for In Vivo Lactation Studies**
Dr. Domenico Ventrella, Alma Mater Studiorum - Università di Bologna, (IT)

12:20 Lunch

13:00 **Posters**

14:00 **From lab to the dose – Getting the dose right**
Chairs: Prof. Karel Allegaert and Dr. Rick Greupink
Abstract presentations:

- Prospective Assessment of Observed and Predicted Vancomycin Levels Using Model Informed Precision Dosing Support Tool in Neonates
  Assoc. Prof. Nadir Yalcin

- A physiology-based pharmacokinetic modeling study to estimate fetal brain exposure and expected dopamine-receptor occupancy following maternal metoclopramide dosing: concern for extrapyramidal symptoms in the newborn?
  Hedwig van Hove
- Mathematical albumin function for neonates undergoing therapeutic hypothermia in comparison with control neonates
  Dr. Zoë Vander Elst
- Studying paracetamol disposition in children using a minimally invasive microsampling technique: a preliminary PK analysis
  Ir. Isis Van herteryck
- Modelling of expected amoxicillin concentrations aids interpretation of clinical non-inferiority of lower compared to higher daily oral amoxicillin doses in a randomised controlled trial
  Prof. Julia Anna Bielicki
- Characterizing meropenem pharmacokinetics in paediatric critical care patients: a population-based analysis
  MSc Thi Van Anh Nguyen

15:00 Coffee Break

Chairs: Prof. David Burger and Assistant Professor Jacqueline Tiley

15:20 **Obstetric PK**
Dr. Karen Yeo, SIMCYP, Sheffield (UK)

15:40 **Pro/Con: do we need more PK or can we extrapolate?**
Prof. Catherijne Knibbe (presentation), University Leiden (NL)
Dr. Verena Gotta (presentation), University Basel (CH)
Dr. Pavla Pokorna (panel), Charles University Prague (CZ)
Prof. Pieter de Cock (panel), Ghent University Hospital (BE)
Prof. Anne Smits (panel, UZ Leuven University (BE)

16:40 **ESDPPP working groups**

17:10 **General Assembly**

18:00 **Closure**

19.00 **Dinner at the "Pannenkoekenboot"**

Thursday 26 June 2025 – Congress Day 2

Auditorium

Does it work?
Chairs: Prof. David Burger and Dr. Pavla Pokorna

09:00 **Extrapolation in paediatrics**
Dr. Roberto De Lisa, European Medicines Agency (NL)

09:20 **Conect4children: innovative trial design and smooth trial operations**
Paediatric expert advice
Prof. Mark Turner, c4c-S, University Liverpool (UK)

09.40 Abstract presentation: Reaching sufficient evidence in small populations: A scoping review of methods and regulatory guidance
Laurens Sluijterman

09.50 **Discussion**

10:00 **Keynote, AI aided Knowledge Discovery**
Prof. Rens van de Schoot, University Utrecht (NL)

10:30 Coffee Break

10:50 **Does it work - Is it safe? - From formulation to registration**
Chairs: Prof. Anne Smits and Dr. Violette Gijsen
Abstract presentations:

- Chronic medication and breastfeeding, avoiding behavior in Dutch women
  Dr. Anneke Passier
- "Impact of maternal low-dose aspirin on intracranial hemorrhage risk in very preterm newborns: a retrospective cohort study"
  Ph.D. Florian Joly

11:10 **Providing evidence on use and safety of medications in pregnancy when randomized clinical trials are not feasible**
Dr. Marleen van Gelder, Radboud University Medical Center, Nijmegen (NL)

11:30 **Drug safety in Neonates**
Prof. Karel Allegaert, University Leuven (BE)

11.50 **Microdosing studies in pregnancy**
Wouter Vaes, TNO (NL)

12:10 Lunch

13:00 **Posters**

14.00 **From formulation to registration**
Chairs: Prof. Antje Neubert and Dr. Christiane Garnemark

A joined presentation on the LENA project: from formulation to market authorization
Prof. Stephanie Laer
Prof. Joerg Breitkreutz
Peter McBride

14:45 **Does it work - Is it safe? - From formulation to registration**
Chairs: Prof. Antje Neubert and Dr. Christiane Garnemark
Abstract presentations:

- 3D printing of drugs: Bringing personalized medicine to Pediatrics

Eveline van Kampen

- Maternal adverse events and sotalol in pregnant women treated for foetal tachycardia; is there more to this story?
  Dr. Violette Gijsen
- The Lancet Child & Adolescent Health, Commission on the future of neonatology
  Prof. Mark Turner

15:15 Coffee Break

Regulatory challenges

Chairs: *Dr. Verena Gotta and Anna-Maria Wiesinger*

15:35 **Benefit-risk in pregnancy and lactation, the regulator's view**
Charlotte Bakker, European Medicines Agency (EU)

15:55 **Industry's view**
Licínio Craveiro, MD MSc PhD, F.Hoffmann-La Roche Ltd, Basel (CH)

16.15 **Discussion**

16:30 **Excursion to Anatomical Museum**

18:00 **Closure**

19:00 **Congress dinner party at "De Vereeniging"**

Friday 27 June 2025 – Congress Day 3

Auditorium

Use in practice/implementation

Chairs: *Prof. Pieter de Cock and Dr. Violette Gijsen*

09:15 **Keynote: Antithrombotic therapy in pregnancy**

Prof. Saskia Middeldorp, Radboud University Medical Center, Nijmegen (NL)

09:45 **Getting the therapy to bedside - Other**

Abstract presentations:

- Parental Perception of Treatment Options for Mucopolysaccharidosis: A Survey to Bridge the Gap for Personalized Medicine
  Anna-Maria Wiesinger
- The continuing problem of medicine shortages increases medication safety risks in children
  MSc Maaike Rutten - van Kranenburg
- A pooled population PK analysis investigating once-daily standard dosing of dolutegravir in HIV/TB co-infected children weighing 3 kg or more
  MSc Lisanne Bevers
- SMAART: A Clinical Quality Intervention tool embedded in electronic medical records to Identify and Challenge Children with Low-Risk Penicillin and Cephalosporin Allergies
  Dr. Duaa Gaafar
- Continuous glucose monitoring as reference for personalized monitoring for diabetic and healthy people of any age
  Florian Kinny
- Optimising paediatric HIV treatment: recent developments and future directions
  PharmD Anne Kamphuis

10:45 Coffee Break

Chairs: *Prof. David Burger and Dr. Marleen van Gelder*

11:00 **Paediatric Formularies**

Prof. Antje Neubert, University Hospital Erlangen (DE)

11:20 **Pregnancy Formulary**

Anneke Passier, PhD, Teratology Information Service Lareb, 's-Hertogenbosch (NL)

11:40 **The case of empagliflozin**

Dr. Terry Derks, University Medical Center Groningen (NL)

12:00 **Closure and farewell***

Prof. Saskia de Wildt, Radboud University Medical Center, Nijmegen (NL)
Prof. Antje Neubert, University Hospital Erlangen (DE)

* there is an option for a take away lunch

Oral session: From lab to dose – Getting the dose right: Wednesday 25 June 2025

3D printing of hydrocortisone tablets: a solution for pediatric dose customization

Authors:
Holst A.J.[1], Ayyoubi S.[1], Maduro J.E.[1], van Ee R.J.[2], Aulbers A.[2], van den Akker E.L.T.[3], Ruijgrok E.J.[1]

[1] Erasmus MC, Rotterdam, the Netherlands. [2] TNO, Eindhoven, the Netherlands.[3] Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands.

Introduction:
Due to the lack of suitable pediatric dosages, existing medicines are often modified by crushing, splitting, or dissolving tablets to adjust the doses, which increases the risk of errors. 3D printing offers a solution by enabling the production of personalized doses. This study investigates the feasibility of printing low-dose hydrocortisone.

Methods:
The semi-solid extrusion (SSE) printing technique was used to produce immediate-release hydrocortisone tablets. Formulations with a 4% and 10% drug load were prepared. After mixing the raw materials using a speed mixer, the formulation was loaded into the Superion SSE 3D printer, provided by TNO. Tablets with varying dosages were printed and evaluated for dissolution and content uniformity to assess compliance with pharmacopeial standards. Samples were analyzed using UPLC. Additionally, the feasibility of printing 10 mg sustained-release tablets was explored using the SSE technique. A formulation with a 10% drug load was used to print the sustained release tablets.

Results:
Both immediate- and sustained-release hydrocortisone tablets were successfully printed. For immediate-release tablets, a dosage range of 0.5 to 10 mg in steps of 0,1. Using the 4% formulation, doses from 0.5 to 3 mg were printed, while the 10% formulation enabled printing doses from 3 to 10 mg. The smallest tablets measured 3 mm in diameter, 1.37 mm in height, and weighed 12.6 mg. Tablets in the 0.5 to 10 mg range dissolved within 35 minutes. The sustained-release hydrocortisone tablet was also successfully printed, releasing hydrocortisone over 24 hours, with a drug release exceeding 80% at the 24-hour mark.

Conclusion:
3D printing enables the production of high-quality hydrocortisone tablets with precise dosages. Additionally, it allows for the customization of release profiles, a capability not achievable with conventional manufacturing methods. The ability to produce low-dose mini tablets makes this technology particularly suitable for personalized pediatric dosing.

Targeted SLC and ABC proteome quantification in human placenta cell lines

Authors:
Chang N.M.[1], Tiley J.B.[1], Fallon J.K.[2], Campbell M.J.[3], Brouwer K.L.R.[1], Illsley N.P.[3,4], Aleksunes L.M.[3]

[1] Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [2] Division of Pharmacoengineering and Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [3] Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA. [4] Placental Research Group, LLC, NJ, USA.

Introduction:
A key challenge in placental transporter research is the incomplete proteome characterization of SLC/ABC transporters, which are essential for maternal-fetal barrier function and nutrient exchange. The Integrated Transporter Elucidation Center aims to comprehensively compare transporter profiles in commonly used placental cell lines to healthy/term placentas using quantitative targeted proteomics (QTAP).

Methods:
High mRNA expression from placenta trophoblasts guided the selection of SLC/ABC proteins for QTAP analysis by microLC-MS/MS. R code accelerated proteotypic analysis by identifying unique missed cleavage-free peptides. These peptides were searched for in term placental tissue (n=4) and three human placental cell lines (n=6; JAR, BeWo, and HTR-8/SVneo) using an M-Class Acquity LC coupled to a SCIEX Triple Quadrupole 7500. Cells from the three cell lines were seeded at 1 × 10^6 cells/well, cultured for 48 hours and membrane proteins from all samples were extracted by differential detergent fractionation. QTAP analysis followed trypsin digestion, incorporating stable isotope labeled peptides for quantification.

Results:
Some transport proteins (NET1, 1.07 ± 0.41 pmol/mg protein; OAT4, 2.46 ± 0.88 pmol/mg protein) were detected in digested human placental tissue membranes but not membranes from the three placental cell lines. LAT1 and CD98 showed higher levels in cytotrophoblast-like cell lines (JAR, 64.20 ± 7.61 and 94.94 ± 14.92 pmol/mg protein, respectively; BEWO, 39.76 ± 13.86 and 69.01 ± 22.04 pmol/mg protein, respectively) compared to the extravillous trophoblast cell line (HTR-8/SVneo, 12.30 ± 2.44 and 20.52 ± 3.28 pmol/mg protein, respectively) and placental tissue (4.86 ± 1.54 and 12.65 ± 3.92 pmol/mg protein, respectively).

Conclusion:
These data are useful in extrapolating data from in vitro studies to inform PBPK models and predict maternal-fetal drug disposition. Further studies will expand proteomic profiling to include placentas from pregnancies with complications to understand their impact on nutrient transfer and placental barrier function.

Supported by NIH UC2HD113039 and S10OD032350.

Mapping the localization of placental transporters using extracellular vesicles derived from ex vivo tissue perfusions

Authors:
Lewis K.M.[1], Chang N.M.[1], Patrikeeva S.[2], Fallon J.K.[3], Nanovskaya T.N.[2], Aleksunes L.M.[4], Rytting E.[2], Tiley J.B.[1]

[1] Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA. [2] Maternal-Fetal Pharmacology and Biodevelopment Laboratories, Department of Obstetrics & Gynecology, University of Texas Medical Branch, Galveston, TX, USA. [3] Division of Pharmacoengineering and Molecular Pharmaceutics, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA. [4] Department of Pharmacology and Toxicology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA.

Introduction:
The placenta, as many other organs, sheds extracellular vesicles (EVs) from cell surfaces that contain proteins from their origin cell. Membrane transporters are essential to the placental barrier and regulate nutrient transfer to the foetus during pregnancy. Placental EVs may provide information on localization of placental transporters in the syncytiotrophoblasts.

Methods:
Our study compared transporter levels in EVs found in media from ex vivo perfusions and villous tissue from matched human placentas. Maternal placenta perfusion media (mPPM) was collected fresh and preconditioned (centrifuged 10 minutes, 3000 x g, 4°C) after a closed 3-hour perfusion of healthy, term human placentas (N=3). mPPM-derived EVs were extracted by the commercially available ExoEasy Kit and placenta tissue membrane proteins were extracted using differential centrifugation (homogenized, centrifuged 10 minutes, 9000 x g, 4°C and 1h, 100,000 x g, 4°C). After a trypsin digestion, placental transporter levels were measured by nano-LC-MS/MS quantitative targeted absolute proteomic (QTAP) analysis.

Results:
Transporter levels measured in mPPM-derived EVs showed good correlation compared to matched placental tissue (R2=0.92). These included transporters (BCRP, ENT1, GLUT1, GLUT3, P-gp, OATP2A1) and membrane markers (placental alkaline phosphatase and Na+/K+-ATPase) known to be expressed on the maternal/apical membrane side of syncytiotrophoblasts. The OCT3 and the OATP2B1 transporters, which are both known to be only expressed on the foetal/basolateral membrane side of syncytiotrophoblasts, were not detected in the mPPM-derived EVs. We are analysing a larger panel of other transporters containing amino acids, neurotransmitters, metal, and organic transporters identified as high priority by the NIH Integrated Transporter Elucidation Center.

Conclusion:
These data show the potential use of placental EVs to map the apical localization and quantify levels of transporters in human placental tissue. This unique approach enhances our understanding of placental physiology and its impact on foetal development and maternal health.

Supported by NIH UC2 HD113039-01 and S10 OD032350-01.

Prospective assessment of observed and predicted vancomycin levels using model informed precision dosing support tool in neonates

Authors:
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[1] Hacettepe University, Faculty of Pharmacy, Department of Clinical Pharmacy, Ankara, Türkiye. [2] Hacettepe University, Faculty of Medicine, Division of Neonatology, Ankara, Türkiye. [3] Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium.

Introduction:
Model-informed precision dosing (MIPD) tools, such as InsightRx, aim to optimize vancomycin by improving dose individualization. This study evaluates the correlation between observed and predicted vancomycin levels in neonates using InsightRx, providing insight into its clinical applicability and accuracy in therapeutic drug monitoring and target concentration intervention with real word data.

Methods:
This prospective cohort study included neonates receiving vancomycin in a NICU from tertiary referral care hospital. Vancomycin trough levels were observed using High Performance Liquid Chromatography and predicted using the InsightRx web-based platform. The correlation between observed and predicted values was analyzed using Spearman's correlation coefficient. Mean Absolute Error (MAE), Mean Absolute Percentage Error (MAPE), and other accuracy metrics were calculated to assess model performance. The study aimed to determine whether InsightRx provides reliable dose predictions for neonates, supporting individualized vancomycin dosing in clinical practice.

Results:
A total of 25 neonates [median (IQR) gestational age: 35 2/7 (5) weeks; birth weight: 2435 (1429) g], 56.7% of whom were male, were included in the study. According to the first and only observed [median (IQR): 5.6 (8) mg/L] and predicted [median (IQR): 10.9 (8) mg/L] vancomycin plasma levels (r_s = 0.407, p = 0.048), Mean Absolute Error (MAE) was 5.17, Mean Absolute Percentage Error (MAPE) 166.8%, Mean Squared Error (MSE) 44.4, Root Mean Squared Error (RMSE) 5.2, Mean Bias Error (MBE) 3.6, and Symmetric Mean Absolute Percentage Error (sMAPE) 24.2% [intermediate (43.3%) and poor (36.7%) model fit].

Conclusion:
Correlation between observed and predicted levels was moderate. High MAPE and MAE indicate substantial prediction errors, suggesting variability in model accuracy. However, sMAPE and model fit suggest partial reliability for dose optimization. Studies with multiple plasma levels and MIPD-based dose optimization are needed to assess the clinical impact.

A physiology-based pharmacokinetic modeling study to estimate fetal brain exposure and expected dopamine-receptor occupancy following maternal metoclopramide dosing: concern for extrapyramidal symptoms in the newborn?

Authors:
van Hove H.[1], van der Heijden J.E.M.[1], van den Broek P.[1], van Drongelen J.[2], de Wildt S.N.[1,3], Greupink R.[1]

[1] Department of Pharmacy, Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, The Netherlands. [2] Department of Obstetrics and Gynecology, Radboud University Medical Center, Nijmegen, The Netherlands. [3] Department of Neonatal and Pediatric Intensive Care, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands.

Introduction:
About 50% of women experience nausea and vomiting during pregnancy, of whom approximately 10% receives pharmacotherapy. Metoclopramide, a combined D2 and 5-HT3/4 receptor antagonist, is one of the treatment options. Despite its widespread application, it remains unknown whether effective maternal dosing leads to relevant fetal exposure. In particular, a high degree of peripartum fetal brain D2-receptor occupancy could result in extrapyramidal symptoms (EPS) in the newborn (threshold > 80% receptor occupancy). We now investigate this via a pregnancy physiology-based pharmacokinetic/pharmacodynamic modeling (p-PBPK/PD) approach.

Methods:
A p-PBPK model, including pregnancy-related changes, was established for metoclopramide in Simcyp V21 (Certara, Sheffield). To enable fetal exposure predictions, placental transfer parameters, derived from human single cotyledon perfusion experiment data, were incorporated in the p-PBPK model. Model performance was verified against available pharmacokinetic data. Subsequently, steady state maternal and fetal total plasma concentrations, as well as total and unbound fetal brain concentrations were simulated following the standard 3 dd 10 mg dosing regimen. A Hill equation-type Bmax receptor-occupancy model, parametrized with in vitro metoclopramide D2-receptor affinity data (Kd), was used to estimate fetal brain D2-receptor occupancy.

Results:
The model accurately predicted pharmacokinetics in a virtual population of non-pregnant individuals (predicted to observed ratio for maximal concentration (Cmax) and area under the curve of 0.96 ± 0.31 and 0.58 ± 0.2, respectively). Pregnancy pharmacokinetic data were lacking, which we then simulated with the p-PBPK model. Simulations resulted in average total Cmax at steady state of 29.1 ± 20.5 ng/mL, 14.0 ± 10.7 ng/mL and 45.3 ± 37.0 ng/mL, respectively, for maternal plasma, umbilical cord blood or fetal brain. The mean calculated fetal unbound brain concentration were 13.6 ± 10.9 ng/mL, corresponding to 53.5 ± 15.8 % D2-receptor occupancy.

Conclusion:
Our modeling data suggest that maternal dosing of 3 dd 10 mg metoclopramide, results in steady state fetal brain D2-receptor occupancy of around 53%, which is considerable, but below the suggested threshold value associated with EPS risk in the newborn.

Mathematical albumin function for neonates undergoing therapeutic hypothermia in comparison with control neonates

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Introduction:
Hypoxic-ischemic encephalopathy (HIE) resulting from perinatal asphyxia presents a substantial risk of mortality and morbidity in neonates. Whole body therapeutic hypothermia (TH) improves both short- and long-term outcomes in near-term/term neonates. While these neonates often require polypharmacy, the impact of HIE and TH on the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs remains unclear. Given its influence on the PK and PD of albumin-bound drugs, the aims of this study were to describe human serum albumin (HSA) trends in neonates undergoing TH compared to controls, and to compare HSA concentrations between moderate and severe HIE cases.

Methods:
This retrospective study pooled data from NICU patients in Leuven (Belgium), Ankara (Turkey), and four centres in the United Kingdom. Linear mixed models were used to analyse longitudinal HSA trends. Differences in HSA concentrations between cohorts (TH versus controls, moderate versus severe HIE) were investigated, estimating the difference at each postnatal day or applying a main effects model. A mathematical function for HSA concentrations in neonates with HIE undergoing TH (AlbuCool function) was derived.

Results:
The dataset contained 330 TH cases and 425 controls with 1725 and 1415 HSA observations, respectively. Median (IQR) HSA concentration was 27.0 (23.0-31.0) g/L and 32.1 (28.4-35.7) g/L for the TH and control cohort, respectively. Estimated mean HSA concentrations of TH cases were significantly lower ($p<0.001$) than controls, as well as for severe compared to moderate HIE cases ($p<0.001$) over the first seven postnatal days. The derived HSA function for the TH cohort was: HSA (g/L) = 32.28-2.94*PNA+0.33*PNA^2 (PNA=postnatal age).

Conclusion:
This large, multicentre study derived a mathematical function to describe HSA trends in neonates with HIE undergoing TH. Integrating this function into future (physiologically-based) PK models may enhance the predictive performance of these models, and consequently, the pharmacotherapy of HSA-bound drugs in this vulnerable patient population.

Studying paracetamol disposition in children using a minimally invasive microsampling technique: a preliminary PK analysis

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Introduction:
Paracetamol, the most used analgesic, undergoes hepatic metabolism, with toxic NAPQI potentially causing liver damage. Data on infants remains scarce. This study explores target concentration attainment in paediatric patients, aiming to minimize toxicity. We describe paracetamol pharmacokinetics, metabolites, and factors influencing inter-individual variability and metabolic pathways in children.

Methods:
Children included in this observational study received preoperative acetaminophen (15-20 mg/kg) intravenously. Blood was collected at predefined time points with a volumetric absorptive collection device (VAMs) of 10 µL and analyzed via LC-MS/MS. Blood concentrations of acetaminophen and its metabolites (glucuronide, sulfate, cysteine, mercapturate, and glutathione) were determined. Area under the plasma concentration-time curves (AUC) was determined with non-compartmental analysis performed with PKanalix (MonolixSuite).

Results:
Sixteen patients (median age 11 years, weight 32.5 kg) had a median AUC of 78.70 mg·h/L, clearance of 5.46 L/h, and volume of distribution of 21.2 L. The median time above the 6.6 mg/L target concentration was 4 h 5 min, but 50% did not maintain it for 4 h. Sulfation was the primary metabolic pathway, though glucuronide levels exceeded sulfate in blood after 3 h. CYP2E1 metabolite concentrations reached a median of 0.37 mg/L after 2 h. Preliminary data suggest age-related differences in metabolic pathway contributions.

Conclusion:
Target attainment analysis showed suboptimal paracetamol exposure, suggesting inadequate analgesia. Glucuronidation increased with age, but sulfate was the major pathway. CYP2E1 metabolites (cysteine, mercapturate) were higher than in adults, with unclear relevance. Larger Population Pharmacokinetic studies are needed to further investigate pediatric paracetamol metabolism.

Modelling of expected amoxicillin concentrations aids interpretation of clinical non-inferiority of lower compared to higher daily oral amoxicillin doses in a randomised controlled trial

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Introduction:
The 2014 British National Formulary for Children (BNFC) doubled the recommended oral amoxicillin dose to address concerns about underdosing. We conducted a modelling and simulation study to aid interpretation of the UK-based CAP-IT trial for the amoxicillin dose comparison.

Methods:
(I) 814 children with pneumonia were randomised to either 35-45 mg/kg/day or 70-90 mg/kg/day oral amoxicillin administered 12-hourly. Baseline pneumococcal nasopharyngeal carriage and susceptibility (minimal inhibitory concentration, MIC) were ascertained. (II) Data to model amoxicillin plasma concentrations were available from a PK study conducted in childhood pneumonia (PMID 12604533). (III) We simulated expected amoxicillin concentrations and evaluated target attainment (fT>MIC: fraction of time of free drug concentration above MIC during 1st dose interval) based on trial microbiology. Amoxicillin MICs for non-colonized children or those with missing samples were substituted by the 90th percentile of observed trial MICs. A fraction unbound amoxicillin of 0.8 was assumed.

Results:
(I) Lower doses were non-inferior to higher doses for clinically indicated antibiotic retreatment for respiratory tract infection within 28 days (PMID 34726708). Baseline microbiological samples were available for 647/814 (79%) children with 272/647 (42%) pneumococcal carriage, median amoxicillin MIC=0.016 mg/L [IQR 0.016-0.032] and only 4/272 (1.5%) amoxicillin-resistant isolates (amoxicillin MIC>1mg/L). (II) A one-compartment model with inclusion of body weight as covariate for clearance and distribution volume was developed. (III) Simulated amoxicillin concentrations in the higher-dose and lower dose group resulted in median [IQR] fT>MIC=100% [98-100%] with missing MICs substituted by the trial 90th percentile (0.064mg/L).

Conclusion:
Clinical non-inferiority of lower oral amoxicillin doses aligns with 80% children achieving ≥95% fT>MIC for the clinically relevant scenario (90th percentile MICs imputed for missing values = 0.064mg/L). This calls into question the rationale for the 2014 BNFC dose revision.

Characterizing meropenem pharmacokinetics in paediatric critical care patients: a population-based analysis

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Introduction:
Meropenem is a commonly used beta-lactam antibiotic to treat severe infections in critically ill children. Little is known about the pharmacokinetics (PK) of meropenem and optimal dosing regimen. This study aims to investigate meropenem PK in this patient population and identify predictors for inter-individual PK variability.

Methods:
An observational pharmacokinetic study was conducted in children admitted to the paediatric intensive care unit (ICU) in whom meropenem treatment was clinically indicated. Blood samples were collected and measured by the liquid chromatography tandem mass spectrometry (LC-MS/MS) method. Population pharmacokinetic data were analysed using the non-linear mixed effect modelling software MONOLIX (2024R1). Model fit and model robustness were tested using internal model validation methods and a sensitivity analysis.

Results:
A total of 444 blood samples from 54 patients (median age: 0.75 years, range: 0.02 - 14.5; median weight: 7.6 kg, range: 1.2 – 63) were collected. A two-compartment model with allometric scaling and a sigmoidal maturation function accounting for the effect of growth and development best described the observed data. Neither the inclusion of estimated glomerular filtration rate derived from creatinine nor cystatin C significantly improved the model. The typical values for clearance, central volume of distribution, inter-compartment clearance, and peripheral volume of distribution were 13.15 L/h/70 kg, 12.51 L/70 kg, 23.92 L/h/70 kg, and 16.26 L/70 kg, respectively.

Conclusion:
A population PK model of meropenem was successfully developed, demonstrating large interpatient PK variability. This PK model will now be used for Monte Carlo simulations to

evaluate the probability of target attainment of current and alternative dosing regimens of meropenem in this patient population.

Oral session: Does it work – Is it safe? – From formulation to registration: Thursday 26 June 2025

Reaching sufficient evidence in small populations: a scoping review of methods and regulatory guidance

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All authors were Funded (or Co-funded) by the European Union's Horizon Europe Framework programme under grant agreement 101136365 (INVENTS). Views and opinions expressed are those of the author(s) only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them.

Introduction:
Clinical research in special populations, such as paediatric patients and pregnant women, is inherently challenging. Limited sample sizes often prevent trials from reaching sufficient levels of evidence. This requires alternative strategies tailored to these populations.

Methods:
We identified three general approaches to achieve sufficient evidence in small populations:
1. Increasing trial size: For example, through multi-centered trials, possibly using Bayesian Federated Inference, or by broadening enrollment criteria.
2. Designing more informative trials: Includes selecting sensitive and relevant endpoints and employing innovative trial designs, including both frequentist and Bayesian methodologies.
3. Incorporating external information: Utilizes data from previous clinical studies or real-world data to supplement primary trial data. Crucially, this approach can also be used to inform the previous two strategies.

Additionally, we discuss various modeling techniques applicable to each approach and review existing regulatory guidance provided by the ICH, FDA, and EMA.

Results:
We identified nearly 40 guidance documents and summarized key points, structuring our findings along the aforementioned three main categories. We also address important concepts such as the context of use for model evaluation and the "fit-for-purpose" principle for the use of real-world data.

Conclusion:
Our review of methodologies and regulatory guidance demonstrates that clinical trials can be effectively tailored to the unique needs of special populations. By providing an overview and discussion of existing regulatory guidance, this work offers a starting point for designing clinical research that can achieve sufficient levels of evidence even in small populations.

Chronic medication and breastfeeding, avoiding behavior in Dutch women

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Introduction:
Breastfeeding offers many advantages, both to mother and child. For women with chronic medication, a careful consideration should be made if breastfeeding will be safe for the infant. We studied the situation in the Netherlands: do mothers decide to refrain from breastfeeding for the right reasons?

Methods:
Data from the Dutch Pregnancy Drug Register were used for this study. This register was set up to obtain insight into the safety of drug use by women during pregnancy and breastfeeding. Pregnant women in the Netherlands are invited to sign up. Participating women receive 6 online questionnaires, three during pregnancy and three after birth.
We selected participants who decided not to breastfeed because of the medication they used. The most frequently mentioned drugs were used for further analysis. How many participants who use that particular drug will / will not start breastfeeding?

Results:
About 12% decided not to start breastfeeding. Within this group, 11% (n=57) described medication as the reason for not starting. Drugs most often mentioned were lithium, lamotrigine and SSRIs, all used for chronic diseases.
Further analysis showed that all 4 women in the register on lithium did not start breastfeeding. Of the 13 women taking lamotrigine, 5 (almost 40%) did not start breastfeeding due to concern about the drug. Of the 37 women using an SSRI, 8 (22%) did not start breastfeeding out of concern about the drug.

Conclusion:
Among the 12% of women who decided not to start breastfeeding, 1 in 10 (11%) mentioned that drug use played a role in their decision. However, the use of some of the mentioned drugs like lamotrigine or an SSRI is no reason to be concerned about negative effects on the infant. With better information for both healthcare provider and pregnant women we hope to improve this situation.

Impact of maternal low-dose aspirin on intracranial hemorrhage risk in very preterm newborns: a retrospective cohort study

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Introduction:
Preterm infants face heightened risk of intracranial hemorrhage (IVH). While low-dose aspirin is used during pregnancy to prevent obstetric complications, its impact on neonatal outcomes remains unclear. This study investigates whether maternal aspirin exposure affects IVH incidence in preterm newborns.

Methods:
This retrospective cohort study analyzed data from the French SNDS database (2013-2022). We compared aspirin-exposed versus unexposed very preterm births (≤32 weeks gestation). Exposure was defined as maternal aspirin use at delivery. IVH diagnosis was identified through ICD-10 codes in medical records. We performed matched patients to balance baseline characteristics between groups and conducted logistic regression analysis to assess the association between maternal aspirin exposure and IVH, adjusting for potential confounding factors.

Results:
Among 80,819 very preterm newborns, 3,532 (4.4%) were exposed to maternal aspirin. IVH incidence was comparable between aspirin-exposed and unexposed groups (18.5% vs 19.2%, respectively). After adjustment for confounding variables, aspirin exposure showed no significant association with overall IVH risk (adjusted OR 1.00, 95% CI: 0.90-1.11). Subgroup analysis stratified by IVH severity similarly demonstrated no significant associations between maternal aspirin use and specific IVH grades.

Conclusion:
Maternal low-dose aspirin during pregnancy was not significantly associated with increased or decreased risk of intracranial hemorrhage in very preterm newborns, suggesting its use for preventing obstetric complications remains appropriate.

3D printing of drugs: bringing personalized medicine to pediatrics

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Introduction:
Lack of age-appropriate drugs hinders pediatric pharmacotherapy. 3D pharma printing allows for customization based on patient needs. For adequate uptake of this new technique, we studied implementation steps for hospital use. Besides that, we described use cases by identifying commonly manipulated medicines at Erasmus MC Sophia Children's Hospital.

Methods:
An inventory of facility requirements for 3D pharma printing was made, and a 3D pharma printer was developed by TNO. We created the necessary quality documentation to ensure the printer meets requirements. Upon that, we studied whether our process could be implemented in the current workflow of compounding medication, from prescribing to reimbursement. To identify commonly manipulated medicines in children, we used prescription data from Erasmus MC Sophia Children's Hospital and 5 community pharmacies. We included prescribed drugs that require the handling of a patient or healthcare professional before administration, which introduces a risk of inadequate dosing.

Results:
The requirements for 3D pharma printing premises for hospital implementation were met, and the necessary quality system documents were developed by a multidisciplinary team. The production process was successfully tested, making the technique suitable for manufacturing 3D printed drugs for patient care.To identify candidates for 3D pharma printing, we listed the top 25 manipulated prescribed medicines. In Erasmus MC Sophia Children's Hospital, 10.5% of prescribed drugs were manipulated before administration, compared to 8.5% in community pharmacies. For oral, vaginal, and rectal administrations, the manipulation rate was 40.9% in the hospital. Cardiovascular, alimentary tract, and nervous system drugs were more prevalent in the hospital, compared to antibiotics and anti-infectants in community pharmacies.

Conclusion:
This work supports hospitals in adopting 3D pharma printing, providing documents and practical experience for implementation, qualification, and validation. It also identifies the most manipulated pediatric medicines in Erasmus MC Sophia Children's Hospital and community pharmacies, guiding a targeted approach to 3D pharma printing

Maternal adverse events and sotalol in pregnant women treated for foetal tachycardia; is there more to this story?

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Introduction:
Foetal tachycardia is a rare and life-threatening condition often treated with sotalol. Recent physiologically based pharmacokinetic modelling suggests that with the current maximum dosages used, supratherapeutic concentrations in pregnant women are reached possibly leading to more adverse events. However, clear data are lacking on the prevalence of adverse events and a dose-response relationship between sotalol and adverse events.

Methods:
A retrospective cohort study was conducted at the Radboud University Medical Centre involving all pregnant women treated with sotalol for foetal tachycardia at any time during pregnancy between 2014 and 2023. Data was collected by medical chart review.

Results:
37 women with singleton pregnancies were included. The median gestational age at start of treatment was 32 weeks and 1 day (range: 16 weeks and 4 days). The successful treatment for 32 foetuses was 87% for sotalol monotherapy, four foetuses were treated with a combination of sotalol and digoxin (11%) and one eventually with digoxin only (3%). Twenty women experienced any adverse events (54%), three cardiac adverse events (8%) and seventeen mild adverse events (46%). The most common reported mild adverse events were dizziness (27%) and fatigue (30%). Other mild adverse events reported were nausea (3%), vomiting (3%) and dyspnoea (3%). Women who experienced mild adverse events, had higher sotalol doses at the time of the adverse event compared to those who didn't experience a mild adverse event (277 ± 101 versus 235 ± 85 mg/day p = 0.02). A positive correlation was found (r = 0.153, p = 0.020) between the sotalol dose and the occurrence of a mild adverse event.

Conclusion:
This is the first report on the prevalence of maternal adverse events when treating women for foetal tachycardia with sotalol. Importantly, mild adverse events are common and as expected more often present at higher sotalol dosages.

Oral session: Getting the therapy to bedside – Other: Friday 27 June 2025

Parental perception of treatment options for mucopolysaccharidosis: a survey to bridge the gap for personalized medicine

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Introduction:
Mucopolysaccharidosis (MPS) are a group of lysosomal storage diseases characterized by significant unmet medical needs – for both patients and caregivers. While approved therapies are available, they remain limited, and investigational therapies are often perceived ambiguously.

Methods:
We employed an innovative survey technique based on the discrete choice experiment (DCE) methodology, incorporating scenarios for both neuronopathic and non-neuronopathic MPS patients. The survey aimed to evaluate parental preferences and perceptions of various approved and emerging therapies for MPS. The questionnaire was disseminated through patient organizations in Germany, Switzerland, and Austria.

Results:
Sociodemographic differences were observed based on gender, education, health coverage, and patients' CNS involvement. Respondents' personal decisions on therapies for neuronopathic and non-neuronopathic patients were very similar. Most likely parents would choose a personalized repurposing approach for their child (82% and 94%), followed by enzyme replacement therapy (both 88%), hematopoietic stem cell therapy (70% and 76%), and finally gene therapy (58% and 53%). The vast majority (88%) indicated patient organizations as their main source of information.

Conclusion:
This study is the first to underscore the critical importance of personalized medicine in addressing the unmet needs of MPS patients and their caregivers. It highlights the pivotal role of patient organizations in providing comprehensive information to support informed decision-making regarding innovative therapeutic approaches. These findings lay the groundwork for developing targeted communication strategies and facilitating informed choices for personalized medical interventions in MPS and beyond.

The continuing problem of medicine shortages increases medication safety risks in children

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Introduction:
Medicine shortages are a growing global concern. The limited availability of medicines with a safe, evidence-based use in children and in an appropriate formulation makes shortages particularly critical for this vulnerable population. This potentially leads to suboptimal treatment and increased safety risks requiring prioritization among decision makers dealing with shortages.

Methods:
This study assessed the impact of drug shortages on pediatric patients in a tertiary care pediatric hospital between January 2022 and June 2023 using a qualitative and semi-quantitative approach. A scoring methodology was applied to evaluate alternative treatments with respect to clinical efficacy, safety profile, medication safety aspects, disease severity, patient susceptibility, number of patients and cost implications. Impact scores for each component ranges from 1 to 3, indicating low to high impact. The total impact score for a drug shortage is a multiplication of the individual component scores. Additionally, increased safety risks associated with specific shortages were further analyzed.

Results:
A total of 33 shortages were analyzed, with 15 classified as high impact and 8 as moderate impact. The most frequently affected drug categories were anti-infective and central nervous system medicines. Patient susceptibility and number of patients had the highest influence on the total impact score of a shortage. Challenges include variations in dosing regimens, differing dosage forms, the presence of undesirable excipients, and limited evidence for use in pediatric patients.

Conclusion:
Our study highlights the significant burden of drug shortages on pediatric patients and healthcare professionals in delivering optimal treatment. This systematic impact assessment emphasizes the urgent need to structurally include specific aspects for safe and effective medication use in children when developing policy and mitigation strategies dealing with drug shortages.

A pooled population PK analysis investigating once-daily standard dosing of dolutegravir in HIV/TB co-infected children weighing 3 kg or more

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Introduction:
Dolutegravir is a key HIV treatment, but rifampicin increases its clearance via UGT1A1 and CYP3A4. This is usually managed by doubling the dose for twice-daily (BID) dosing, which can affect adherence in children. Griesel et al. (2021) showed that once-daily (OD) dosing achieves similar virological suppression in adults. We developed a population pharmacokinetic model to explore this in children.

Methods:
We developed a paediatric population pharmacokinetic model of dolutegravir in NONMEM (v7.5) using data from three trials: ODYSSEY, CHAPAS-4, and EMPIRICAL. Volume and flow parameters were scaled to 70 kg, and maturation of dolutegravir clearance was assessed. Covariates were tested using dOFV and VPC. Simulations were performed with a virtual population of 7000 children (3-<40 kg). The main endpoint was the proportion of children reaching dolutegravir trough levels above the PA-IC90 (0.064 mg/L).

Results:
Using 1942 dolutegravir concentrations from 235 children (3 months to 18 years), a two-compartment model with first-order elimination and Erlang-type absorption was developed. Rifampicin coadministration increased dolutegravir clearance by 61%. A broken-stick model described the maturation of clearance, reaching adult levels by 2.67 years. Film-coated tablets (FCT) with food had 22% higher bioavailability, while dispersible tablets (DT) with food had 47% lower bioavailability. Simulations based on the optimal scenario (DT without food, FCT with food) showed that 94.5% of children reached dolutegravir trough levels above the PA-IC90 with once-daily dolutegravir co-administered with rifampicin.

Conclusion:
Simulations showed that 94.5% of children in the virtual population reached dolutegravir trough levels above the PA-IC90 with once-daily dosing and rifampicin, compared to 78% in adults (Griesel et al.). These results suggest that once-daily standard-dose dolutegravir could be an effective treatment for children with HIV-TB coinfection.

SMAART: a clinical quality intervention tool embedded in electronic medical records to identify and challenge children with low-risk penicillin and cephalosporin allergies

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Introduction:
Beta-lactam allergies are the most common antibiotic-associated allergies reported in children. These antibiotic allergy labels (AALs) are associated with poorer clinical outcomes and increased use of restricted antibiotics, when compared to unlabeled children. Prior studies showed that only 5% of children admitted to hospital were evaluated for their AALs. Aims: This study aimed to develop, implement, and audit a Stratified autoMated Allergy Assessment Risk Tool (SMAART) for penicillin and cephalosporin AALs.

Methods:
The SMAART tool was implemented in the electronic medical record (EMR) at the Royal Children's Hospital Melbourne to risk-stratify children with AAL. Children aged 0-18 years with an AAL were included. Low-risk patients were either directly delabelled based on history, offered an inpatient oral challenge test (OCT), or, if they declined, referred to a drug allergy clinic or nurse-led outpatient drug oral challenge clinic (DOCT). Antibiotic prescribing was recorded, including the use of restricted antibiotics.

Results:
During the 36-month study period, 331 admitted children had an AAL. The SMAART tool identified 261 (79%) as low risk. Of these, 74 (28%) had an inpatient OCT, 15 (6%) were directly delabelled, 63 (24%) were referred to drug allergy clinic, 39 (15%) were referred to DOCT, 49 (19%) were missed, and 21 (8%) declined testing or follow up. Of the 261 children identified as low risk using the SMAART tool, 147/147 (100%) of those who had an OCT were confirmed to be at low risk. The specificity of the SMAART tool in diagnosing low-risk allergies is 100%.

Conclusion:
This is the first (EMR)-embedded (AAL) risk stratification tool for children. Using the SMAART tool, 73% of children were followed up for their drug allergy.

Continuous glucose monitoring as reference for personalized monitoring for diabetic and healthy people of any age

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Introduction:
Continuous glucose monitoring (CGM) is part of diabetes control as well is becoming part of healthy lifestyle activities in adolescents and young adults for understanding glucose metabolism and preventing metabolic diseases. Comparable CGM profiles in children, adolescents, and adults have been previously reported in the literature. However, there is a lack describing individual glucose responses to everyday situations with appropriate metrics. To provide metrics which describe individual glucose responses to lifestyle factors including diet, exercise, and stress in healthy, young people.

Methods:
Ten participants wore a CGM device (FreeStyle Libre3®) for 14 consecutive days while completing nine standardized interventions (challenges) consisting of food, sport, and the Trier Social Stress Test (TSST). Individual glucose responses after each challenge were assessed over four hours, using following metrics: AUC0-4, the max glucose, the time to max glucose, the glucose excursion, and time required for glucose levels to return to baseline (Glucose Recovery Time to Baseline (GRTB)).

Results:
Anaerobic exercise resulted in a significantly greater glucose excursion (28.7 ± 21.46 mg/dL) compared to aerobic exercise (8.77 ± 4.94 mg/dL, p=0.0228). Carbohydrate-rich foods caused the highest glucose increase (161.4 ± 15.59 mg/dL). TSST significantly elevated saliva cortisol levels, indicating a significant difference in baseline-corrected glucose concentrations over time as revealed by a two-factor repeated-measures ANOVA (p=0.0113).

Conclusion:
We provide reference data of glucose response to lifestyle factors such as diet and exercise in healthy people. As psychosocial stress was also included, where we assessed a substantial glucose response in healthy people. The new methodology of GRTB may quantify the lifestyle stimulus on the important metabolic pathway and can be utilized alongside kinetic metrics for describing individual glucose responses. The findings of this study conducted with adults may provide valuable insights and serve as a basis for further research in children.

Optimising paediatric HIV treatment: recent developments and future directions

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Introduction:
Paediatric antiretroviral formulations for treatment of HIV have historically been generally less palatable and more difficult to use compared with those for adults. However, over the past decade significant progress has been made. Through this review, we aimed to outline the recent developments in paediatric HIV treatment and future directions for drug optimisation.

Methods:
This review draws on key studies and clinical study databases. Relevant literature was identified through searches in PubMed, Google Scholar and through citation searching. Additionally, insights from expert discussions and clinical experience were incorporated to contextualize recent developments and future directions.

Results:
Antiretroviral formulations previously available for adults have been developed in paediatric dosages, including dolutegravir, abacavir/lamivudine, and zidovudine/lamivudine tablets. Recently, a paediatric fixed-dose combination of abacavir/lamivudine/dolutegravir was approved, improving palatability, ease of administration and storage, and avoids

unintentional monotherapy. Upcoming fixed-dose combinations are dolutegravir/emtricitabine/tenofovir alafenamide and darunavir/ritonavir. With modern antiretrovirals, two-drug regimens can be as effective as standard three-drug regimens, offering benefits like reduced long-term toxicity and smaller tablets. Oral combinations currently assessed in children are dolutegravir/lamivudine and dolutegravir/rilpivirine. Even with these optimized regimens, challenges remain for some children in achieving virological suppression due to adherence issues, intolerance, toxicity and resistance. New agents and innovative administration strategies are essential. Ongoing studies in children explore long-acting injectables, agents from new antiretroviral classes or alternative options, e.g. broadly neutralising antibodies. Additional formulations being investigated to maximise convenience by reducing dosing frequency and easing administration are micro-array patches, implants and oral dispersible films.

Conclusion:
The paediatric HIV treatment landscape has evolved towards more effective once-daily regimens with fewer side effects and greater tolerability. However, even with the current best-available regimens, virological suppression rates remain below the desired level in children, highlighting the need for novel delivery methods. The field is quickly evolving with promising new strategies and advancements for paediatric HIV.

Poster presentations

1. Lamotrigine use in lactating women: passage into breast milk and infant exposure

Authors:

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Introduction:
Lamotrigine, an antiseizure medication used for epilepsy and bipolar disorders, is often prescribed to women of childbearing age due to relatively low teratogenic risk. It is known that lamotrigine use in lactation leads to detectable concentrations in breast milk, although concentrations vary significantly among individuals.

Methods:
At our hospital we conducted an analysis of milk and plasma samples obtained from a limited cohort of lactating women (n=6) using lamotrigine at dosages ranging from 50 to 300 mg per day, divided in two doses (n=15 plasma and n=16 milk samples). In the same cohort of lactating women using lamotrigine, we also measured single-point plasma concentrations in their suckling neonates (n=5).

Results:
The calculated Milk/Plasma ratio in our cohort, using an Area Under the Curve based approach, was 0.76 (range 0.47-1.2). The calculated Absolute Infant Dose was 0.29 mg/kg/day, which corresponds to a Relative Infant Dose of 10.1% (range 8.7-15.7%) in our cohort. The mean measured infant lamotrigine plasma concentration was 1.3 mg/L (range 0.5-2.2 mg/L).

Conclusion:
Although lamotrigine is excreted into breast milk, and detectable in infants, the benefits of breastfeeding should not be overlooked. Higher plasma concentrations generally lead to higher breast milk concentrations, so aiming for the lowest possible maternal plasma levels is beneficial. These findings underscore the importance of measuring plasma levels in this population.

2. Identifying high-risk medication during pregnancy for adverse pregnancy outcomes in Electronic Patient Files (EPF) using disproportional analysis

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Introduction:
Some women enter pregnancy with medical conditions that require ongoing or episodic treatment (e.g., asthma, epilepsy, hypertension). As the prevalence of using a specific drug during pregnancy is generally low, neonatal side effects (lower birthweight, lower APGAR scores, congenital malformations) of these drugs may be hard to recognize.
Therefore, for possible hazardous drugs, a new method adapting from pharmacovigilance studies was developed for adverse pregnancy outcomes using real-world data.

Methods:
All women (>18 years) with a clinical delivery from 2018 until 2024 in Isala (Zwolle, The Netherlands) were selected using CTCue (IQVIA, The Netherlands) with relevant possible confounding variables, using Electronic Patient Files (EPF). Medication was grouped according to the ATC codes at 3 different levels, the first three, five and seven positions. Small for Gestational Age (SGA) and Large for Gestational Age (LGA) were defined according to Hoftiezer et al..[1] Congenital malformations were taken from the EPF. An "event" was defined if any pregnancy ended with a neonate with low APGAR scores (<7), SGA, LGA, pregnancy duration < 33 weeks or congenital malformations. Disproportional analysis (DA) was used to identify drugs with an "event", using the "pvda" package in Rstudio. The "information component", IC, was used as a log-2-transformed observed-to-expected ratio based on the relative reporting rate. Any disproportional signal, IC>3 and lower confidence interval >1, should be followed up by further analysis considering possible confounders.

Results:
In a cohort with over 18K pregnancies, disproportional signals were found for all three levels of ATC.

Conclusion:
DA is a promising tool for detecting adverse pregnancy outcomes. Upscaling in more hospitals may improve results for DA.

3. Medication screening in pregnant women for cord blood donation in extremely preterm neonates

Authors:
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Introduction:
Red blood cell (RBC) transfusions derived from cord blood (CB) are currently in development for use in extreme premature neonates in order to maintain physiological fetal hemoglobin levels. In order to fulfill donor requirements for RBC-CB transfusions, maternal donors should fulfill current donor screening criteria, such as medication safety.

Methods:
We assessed the currently used Dutch donor medication screening list supplemented with drugs prescribed during pregnancy or obstetric anesthesia for CB-RBC donation using the following three criteria for disapproval: (1) currently disapproval by Dutch Blood Bank criteria, (2) known neonatal drug toxicity and (3) no data available on neonatal drug toxicity or safety. For this we have used national public pharmacotherapeutical databases (KNMP Kennisbank and Lareb center of drug-toxicity) as well as international Library of Medicine's (PubMed).

Results:
Of the 418 evaluated drugs, 314 (75%) were unsuitable for CB-RBC donation. Among these, 138 of 314 (44%) were already contraindicated in the current Sanquin guidelines, while 176 (56%) were newly identified as potentially unsafe for CB-RBC transfusion due to placental transfer and neonatal risks. The most common reasons for contraindication included teratogenicity, reported neonatal adverse effects or insufficient safety data.

Conclusion:
This study highlights the need for a CB-specific medication screening protocol to ensure the

safety of CB-RBC transfusions in extremely preterm neonates. It underlines the significant knowledge gap in pharmacological research in this population and provides a dynamic list medication that can be used safely by a CB-donating mother.

4. Spontaneous adverse drug reaction reporting of congenital malformations, a Danish national register study

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Introduction:
Maternal use of both new and established drugs medication during pregnancy still poses a risk of teratogenesis, particularly if the teratogenic effects are probabilistic and not deterministic. Potential underreporting can obscure the signals of drug-related congenital malformations. This study aims to evaluate potential medication-associated congenital malformations in Denmark.

Methods:
An observational cross-sectional study was conducted using data from the national pharmacovigilance database, which includes all spontaneous ADR reports submitted to the Danish Medicines Agency from July 1, 2013 to June 30, 2023. As defined by the European Medical Agency, reported incidents were deemed serious if they resulted in death, were life-threatening, required hospitalization or an extension of existing hospi-talization, led to persistent or significant disability or incapacity as determined by the reporter, or were associated with a congenital anomaly or birth defect. Maternal antenatal drug use was identified, and reported ADRs were assessed for congenital malformations.

Results:
We identified reports of potential ADR-related congenital malformations in 75 children, with a total of 92 diagnoses as classified by ICD-10. In 8 of the 75 included children, the ADRs were reported to have resulted in a fatal outcome. Eighty-five different drugs from 58 ATC codes were implicated. The top three reports were all focused on psychotropics, specifically Quetiapine, Sertraline, and Nortriptyline.
The reports were generally sporadic, and only three diagnoses were reported in five or more children. Given the scarcity of the more seldomly occurring malformations (i.e. < 5) and the relatively high number of reported drugs, no signals were observed between malformations an preceding drugs.

Conclusion:
Public awareness is crucial in novel medications, as these may be teratogenic. Continuous surveillance of potential ADR-associated congenital malformations is essential.

5. Pediatric medication from off-label to on-intelligent-evidence

Authors:
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Introduction:
In many cases, no medication is approved for either the disease, the route of administration, or the patient subgroup, a situation referred to as off-label. In the pediatric population off-label medication is particularly common, across all jurisdictions, with the highest prevalence among the youngest children and the hospitalized children.

Methods:
We aimed to perform a literature search for consensus on off- and on-label medication use in the pediatric population, with a scooping review by extracting relevant global publications on definitions of pediatric off-label use of medication to December 2024 from PubMed. We did a bibliometric study. In addition, we obtained information from relevant websites (EMA, FDA, CJEU, ESDPPP). We used the information for mapping and timelining of trends and hotspots regarding clinically readily useable definitions of pediatric off-label use of medication.

Results:
Unlike off-label use, on-label medication follows a structured stepwise process. Starting with a regulatory evaluation of efficacy and safety, followed by a healthcare technology assessment (HTA) that provides contextual value. The final clinical decision is then made, considering factors such as clinical guidelines. A clinical consequence of off-label use is the lack of regis-tered data on adverse drug reactions in this context. Additionally, off-label use does not bene-fit from the legal protection associated with on-label situation medication. In the EU, the EMA provides an SmPC (summary of product characteristics), and in the US, the equivalent doc-ument is the FDA label.

Conclusion:
The current off-situation could advantageously be complimented by an on- label approach developed by a multidisciplinary international collaboration. We propose a patient-centered, dynamic tool as add on to the SmPC/label and the HTA process, integrating clinical experi-

ences and guidelines. This would enhance the off-label situation into an ‘on-intelligent-evidence’ (OIE) situation.

6. Angiotensin II/angiotensin I ratio as pharmacodynamic parameter in healthy adults and children with heart failure treated with enalapril: insights from an adult population pharmacokinetic-pharmacodynamic model and the LENA studies

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Introduction:
Enalapril decreases angiotensin II and increases angiotensin I in healthy adults. The aim was to develop a population pharmacokinetic/pharmacodynamic model describing the effect of the active metabolite enalaprilat on angiotensin II/angiotensin I ratio in healthy adults, and to use the prediction to compare it to the angiotensin II/angiotensin I ratio of children with heart failure treated with enalapril orodispersible minitablets.

Methods:
The serum concentrations of enalaprilat and the angiotensin II/angiotensin I ratio of nine healthy adults after a single dose of 20 mg enalapril maleate were analysed and a population pharmacokinetic/pharmacodynamic model was developed using Monolix (version 2024R1). Visual predictive checks were used to evaluate the model and to compare the angiotensin II/angiotensin I ratio before and after enalapril administration in healthy adults with that in children with heart failure. Angiotensin II/angiotensin I ratios (n=54) of 27 previously angiotensin-converting enzyme inhibitor naïve children with heart failure from the LENA (Labeling of Enalapril from Neonates up to Adolescents) studies served for comparison.

Results:
A two-compartment model with transit compartments for enalaprilat combined with a sigmoidal Imax model with an effect compartment was selected as pharmacokinetic/pharmacodynamic model for healthy adults. The parameter estimate was 0.043 for the baseline effect E0 and 30.01 µg/L for the half-maximal inhibitory concentration IC50. The comparison showed that at the given dose (median 0.04 mg/kg, range 0.02–0.10 mg/kg) of enalapril in children with heart failure (median age at measurement 0.36 years, range 0.07-2.2 years), a similar angiotensin II/angiotensin I ratio was achieved as in adults.

Conclusion:
An appropriate pharmacokinetic/pharmacodynamic model for healthy adults was developed and the comparison performed suggests that a similar effect on the angiotensin II/angiotensin I ratio is achieved in children with heart failure treated with enalapril as in adults.

7. A pharmacovigilance study on the association between proton-pump inhibitors and inappropriate neonatal use based on the FAERS database

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Introduction:
Proton pump inhibitors (PPIs) are widely used for acid suppression, yet their efficacy and safety in neonates and infants remain unclear. While esomeprazole is the only FDA-approved PPI for infants, other PPIs are also frequently prescribed. This study utilizes FAERS data to evaluate potential adverse drug events (ADEs) of PPIs, providing crucial insights into their safe use in this vulnerable population.

Methods:
This observational cross-sectional study was conducted using the FDA Adverse Event Reporting System (FAERS) database. A total of 464 patients aged 0-2 months and 2 months-2 years with a body weight of ≤12 kg were included. Only patients receiving omeprazole, pantoprazole, lansoprazole, rabeprazole, or esomeprazole monotherapy were evaluated. The most frequently prescribed PPI, the most common indication, the most reported ADE, seriousness of adverse events and the countries reporting the highest number of adverse events were analyzed.

Results:
A total of 464 patients were analyzed. Among them, 203 (43.75%) were female, 217 (46.77%) were male. Lansoprazole (213, 45.90%) was the most frequently used PPI, while gastroesophageal reflux disease (71, 15.30%) was the most common indication for PPI prescription. The most frequently reported ADE was vomiting (8 cases, 1.72%). Among reported adverse events, 323 (69.61%) were classified as serious, while 141 (30.39%) were non-serious. Accidental exposure was reported in 15 cases (3.23%). In 12 cases (2.58%), the treatment was reported to be ineffective. Off-label PPI use was reported in 16 patients (3.45%). Prescribing errors were reported in 26 cases (5.60%), while 35 cases (7.54%) were related to age-related inappropriate prescribing. Reports were mostly submitted by healthcare professionals (258, 55.40%), followed by consumers (173, 37.28%). The United States accounted for the highest number of reports, with 148 cases (31.90%).

Conclusion:
FAERS is a valuable pharmacovigilance tool but the lack of causality assessment, limits its ability to confirm that whether the ADEs are truly caused by the suspected drug. Integrating

neonatal-specific algorithms could enhance drug safety evaluations, strengthen evidence-based decision-making, and improve risk-benefit assessments in neonates.

8. AMI FABRY – A triple relief for pain, gut, and mood in Fabry Disease using amitriptylin

Authors:
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Introduction:
Fabry disease (FD) is a rare lysosomal storage disorder characterized by debilitating neuropathic pain, gastrointestinal (GI) symptoms, and mood disturbances, significantly impacting the quality of life. Currently approved therapies fail to address these symptoms effectively. Amitriptyline, a tricyclic antidepressant, has demonstrated efficacy in neuropathic pain, GI dysfunction, and mood disorders in other conditions, suggesting its potential utility in children with FD.

Methods:
A systematic literature review was conducted to evaluate the use of amitriptyline in paediatric populations for GI manifestations, neuropathic pain, or depressive disorders. Fifteen articles met the inclusion criteria, focusing on English-language studies (clinical trials, case reports, or case series) involving amitriptyline and paediatric populations. Data analysis included group comparison and multivariate analysis were applied to assess efficacy and identify predictors of response.

Results:
Among 768 children treated with amitriptyline, 55% achieved statistically significant symptom improvement compared to placebo or alternative treatments, 34% experienced non-significant efficacy, and 11% showed lower efficacy. GI symptoms exhibited the most consistent response, with all included studies (n=247) reporting 100% efficacy in symptom relief. Only one study investigated amitriptyline for neuropathic pain in children (n=14), demonstrating efficacy comparable to gabapentin. However, a single case report in FD showed the beneficial use of amitriptyline (0.25 mg/kg at bedtime) for neuropathic pain management. Our analysis revealed a dose range of 0.2-6 mg/kg/day, with lower doses typically used for GI symptoms and higher doses for depressive disorders. Multivariate analysis indicated that early treatment initiation and lower baseline symptom severity were associated with better outcomes, while gender and age had no significant effect.

Conclusion:
Amitriptyline demonstrates significant promise as a repurposed therapy for FD-related symptoms in children. Its multifaceted mechanisms, including neuropathic and dysfunctional pain modulation, anticholinergic effects, and serotonergic action, provide a holistic approach to symptom management, highlighting its potential in managing diverse FD symptoms.

9. Drug interactions in critically ill neonates undergoing therapeutic hypothermia: a single centre study

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Introduction:
Drug interactions (DIs) are generally described mainly from pharmacokinetic (PK) and pharmacodynamic (PD) data gathered from clinical studies in adults and geriatric patients. However, there is only limited evidence concerning DIs in paediatric and neonatal populations, especially when other factors - therapeutic hypothermia (TH), for instance, may be taken into consideration.

Methods:
Complex demographic data from ten neonates (median age upon admission 2 hours 56 mins; weight 3617,6 g; APGAR: 1-4-5,5; length 52,25 cm; head circumference 36,25 cm) undergoing TH were collected and DIs were evaluated. TH was initiated within 6 hours after birth in 80% of patients. First, three different interaction checkers were used: NEO-DEER Prediction Tool, Lexicomp® and Drug Agency. Next, possible developmental and TH factors influencing PK and PD were then further applied to the preliminary results to receive results as close to reality as possible.

Results:
The NEO-DEER prediction tool confirmed that there will be a drug interaction present in our cohort. Lexicomp® found 25 possible drug interactions (of both PK and PD nature), whereas DrugAgency tool found 7 (all confirmed by Lexicomp®). Most found interactions were classified as C or 3 (moderate, monitor therapy, e.g. phenytoin + dobutamine), three interactions were classified as D or 4 (major, consider therapy modification, e.g. sufentanil + phenobarbital) with therapy adjustment recommendations.

Conclusion:
The majority of potential DIs were found probably relevant mostly on a theoretical basis, under hypothermia not well understood in the small sample size (limitations of the study). Clinically relevant interactions were found as well (as was predicted by the NEO-DEER tool), but with careful titration of doses, all of them were handled without further complications. However, the time of observation was very short, therefore, further studies should be performed to confirm our suspicions.

10. Leveraging existing evidence on off-label prescribed drugs to support effective and safe pharmacotherapy: pediatrics as an example

Authors:
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Introduction:
Previous research shows that for all drugs (>850) listed in the pediatric formulary, >40% are still off-label for indication or age group. More worrisome is lack of high quality evidence for the majority of these off-label drugs. Finding innovative ways to leverage existing data to support and enhance a benefit-risk analysis and potentially a market authorization could be the way forward, as clinical trials for all these drugs will be unfeasible. We aimed to perform a SWOT analysis on this approach supported by multi stakeholder interviews.

Methods:
Stakeholders (n=37) from regulatory science and medicines agencies, marketing authorization holders (MAHs), professional societies, healthcare professionals (HCPs), policymakers and governmental organizations, research networks and patient organizations were identified through the researchers' network and invited to participate in group interviews. We asked stakeholders to reflect on their views on innovative methodologies for evidence generation, leveraging existing evidence and the biggest challenges and opportunities to this approach. All interviews(n=13) were recorded, transcribed and coded using Atlas.ti. Results were categorized as strengths, weaknesses, opportunities and threats (SWOT).

Results:
Stakeholders agreed that the continued lack of proven efficacy and safety of drugs used in pediatrics is an urgent problem that mandates innovative, pragmatic resolution. Strengths: clear primary end goal of the approach; well supported by diversity of stakeholders. Weaknesses: Lack of financial resources and infrastructure to execute this ambitious project. Opportunities: Hospitals already collect structured data, aiding the use of real-world evidence. regulatory opportunities provided by revision of EU Pharmaceutical Regulation. Threats: involvement of MAH's needed for label changes; increased pricing for repurposed drugs. Stakeholders from regulatory science, medicines agencies and MAH's believe licensing is the ultimate goal, while closing the knowledge gap is most important to HCPs.

Conclusion:
The SWOT analysis of stakeholder perspectives provides guidance on future steps to close the off-label information gap.

11. A review on the role of extrapolation as basis for paediatric marketing authorisation applications of medicines in the EU

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Introduction:
For new medicines, drug companies obtain regulatory approval on the strategy to generate paediatric evidence, which can be supported by extrapolating evidence obtained in a reference population. This study investigated the impact of extrapolation based on exposure-matching on the success and efficiency of paediatric marketing authorisation applications (PMAAs).

Methods:
Data was extracted from completed paediatric investigation plans (PIPs), associated drug labels and public assessment reports published on the European Medicines Agency website. Assessment reports were evaluated to assess whether PMAAs were supported by extrapolation based on exposure-matching. Wilcoxon rank-sum tests were used to compare PMAAs supported and not supported by extrapolation based on exposure-matching for outcomes including the duration of drug development completion, restrictions in use of the medicinal product in targeted paediatric population in terms of minimum body weight and age, and subgroups.

Results:
Exposure-matching supported the benefit/risk assessment of 39.6% of the PMAAs. Targeted and approved minimum age of the paediatric population were comparable for PMAAs where extrapolation based on exposure-matching supported the benefit/risk assessment (2.0 vs. 2.0 years, P-value = .72), but not for PMAAs not supported by extrapolation (0.2 years vs. 0.5 years, P-value = .05). Completion of drug development was 5.4 years vs. 4.3 years (P = .04) in PMAAs supported by extrapolation based on exposure-matching compared to those not supported by extrapolation, respectively.

Conclusion:
PMAAs supported by extrapolation based on exposure-matching were more successful in terms of obtaining marketing approval in the targeted paediatric population than PMAAs not supported by exposure-matching, but were also less time efficient as the time to complete drug development was prolonged when using extrapolation based on exposure-matching.

12. Preventing life-threatening symptoms of Noonan syndrome: Is it feasible to treat intra-uterine with trametinib?

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Introduction:
Noonan syndrome (NS) is a genetic multisystem disorder, characterized by dysregulation of the Ras-mitogen-activated protein kinase (RAS/MAPK) pathway, leading to severe, potentially fatal lymphatic anomalies. Trametinib, a mitogen-activated protein kinase (MEK) inhibitor, appears promising to treat lymphatic anomalies, especially in neonates. Recently, intra-uterine trametinib treatment was proposed for a foetus with severe hydrops fetalis. However, it remains unknown whether therapeutic foetal concentrations are achieved. Therefore, we aimed to predict the maternal and foetal plasma concentrations, using placental perfusion and physiology-based pharmacokinetic (PBPK) modelling, to propose a safe and effective dosing regimen for foetal trametinib therapy.

Methods:
Placental transfer of trametinib was studied using ex vivo single cotyledon placenta perfusions in maternal-to-foetal direction. Intrinsic unbound clearances from these experiments were implemented in a trametinib PBPK model in Simcyp (version 23). Maternal and foetal drug concentrations following oral maternal dosing were predicted. We assumed an effective foetal concentration range of 4-7 ng/mL, while maternal plasma concentration should not exceed 10 ng/mL to prevent adverse events.

Results:
After a 3-hour placental perfusion experiment, 19.2% ± 1.3% of the total amount of trametinib dosed crossed the placenta from maternal-to-foetal circulation. After incorporating this into a pregnancy PBPK model, we estimated that 2 mg trametinib once daily for 2 weeks would result in foetal plasma concentrations of 5.00, 9.40, and 12.1 ng/mL if therapy starts at 15-, 24-, and 32-weeks of gestation, respectively. Maternal plasma concentrations reached 18.4, 17.7, and 17.0 ng/mL in these scenarios.

Conclusion:
Intra-uterine trametinib treatment for NS appears feasible, as effective foetal concentration are reached after oral dosing for 2 weeks with 2 mg trametinib once daily. However, the maternal threshold is exceeded, suggesting maternal toxicity. Model-informed dose optimalization studies should be performed to balance foetal efficacy and maternal safety to propose a dosing regimen for further clinical testing.

13. On-label paediatric drug product information in Switzerland – the neglected child

Authors:
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Introduction:
Developmental pharmacology is influenced by changes in body composition and organ function maturation. Healthcare professionals who prescribe, prepare, and administer drugs to children must consider this. Information on the age-appropriate use (including prescription, preparation, and administration) of authorised medicinal products is frequently incomplete within the Summary of Products Characteristics (SmPC).

Methods:
We aimed to create a list of topics that are particularly relevant for safe and effective drug use in paediatrics, but which were identified as either missing or incompletely reported. The list of topics was compared with the reporting obligations imposed by the statutory provisions in Switzerland. For each topic, SmPC examples relevant for clinical practice were collected.

Results:
We identified 16 topics: 1) authorised child ages, 2) posology information, 3) age-specific contraindications, 4) update upon change in state-of-the-art, 5) dissolution concentration, 6) solvents / diluents compatibility, 7) administration concentrations, 8) osmolarity / pH, 9) reconstitution / dilution stability, 10) shelf-life, 11) central or peripheral vein administration, 12) infusion rates and administration duration, 13) dosing aids, 14) filter for administration, 15) extravasation, 16) taste. Among these, 5 (31%) are subject to reporting obligations, 7 (44%) require further clarification regarding the information to be reported under the statutory provisions, and 4 (25%) are not subject to any reporting obligations.

Conclusion:
We provide this list of topics as a proposal of indispensable pediatric-specific information that should be available for authorised medicinal products. Moreover, it is paramount that the safe and effective use of drugs with paediatric authorisation is appropriately described for all age populations within the label.

14. Evaluation of nine population pharmacokinetic models for model-based vancomycin concentration monitoring in a local population of neonates

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Introduction:
To optimize vancomycin use and enhance therapeutic drug monitoring (TDM) in neonatology, model-informed precision dosing (MIPD) using suitable population pharmacokinetic (PopPK) models is proposed. We aimed to evaluate the potential suitability (predictive performance) of published PopPK models for vancomycin concentration prediction in our local population of neonates.

Methods:
Retrospective study analysing vancomycin measurements from neonates treated between 2018-2023 at the University Children's Hospital Basel. Nine models predicting PopPK of vancomycin in neonates were evaluated using the Tucuxi software. Initial vancomycin measurements were used in combination with PopPK models to estimate individual pharmacokinetic parameters. Those individual pharmacokinetic parameters were then used to predict initial concentrations and to forecast subsequent 2nd concentration measurements. Predictive performance was evaluated regarding bias (mean prediction error) and precision (root mean squared error). Secondary outcomes included target exposure achievement (nationally defined as trough concentration 10-20 mg/L), TDM timing and safety/effectiveness-related clinical outcomes.

Results:
A total of 78 vancomycin level measurements of 32 neonates (median weight: 1834 g, post-menstrual age: 31.9 weeks) were collected. Lowest bias (<7%) and highest precision (20-32% for initial measurements, 42-44% for forecasted 2nd measurements) was obtained by PopPK models from Mehrotra 2012 and Frymoyer 2019. Nationally recommended target trough concentration was reached in 41/78 (52.6%) of measurements (internal target of 5-15 mg/L reached in 48/78 (61.5%)). Initial measurements were taken at steady state in 17/32 (53%) of cases. Acute kidney injury and mortality during treatment (within the infection episode) were each observed in 2 neonates (6.25%).

Conclusion:
MIPD-guided vancomycin concentration monitoring requires careful local evaluation before implementation. We identified two potentially suitable PopPK models that may allow to handle non-steady-state measurements and predict area-under-the-curve as emerging

preferred exposure metric. There is room for improvement in neonatal vancomycin use and monitoring, involving clarification of proposed targets in neonates.

15. MEDeHelp –development of an emergency mobile application for Europe

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Introduction:
In emergency medicine patient specific drug administration presents a major challenge. Variations among patients, from newborns to adults, along with distracting factors and stressors, complicate the process. To support healthcare professionals, a mobile application was developed that provides patient-specific drug information through certified algorithms.

Methods:
The emergency app was planned and developed under PEDeus AG's certified quality management system (ISO 13485 and EU Medical Device Regulation). The app leverages certified algorithms provided by the associated class IIa medical device core tool, PEDeDose. User experience was optimized with a team of dedicated specialists. The design concept and the content requirements were defined with a diverse group of Swiss emergency medicine experts.

Results:
The MEDeHelp mobile application was designed for emergency care medicine staff. It enables quick online and offline access to patient specific dosages, along with preparation and administration information for drugs commonly used in emergency situations. The drug information is tailored to the patient's body weight, age or height and considers neonates, children and adults. MEDeHelp provides further information such as norm values, equipment specifications and treatment guidelines. The app will be available in German, French, and English, and will be compatible with iOS and Android operating systems. The launch is scheduled for the second half of 2025.

Conclusion:
Safe apps for emergency medicine fulfilling European regulations and standards for drug information are an unmet need. We applied our existing expertise in both, paediatric drug safety and medical software development to build an app that enables fast and safe patient specific drug information for all patient groups.

16. Paracetamol concentrations and time-course of ductus arteriosus diameter in extreme preterm neonates: a population pharmacokinetic-pharmacodynamic analysis

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Introduction:
Patent ductus arteriosus is a common complication of extreme prematurity. Treatment with indomethacin or ibuprofen has shown efficacy on ductus closure but without reducing of mortality and morbidity. Prophylactic treatment by paracetamol could be a safer alternative. The aim was to build a pharmacokinetic-pharmacodynamic model describing the effect of paracetamol on the time-course of the ductus arteriosus diameter.

Methods:
Preterm neonates of 23-26 weeks of gestation were treated with prophylactic intravenous paracetamol within 12 hours after birth for five days (two dose levels: 20 mg/kg followed by 7.5 mg/kg/6h or 25 mg/kg followed by 10 mg/kg/6h). The ductus arteriosus diameter was determined by echocardiography performed daily until day 7. The model was build using an

Imax model with an effect compartment and exponential disease progression model. Concentrations of paracetamol in the effect compartment were simulated with different doses over time for 500 virtual patients.

Results:
A total of 29 extreme preterm neonates were included in the study. Between-subject variability was estimated on transfer rate constant between the central and the effect compartment (ke0) and maximum drug inhibition (Imax) parameters. Two subpopulations with different Imax values were identified: 99% for a subpopulation of 10 patients and 42% for a subpopulation of 19 patients. A negative effect of maximum fraction of inspired oxygen used during transfer to intensive care unit and a positive effect of intubation during treatment were significant on ke0. Simulations showed that both dose levels enabled to achieve 95% of maximal inhibition by the end of treatment, and from day one with the second dose level for 90% of patients.

Conclusion:
Intravenous paracetamol treatment with a loading dose of 25 mg/kg within 12 hours after birth followed by 10 mg/kg/6h appears to be effective to accelerate time to ductus closure with limited benefit of a further dose increase.

17. The REPAIR-NEO study protocol to test a workflow on drug development in neonates undergoing therapeutic hypothermia

Authors:
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Introduction:
Despite advances, perinatal asphyxia (PA) incidence has not decreased in the last decade. PA occurs in 5.4/1000 liveborn newborns, with 1.8/1000 live births diagnosed with hypoxic ischemic encephalopathy (HIE). While therapeutic hypothermia (TH) is effective, still 45% of neonates have poor outcome. Consequently, additional pharmacological interventions are needed, and improving the workflow would be beneficial.

Methods:
Because of pre-clinical evidence (1), we have selected paracetamol as drug to test the workflow developed (repurposing paracetamol to improve asphyxia in neonates) This workflow is based on confirming preclinical evidence (Vannucci model, including dose-response, short- and long-term outcome) (1), development of a TH-specific physiologically-based pharmacokinetic (PBPK) model (2), supported by both in vitro microsomal and in vivo pharmacokinetic observations previously reported (3,4).

Results:
The grant has been awarded, and this CELSA project started in 10/2024. Data sharing on intravenous paracetamol in neonates, including cases undergoing TH can be pooled. Microsomal studies and PBPK modelling and confirmation of the effects previously reported in the animal pre-clinical Vannucci model, while the liver enzyme project is still ongoing.

Conclusion:
Pending the final results, we are confident that we will be able to describe an effective translational workflow for drug development programs in this specific subpopulation of neonates.

(1) Allegaert et al., Arch Med Sci 2020 doi:10.5114/aoms.2020.100715 (2) Smits et al., Front Pharmacol 2020 doi:10.3389/fphar.2020.00587 (3) Haslung-Krog et al., Br J Clin Pharmacol 2023 doi: 10.1111/bcp.15834 (4) Allegaert et al., Arch Dis Child 2011 doi:10.1136/adc.2010.204552.

Funding: FWO senior clinical investigatorship (18E2H24N) FWO iPREDICT (G0D0520N), KU Leuven CELSA REPAIR-NEO (24/022).

18. Quantifying milk and maternal postpartum changes to improve drug safety in breastfeeding

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Introduction:
The lack of robust drug safety data during lactation often leads to discontinuation of breastfeeding. Physiologically-based pharmacokinetic (PBPK) models have emerged as valuable in silico tools to address this gap. To enhance the accuracy of these models, it is crucial to incorporate the physiological changes that occur during lactation.

Methods:
A comprehensive PubMed search was conducted to compile data on changes in milk composition and maternal postpartum physiology. Inclusion criteria for studies were: (1) healthy lactating women, (2) adult individuals between 18 and 45 years of age, (3) no medication use during or after pregnancy, (4) uncomplicated pregnancies, and (5) full-term infants. Data were analyzed in Microsoft Excel, and functions were fitted using postpartum age as a regressor. Weighted least squares regression was predominantly used, with weighting reflecting study sample sizes. Function selection was guided by visual assessments and numerical diagnostics (i.e., weighted sum of squares).

Results:
From 230 studies, 36689 data points were extracted from 20801 postpartum women, encompassing the period from childbirth to 12 months postpartum. Longitudinal postpartum time-dependent functions were derived to characterise changes in maternal plasma volume, breast volume, cardiac output, glomerular filtration rate, haematocrit, human serum albumin, alpha-1-acid glycoprotein, milk pH, milk volume, milk fat, milk protein, milk water content, and daily infant milk intake. Despite limited data beyond 7 months postpartum for certain parameters, mathematical functions were successfully generated for all variables.

Conclusion:
This study derived 13 functions describing changes in postpartum maternal physiology and milk composition from an extensive dataset. These algorithms provide a robust foundation to improve the predictive accuracy of lactation PBPK models, supporting better-informed pharmacological decisions for breastfeeding women.

19. Developing evidence-based dosing recommendations for intravenous ciprofloxacin in critically ill children: a population pharmacokinetic study using total and unbound concentrations

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Introduction:
Optimal antibiotic dosing in critically ill children is influenced by pathophysiological changes and supportive therapies. This study aimed to develop a population pharmacokinetic model for ciprofloxacin in critically ill children to identify predictors of inter-individual variability, evaluate target attainment for both total and unbound exposure, and provide evidence-based dosing recommendations.

Methods:
A prospective, open-label, multicentric pharmacokinetic (PK) study was conducted in 44 hospitalized children (< 16 years) receiving intravenous ciprofloxacin. Blood and urine samples were collected at two dosing occasions (10 mg/kg every 12h) and drug concentrations were assessed in plasma (total and unbound concentrations) and urine. PK parameters were analysed with population PK modelling using Monolix. Probability of target attainment (PTA) was calculated based on the free or total area under the curve (AUC) and was simulated for different dose regimens of ciprofloxacin.

Results:
Ciprofloxacin PK was best described with an allometrically scaled two-compartment model. The typical fraction unbound ciprofloxacin in plasma, and the fraction excreted unchanged in urine were 0.52 and 0.89, respectively. Clearance increased with glomerular filtration rate and decreased when children were on mechanical ventilation. For an MIC of 0.25 mg/L, the study dose achieved a PTA of 74.4% for unbound exposure (fAUC/MIC > 72) and 79.3% for total exposure (AUC/MIC > 125). Adequate PTA (≥ 90%) requires 10 mg/kg every 8h in ventilated patients and 15 mg/kg every 8h (off-label) in non-ventilated patients with normal renal function (80-130 mL/min/1.73m²).

Conclusion:
Standard dosing regimens of ciprofloxacin (20-30 mg/kg per day) fail to achieve adequate target attainment in non-ventilated critically ill children with a normal or elevated renal function. Further research should prospectively evaluate the efficacy and safety of increasing ciprofloxacin doses.

20. In vivo cytochrome P450 1A2 activity in adolescents with and without obesity

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Introduction:
Obesity-induced pathophysiological complications can significantly alter the pharmacokinetics of certain drugs. This study aimed to investigate the in vivo activity of CYP1A2 in a larger sample of obese and non-obese children adolescents as prior research has yielded inconclusive results regarding the impact of obesity on CYP1A2 activity in this population.

Methods:
The study was designed as an open-label, exploratory pharmacokinetic investigation to evaluate the in vivo activity of CYP1A2 and was conducted in Denmark. Children were recruited based on specific eligibility criteria, including age, gender, and body mass index (BMI) Standard Deviation Score (SDS). A total sample size of 64 participants was calculated to detect differences in CYP1A2 clearance. The urinary metabolic ratio (u-MR) of paraxanthine to caffeine was used to evaluate CYP1A2 activity, while hepatic fat content was measured using Magnetic Resonance Spectroscopy (MRS).

Results:
A total of 65 children (31 females, 34 males) completed the study, consisting of 30 children with obesity and 35 non-obese controls. Although significant differences were found in liver fat content, lipid profile and blood pressure, no significant differences were observed in the paraxanthine/caffeine u-MR between the two groups (mean Log10MR: 0.82 vs. 0.82, 95% CI -0.12 to 0.11).

Conclusion:
Obesity was not found to affect in vivo CYP1A2 activity in adolescents aged 11-18 years. These findings suggest that pediatric populations with obesity may not require differential dosing considerations based solely on CYP1A2 activity, though further research is warranted to explore alternate influencing factors on drug metabolism within this demographic.

21. Assessing the predictive performance of a population pharmacokinetic model for paracetamol and its metabolites in an external dataset of neonates, infants, and children receiving paracetamol as analgesic after cardiac surgery

Authors:
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Introduction:
At present, there is limited information on the use of paracetamol in children undergoing cardiac surgery. Previously, a population pharmacokinetic model was developed for paracetamol and its metabolites (sulphate, glucuronide, and oxidative metabolites) in children aged 3 months-3 years after cardiac surgery [1]. Our study aims to evaluate the model's predictive ability in an external dataset [2] including a wider bodyweight and age range.

Methods:
Data were analysed from the paracetamol arm of the Paediatric Analgesia after Cardiac Surgery (PACS) study [2], in which children undergoing cardiac surgery after a morphine loading dose were randomized to receive intermittent intravenous paracetamol or continuous morphine infusion with rescue morphine. Posthoc Bayesian estimates were generated using the previously published model[1] to assess model predictions. The evaluation included goodness-of-fit and plots of the empirical Bayes estimates of model parameters stratified by bodyweight and age.

Results:
For external validation, 1057 observations including paracetamol and its metabolites, from 31 patients (median [range] weight 5.3kg [2.4-13.2], median [range] age 123 days [7-1014]) from the PACS [2] study were available. This external dataset encompassed lower bodyweights than the original study [1] (30 patients, median [range] weight 6.1 kg [4.0-12.9], median [range] age 177 days [92-944]). The model demonstrated the ability to predict the external data reasonably well. A general over-prediction was observed for all analytes across different bodyweight stratifications.

Conclusion:
Given the slight deviations of the published model observed in this external validation study, and in view of the rising use of paracetamol as analgesic after paediatric cardiac surgery, in

future research the current external- and original dataset will be analysed together. Ultimately this will lead to a model that can be used to guide paracetamol dosages after cardiac surgery across all weight groups.

22. Population pharmacokinetics of morphine in children under 3 years after cardiothoracic surgery: External validation and extrapolation of published models

Authors:
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Introduction:
Confidence in drug dosing accuracy is strengthened by external validation of published pharmacokinetic models. This study aimed to externally evaluate and extrapolate our model describing morphine pharmacokinetics after paediatric cardiothoracic surgery (Valkenburg model)[1] using an external dataset from Paediatric Analgesia after Cardiac Surgery (PACS) study[2]. Secondarily, morphine concentration predictions were compared with predictions obtained from Elkomy et al.'s model[3].

Methods:
The PACS study[2] included patients (6 days-3 years) undergoing cardiothoracic surgery. NONMEM® was used for validation and model fitting with Bayesian estimation (MAXEVAL=0). Data processing and visualisation were performed in R. The original Valkenburg model[1] was externally validated (with extrapolation) using data from the PACS study[2], while the Elkomy model3 was used for data predictions for both studies[1,2].

Results:
Samples (N=699) and dosing records of 72 patients (median [range] weight 5.3kg [2.4-13.2]) from the PACS study [2] were available, comprising an on average younger population than the Valkenburg data [1] (N=35; median [range] weight 6.14kg [3.6-12.9]). Although concentrations in the PACS study[2] were generally lower than in the original Valkenburg study[1] resulting from overall lower morphine doses, the PACS data[2] was predicted by our model[1] with minimal trends except for under-prediction of morphine concentrations in a subgroup of neonates aged ≤15 days (16.6% of population) and over-prediction in the oldest quartile of the population. The Elkomy model[3] (N=20; mean [range] weight 7.8kg [3.1-18.5]), predicted morphine concentrations across both studies[1,2] reasonably, except for under-prediction in the youngest half of the population and for high (peak) morphine concentrations.

Conclusion:
This study demonstrated that our Valkenburg model predicted morphine concentrations

reasonably well in children after cardiothoracic surgery. Compared to a literature model, our model performed better in younger children, while Elkomy model was slightly better for older children. This study highlights the need for further individualisation to describe morphine pharmacokinetics in neonates ≤15 days after cardiothoracic surgery.

23. Use of virtual populations to investigate 'weekend-off' efavirenz dosing in adults and adolescents with different CYP2B6 526 G>T genotypes

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Introduction:
Although everyday combination therapy is the standard-of-care for HIV patients, dose reduction strategies are being assessed for their utility to increase compliance, reduce side-effects and cost. Here we use PBPK to assess the impact of CYP2B6 genotype on efavirenz pharmacokinetics in virtual adolescent subjects receiving a 'weekend-off' dosing regimen.

Methods:
A verified PBPK model for efavirenz was used to simulate steady-state pharmacokinetics following continuous dosing (600mg QD) and 'week-end off' dosing (5 days 600mg QD; 2 days no dose and repeat) in adults and in adolescents (>40 kg) with different CYP2B6 516G>T genotypes and in an unselected general population. Simulated Ctrough were compared to the minimum effective concentration (1000 ng/mL).

Results:
Simulated Ctrough following 'weekend-off' dosing was 0.54-fold lower than for continuous dosing in an unselected adult population but still above 1000 ng.mL (1306 vs. 2440 ng/mL). Simulated average Ctrough following 'weekend-off' dosing in CYP2B6 GG, GT and TT individuals were 859, 1123 and 2517 ng/mL. In adolescents, simulated Ctrough following 'weekend-off' dosing was 0.52-fold lower than for continuous dosing in an unselected adolescent population but still above 1000 ng.mL (1428 vs. 2765 ng/mL). Simulated average Ctrough following 'weekend-off' dosing in CYP2B6 GG, GT and TT individuals were 917, 1198 and 2622 ng/mL.

Conclusion:
Simulations indicate adequate average Ctrough concentrations across unselected virtual subjects following 'weekend-off' dosing but highlight CYP2B6 genotype as an important covariate in individuals with the CYP2B6 GG genotype being more likely to have Ctrough <1000ng/mL.

24. optimizing high-dose methotrexate dosing for the treatment of infant acute lymphoblastic leukemia

Authors:
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Introduction:
Currently, there is no pharmacokinetic (PK)-based dose recommendation for high-dose (HD) methotrexate (MTX) in infants. We develop a physiology-based (PB)PK-model describing HD-MTX in infants, targeting an optimal end-of-infusion concentration for efficacy without exceeding the time-above-threshold concentration for toxicity. We first developed this PBPK-model for adults, to scale it to infants.

Methods:
The adult PBPK-model for HD-MTX was developed first, as this group has the most extensive PK-data available. The model was built in Simcyp (v23). Model performance was evaluated iteratively by comparing predictions to PK-data. Model performance was evaluated visually by assessing if the observed concentration-time profiles fell within the 95%-confidence interval of the model predicted profiles. Additionally, the ratios of predicted to observed PK-parameters were calculated.

Results:
For the adult model, the observed concentration-time profiles fall within the 95%-confidence interval of the predicted concentration-time profiles. The ratio of predicted to observed parameters ranged from 0.9 – 2.0 indicating the PBPK-model fits the observed data well. However, the model slightly overpredicts the half-life after 24 hours. Since our toxicity endpoint is a time-above-threshold concentration, we are planning to improve the characterization of the elimination phase by adding a third-space fluid compartment where MTX is known to distribute.

Conclusion:
When the PBPK-model accurately describes HD-MTX in the adult population we will scale the model to children and infants, further evaluating against clinical data. Ultimately, we will evaluate the current dosing schedule for infants to determine if the endpoints for efficacy and toxicity are reached and propose strategies for optimization.

25. Establishing evidence-based, model-informed dose recommendations for amoxicillin in pregnancy

Authors:
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Introduction:
Amoxicillin is commonly used in pregnancy. Dosing guidelines often advise lower doses of amoxicillin compared to non-pregnant individuals. However, pregnancy-related physiological changes may result in antenatal exposure falling below therapeutic levels, which may necessitate dose adjustments. We, therefore, aimed to establish pregnancy appropriate doses using literature data and multidisciplinary consensus.

Methods:
Data on the pharmacokinetics and safety of amoxicillin in pregnancy were collected to develop antenatal dose recommendations using our previously developed Framework for Dose Selection in Pregnancy (FDSP). Proposed doses of amoxicillin were developed to treat mild-to-moderate infections, for prophylaxis during preterm pre-labour rupture of membranes (PPROM), and to prevent early-onset neonatal sepsis (EONS) during childbirth. The FDSP and proposed doses were reviewed by Project MADAM's multidisciplinary working committee, comprising healthcare practitioners like obstetricians-gynecologists and neonatologists, alongside experts such as a medical ethicist and pharmacometrician, and patient representatives.

Results:
Physiologically-based pharmacokinetic modeling simulations show slightly lower (15-20%) amoxicillin concentrations in the second and third trimester of pregnancy compared to non-pregnant individuals. Aligning pregnancy doses with non-pregnant doses for treating mild-to-moderate infections may reduce the risk of antimicrobial resistance, underdosing and associated complications. Recommending the highest dose within a dose range during pregnancy is advisable. For prophylaxis in PPROM, increasing the dose from three oral doses of 500 mg to three oral doses of 750 mg is warranted. The current dosing regimen (2000 mg iv bolus followed by 1000 mg q6h) for prophylaxis during childbirth for prevention of EONS is adequate. The doses were endorsed by the working committee and will be integrated into Dutch clinical practice.

Conclusion:

This evidence review underscores the current risk of underdosing of amoxicillin for most indications and the need to adjust doses accordingly.

26. Optimizing paediatric opioid conversion and methadone tapering: physiologically-based pharmacokinetic modelling in critically ill children

Authors:
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Introduction:
Long-term opioid use is common in critically ill children and can cause withdrawal symptoms at discontinuation. To avoid withdrawal, short-acting opioids are usually converted into a long-acting drug, such as methadone, which is then carefully tapered. However, the exact conversion ratio nor the optimal tapering protocol is known. In this study, we used physiologically-based pharmacokinetic (PBPK) modelling to explore the conversion from intravenous fentanyl and morphine into oral methadone and methadone tapering.

Methods:
We extracted PBPK models for fentanyl, morphine, and methadone from literature, rebuilt the models in Simcyp v23, and verified them with pharmacokinetic (PK) data from published clinical PK studies. After model approval, we simulated opioid infusion (1 µg/kg/h fentanyl, 10 µg/kg/h morphine), opioid-methadone conversion according to different conversion ratios, followed by three different methadone tapering protocols (each consisting of 2-3 tapering schedules, 8 in total). Predicted plasma concentrations were compared to minimal therapeutic concentrations reported in literature (i.e., 1 ng/mL for fentanyl, 4 ng/mL for morphine, and 60 ng/mL for methadone). A pediatric intensivists panel was consulted for recommendations on conversion ratio and tapering protocol.

Results:
Model verification for all models proved adequate. Simulations showed that the opioids reached their mean therapeutic plasma concentrations and that a conversion ratio of 1:10 for fentanyl and 1:1 for morphine led to therapeutic methadone concentrations. Simulations of eight tapering schedules showed that the fastest schedule of two protocols did not reach adequate methadone concentrations. The other six showed similar Cmax and Tmax values, predominantly differing in tapering duration (varying from 8-26 days) and classification of risk categories. The expert panel agreed on the conversion ratios and tapering protocol supported by modelling.

Conclusion:
This study showed that PBPK modelling can support dosing decisions when literature is inconclusive. Conversion and dosing recommendations are implemented in the Dutch Pediatric Formulary to guide paediatric opioid tapering.

27. Physiologically based pharmacokinetic ,odeling of Ivacaftor/Tezacaftor/Elexacaftor in children with cystic fibrosis: evaluating hepatic and intestinal CYP3A4 ontogeny

Authors:
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Introduction:
In pediatric physiologically-based pharmacokinetic (PBPK) modeling, uncertainty persists regarding the ontogeny functions of hepatic and intestinal cytochrome-P-450 (CYP3A4) enzymes. This study evaluates the predictive accuracy of available CYP3A4 ontogeny functions using cystic fibrosis transmembrane conductance regulator (CFTR) modulators ivacaftor, tezacaftor, and elexacaftor, which are widely used in cystic fibrosis (CF) treatment.

Methods:
An adult PBPK model was developed using the physicochemical properties and absorption, distribution, metabolism and excretion characteristics of CFTR modulators, with virtual populations from Open Systems Pharmacology. The PBPK model was calibrated using single-dose data from healthy adults and validated by predicting pharmacokinetic (PK) data following multiple doses in adults with CF. The PBPK model was scaled to children aged 0 to 6 years, accounting for developmental changes in anatomy and physiology, including various CYP3A4 ontogeny functions. The pediatric PBPK model was assessed against observed data for ivacaftor in children aged 4 months to 6 years, and for tezacaftor and elexacaftor in children aged 2 to 6 years. Simulations were performed using each of the five available hepatic (Edginton, Upreti, Salem, Anderson, and Björkman) and two intestinal (Johnson, and Flat) CYP3A4 ontogeny functions to evaluate the predictive performance of these functions. Additional simulations were performed to optimize dosing recommendations of CFTR modulators in children aged 0 to 6 years.

Results:
Overall, the PK predictions generated using Upreti's ontogeny function demonstrated the highest accuracy for hepatic CYP3A4 ontogeny, whereas the Flat ontogeny function provided the most precise predictions for intestinal CYP3A4 ontogeny.

Conclusion:
PBPK modeling of ivacaftor, tezacaftor, and elexacaftor demonstrated that dosing recommendations by the Food and Drug Administration are appropriate for children with CF. Additionally, identifying accurate hepatic and intestinal CYP3A4 ontogeny functions is crucial for application of PBPK modeling in pediatric drug development, especially in the youngest pediatric populations.

28. Evidence-based dose recommendations for preterm and term neonates: the neodose project

Authors:
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NeoDose Workgroup

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Introduction:
Most frequently prescribed drugs in neonatology are off-label, resulting in highly variable dose recommendations (DRs) in local guidelines. Furthermore, neonates are underrepresented in DRs of the Dutch Paediatric Formulary and its international affiliates. We aimed to review the available evidence and provide best evidence-based DRs for preterm and term neonates.

Methods:
Drugs were selected based on NICU prescription frequency, availability of evidence-based DRs for (pre)term neonates, and expert opinion. Literature was reviewed and documented in dose rationale documents (DRDs), considering efficacy, safety, and pharmacokinetics, while accounting for gestational and postnatal age resulting in proposed DRs. An expert board reviewed DRDs and DRs for clinical appropriateness and feasibility, establishing final DRs through consensus. Efficacy was assessed for each drug by age group and categorised as 'licensed', 'high' (meta-analysis, systematic review, or high-quality RCTs), or 'low' (other comparative research or expert consensus). In parallel, the availability of the pharmacokinetic data was assessed.

Results:
DRDs were established for 45 drugs, with 42 DRDs providing DRs for term neonates and 34 including DRs for preterm neonates, covering a total of 75 indications. Licensing information was available for 7/42 DRDs for term neonates and 2/34 DRDs for preterm neonates, while high-level evidence supported DRs for 8/42 and 10/34 DRDs, respectively. DRDs without licensed information relied more on expert consensus for preterm (28%) than term neonates (11%). Pharmacokinetic data were available for 19 drugs, serving as the primary source for substantiating neonatal doses in 63% of cases.

Conclusion:
DRDs and best evidence-based DRs were successfully established for term and preterm neonates, with pharmacokinetic studies providing important guidance for dosing in several cases. DRs for preterm neonates still rely heavily on expert opinions, due to the paucity of studies in this population.

29. Optimization of microdialysis experiments to study antibiotic disposition in children: lessons learnt

Authors:
Van herteryck I.[1], Devreese M.[1], Bauters A.[2], Hermans E.[1], De Paepe P.[1,2], Dhooge I.[1,2], Plasschaert F.[1,2], Van Laecke E.[2], De Cock P.[1]

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Introduction:
Infants need effective antibiotics, but dosing is challenging due to variable pharmacokinetics. This study assessed cefazolin distribution at the target site in the subcutaneous tissue using microdialysis. Cefuroxime was evaluated as internal standard for catheter calibration, which offers advantages over standard methods. A clinical trial validated its feasibility.

Methods:
An observational study was conducted in children (2–15 years) undergoing minor elective surgery with prophylactic cefazolin (30 mg/kg IV bolus). Microdialysis catheters were placed subcutaneously (thigh/arm) to collect samples every 30–60 minutes for 6 hours. For calibration, the catheter was perfused with cefuroxime (20 µg/mL) during and cefazolin (100 µg/mL) at the end of the experiment. Antibiotic concentrations were measured using a validated LC-MS/MS method. Data analysis included Relative Recovery (RR) calculation and non-compartmental analysis (NCA) with PKanalix (MonolixSuite). Target attainment was defined as 100% fT > MIC for 4 hours (MIC: 2 mg/L for S. aureus).

Results:
Microdialysis was tolerated in all infants without adverse events. Sixty samples were collected from six patients (mean age 10 years, weight 33.7 kg). RR was above the advised 20%. Cefuroxime recovery was 21.77% ± 12.31%, and cefazolin 34.09% ± 15.52%, showing high inter- and lower intra-patient variability (RR: CFR 6.69%, CFZ 3.74%). The largest calibration-dependent RR difference (26.94%) significantly impacted cefazolin tissue concentration estimates. NCA results based on cefuroxime calibration were: AUC 207.08 h·mg/L, Cl 5.12 L/h, Vd 8.33 L. Cefazolin calibration estimated AUC 119.32 h·mg/L, Cl 8.96 L/h, Vd 19.92 L. Target attainment was achieved in 100% of patients.

Conclusion:
Microdialysis is a feasible, safe method for continuous sampling in infants. Cefuroxime and cefazolin showed differences in in vivo recovery, highlighting the importance of calibration methods choice in microdialysis studies. A larger trial is needed to better characterize cefazolin pharmacokinetics, variability, and optimise microdialysis studies in this vulnerable population.

30. Weight-based dosing of monoclonal antibodies in paediatrics: a systematic study of population pharmacokinetics studies to evaluate its impact on exposure of infliximab across the paediatric age range

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Introduction:
Monoclonal antibodies, including infliximab, are commonly weight-based in children, which may result in suboptimal drug exposure in paediatric subgroups [1,2,3]. This study reviews paediatric infliximab pharmacokinetic (PK) models and investigates the impact of covariate functions for clearance (CL) and volume of distribution (Vd) on exposure across the paediatric age range.

Methods:
A systematic review was performed to identify the available infliximab PK models using PubMed and the relevant key words: “Infliximab”, “Paediatrics”, “Pharmacokinetics” and “model”. The covariate functions of the selected models were then used to explore CL and Vd changes across different covariates (e.g. body weight and albumin) and to compare the predicted exposure for three typical individuals of 20, 30 and 50 kg after a standard dose regimen of 5 mg/kg at 0, 2 ,6 weeks for induction and every 8 weeks as maintenance [1, 2, 3]. Simulations were performed in NONMEM and R was used for graphical representation.

Results:
In the literature search, 38 articles were identified between 2006-01/2025, including 14 models (9 two-compartment and 4 one-compartment PK models and 1 Target-Mediated Drug Disposition model). The two-compartmental models were used for the subsequent analysis, as they incorporated the largest number of paediatric patients across different age groups and included most covariate functions. Albumin and body weight (BW) were identified as significant covariates for CL in 4 models. Graphical representation of CL functions over BW highlighted large variability across the paediatric range, albumin levels, and disease. Model-based simulations also revealed large differences in infliximab exposure between the three selected individuals.

Conclusion:
In 14 paediatric infliximab PK models, the most prominent covariates for CL were albumin and BW. Upon weight-based dosing, large differences in exposure across different age and weight groups can be expected, emphasizing the need for other dosing approaches such as personalized dosing, BSA-based dosing and/or pharmacokinetic-guided dosing.

31. Plasma protein binding: can we use piglets to study unbound drug disposition in children?

Authors:
Van herteryck I.[1], Bauters A.[2], Hermans E.[1], De Paepe P.[1,2], Dhooge I.[1,2], Plasschaert F.[1,2], Van Laecke E.[2], De Cock, P.[1], Devreese,M.[1]

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Introduction:
Beta-lactams are key in infection therapy and prophylaxis. Pediatric pharmacokinetics remain understudied, but juvenile pig models help predict parameters. Total drug concentrations are often measured, assuming a fixed free fraction. This study examined cefazolin plasma protein binding variability in children and a piglet model.

Methods:
Cefazolin (30 mg/kg IV) was administered to six healthy piglets and ten children undergoing minor surgery. Blood samples were collected at predefined time points: 5 minutes (peak) and 30 minutes (non-peak) in piglets, and 5 minutes (peak) and 120 minutes (non-peak) in children. Unbound cefazolin concentrations were determined via ultrafiltration (PALL NanoSep Centrifugal Filters, 10 kDa cutoff). Samples were pre-incubated for 30 minutes at 38°C (piglets) and 37°C (children), stabilized with phosphate buffer, and centrifuged at 1000g for 20 minutes. A validated LC-MS/MS method quantified cefazolin levels.

Results:
In piglets, median cefazolin concentrations were 67.0 mg/L (peak) and 19.2 mg/L (non-peak), with unbound fractions of 58.5% and 64.3%, respectively. The average free fraction was 63.0 ± 11.8%, with no protein binding saturation ($p=0.081$). In children, concentrations were 303.2 mg/L (peak) and 86.3 mg/L (non-peak), with unbound fractions of 35.8% and 13.8%. Regression analysis showed a significant reduction in the unbound fraction at higher concentrations ($p=7.7 \times 10^{-}6$), indicating saturation of plasma protein binding. A notable difference in unbound percentages between peak and non-peak concentrations (up to 31.6%) was observed ($p=5.6 \times 10^{-}6$).

Conclusion:
This study compares in vivo plasma protein binding in piglets and children, showing cefazolin's saturable binding in children but not piglets at 30 mg/kg. These findings emphasize the need for cautious extrapolation from animal to human PK and further research into optimal PK models for pediatric drug studies.

32. Osmolality of oral liquid medications intended for neonates and infants: a laboratory-based study - is not displayed

Authors:
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Introduction:
Current recommendations suggest that the osmolality of oral liquid medications (OLM) intended for neonates should not surpass 450 mOsm/kg, to reduce the risk for gastrointestinal adverse effects. This study aimed to measure the osmolality of OLMs commonly used in Israel and identify OLMs that require further dilution prior to administration.

Methods:
OLMs commonly used in neonatal and pediatric wards in Kaplan Medical Center were selected for this study. Undiluted and 1:10 diluted samples were collected and osmolality was measured in duplicates by an osmometer using the freezing point depression technique. Based on the results, OLMs were classified into hypo-osmolar, moderately hyperosmolar and severely hyperosmolar preparations (<300, 300-450 and >450 mOsm/kg, respectively).

Results:
A total of 54 OLMs were sampled for this study, of which 27 (50%) were suspensions, 10 (19%) solutions, 11 (20%) syrups and 6 (11%) oral drops/suspending vehicles. Median (range) osmolality was 2313 (13-17675) mOsm/kg. Among the undiluted samples, 6 (11%) were found to be hypo-osmolar and 48 (89%) were severely hyperosmolar. Of those, 40 (83%) samples required further dilution to produce a reading, whereby 33 (83%) became hypo- to moderately hyperosmolar and 7 (17%) remained severely hyperosmolar even after 1:10 dilution.

Conclusion:
Our findings suggest that most OLMs administered to neonatal and pediatric patients in our hospital are severely hyperosmolar. Thus, prior to administration of identified OLMs, the dose should be further diluted in water/human milk as appropriate to reduce osmolar load and risk for gastrointestinal symptoms and complications.

33. Hyperosmolar preparations and necrotizing enterocolitis: can a single overdose tip the balance? a case report - is not displayed

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Introduction:
Preterm infants often require oral medications, but hyperosmolar preparations (HOP) may pose a risk for complications due to an immature gastrointestinal system. We hereby present a case of an extremely preterm infant who received a single overdose of HOP and developed necrotizing enterocolitis (NEC).

Methods:
A female preterm infant was born by an emergency C-section at gestational age of 24+2 weeks and birth weight of 650 g due to placental abruption. Only the first dose of antenatal betamethasone course was administered. Postnatal care included respiratory support, trophic feeding with human donor milk, total parenteral nutrition (TPN) and antibiotic treatment.
A hemodynamically significant patent ductus arteriosus (hsPDA) was demonstrated in an echocardiogram. A 17-dose-course of intravenous acetaminophen (15 mg/kg x 4/day) was started at the age of 48 hours, followed by a 3-dose-course of oral ibuprofen (10 mg/kg once, then 5 mg/kg/day). Enteral feeding was well tolerated and gradually increased.

Results:
At 10 days of age, due to failure of PDA closure, oral acetaminophen (10 mg/kg x 4/day) was initiated while surgery was being considered. During treatment, a 10-fold overdose was erroneously administered. Acetaminophen level measured ~10 hours later was 110 mcg/mL (normal range for PDA closure: 20-30 mcg/mL) with normal liver enzymes and coagulation tests. Treatment with n-acetylcysteine was initiated per common guidelines: 300 mg/kg over 20 hours.
Approximately 14 hours following the overdose, the infant developed fulminant NEC with intestinal perforation. TPN and antibiotic treatment were initiated and abdominal drainage was performed. However, the infant rapidly deteriorated and died 10 hours later.

Conclusion:
Extreme prematurity, hsPDA, exposure to oral HOP and antibiotic therapy are all known risk factors for NEC. Based on temporal proximity, this case suggests that even a single overdose of oral acetaminophen (later found to be HOP: ~3000 mOsm/kg) may contribute to NEC development.

34. Ontogeny of hepatic and intestinal CYP3A activity across the pediatric age range quantified using population physiologically-based pharmacokinetic modelling

Authors:
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Introduction:
Accurately determining drug clearance across paediatric age range is essential for optimizing dosing and drug development. CYP3A enzymes are critical for metabolism, however its maturation remains incompletely quantified. We aim to develop an ontogeny function characterizing hepatic and intestinal CYP3A maturation from birth to adolescence using a physiologically-based pharmacokinetic (popPBPK).

Methods:
Midazolam and 1-hydroxymidazolam plasma concentrations from two PK studies including (a) 43 ICU patients aged 2 days to 5.3 years and receiving IV dose and an oral micro-dose of [14C] radiolabeled midazolam) [1] and (b) 264 post-operative children (aged 1 to 18 years) receiving oral dose of midazolam [2] were analysed using a population PK approach
A previous established popPBPK model [2,3,4] was adapted to include ontogeny functions for CYP3A in the gut and liver. Different ontogeny functions including a bodyweight-dependent exponent (BDE) function [5] were explored.

Results:
The BDE function [5], which allowed low clearances with slow maturation at low body weight (BW) and a sharp increase until adult values, accurately characterized midazolam metabolism across the entire peadiatric age range. The allometric scaling exponent decreased sigmoidal with BW from 2.22 to 0.98. BW50 values were 11kg and 2.83kg, with hill factors of 2.2 and 1.36, for hepatic or intestinal intrinsic clearance, respectively.
Oral bioavailability decreased from 59% at birth to 20% in adolescents, describing CYP3A maturation in gut and liver [2,3,4]. Most rapid changes occur within the first years of life, with enzyme activity approaching adult levels by six years.

Conclusion:
The popPBPK model successfully captured intestinal and hepatic CYP3A maturation across all paediatric age groups, including the crucial first year of life. The ontogeny function presented, provides valuable insights into CYP3A maturation, enabling improved oral and intravenous dosing precision for midazolam and potentially other CYP3A substrates in paediatric patients.

35. Drug utilisation at a German neonatal intensive care unit – Are evidence-based (off-label) dosing recommendations available?

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Introduction:
In neonatology, pharmacotherapy is complex and off-label use is often unavoidable. Our aim was to a) study drug utilisation at our neonatal intensive care unit (NICU) and b) to investigate to which extent the German version of the paediatric drug formulary Kinderformularium provides (off-label) dose recommendations for pharmacotherapy.

Methods:
Over a 10-year period (2013-2022), we retrospectively analysed drug prescriptions at our NICU using electronic medical records of 7002 hospital admissions (29.9% preterm neonates, 56.1% neonates, 13.9% infants). The 40930 prescriptions corresponded to 256 different medications defined as drugs and their routes of administration. All prescriptions were evaluated with regard to the availability of on- or (partially) off-label dosing information in Kinderformularium.DE.

Results:
On average (median) each admission received 3 prescriptions (IQR [2;6]). Systemic anti-infectives, drugs for blood/blood-forming organs, and for the nervous system were most common among the 40930 prescriptions. For 81% (n=33093) of them age-appropriate dosing recommendations were available: 51% on-label, 8% partly on/off-label, and 22% off-label. Two thirds of off-label use was in preterm neonates. For 6% (n=2605) of the prescriptions no monograph was available and 13% (n=5232) related to monographs that did not contain the relevant age-appropriate dosing recommendation. Additional 4 new monographs and age-appropriate information added to 20 monographs would be needed to cover 96% of all prescriptions.

Conclusion:
Kinderformularium.DE provides dosing information for the majority (80%) of pharmacotherapies used at a NICU of a university hospital and proofs to be an important information source for German neonatologists. Furthermore, this analysis identified which additional information is needed for clinical practice in Germany and helps to further improve the platform.

36. Coproporphyrin I as biomarker in a pediatric population: Age-related differences and genetic influences

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Introduction:
Coproporphyrin I (CPI) is an endogenous substrate of hepatic OATP1B-transporters [1] with growing clinical evidence supporting its applicability as a marker of OATP1B1-related-drug-interactions [2]. However, its serum levels in children and the impact of age or genetics remain unexplored. This study investigates these factors and compares pediatric to adult levels.

Methods:
We first performed a systematic review of reported adult CPI plasma and serum levels serving as comparison in our analysis. To establish pediatric reference ranges in different age groups, we set up a clinical study ("PKBioChild-study") where we obtain blood from healthy children within the age of zero to eighteen years requiring a venous line for elective surgery at the University Children's Hospital Basel. Serum samples were analyzed for CPI content after solid-phase extraction using a UPLC-MS/MS method. Moreover, these samples are used for PCR-based genotyping of function impairing variants in SLCO1B1.

Results:
A meta-analysis of CPI plasma and serum levels of healthy volunteers in eight adult studies established a reference mean of 0.83 nM with a 95% confidence interval of 0.67 nM to 0.99 nM. Hitherto we were able to recruit a total of 20 individuals with a median age of 4 years and 11 months and we successfully analyzed CPI levels in those healthy children. Genotype-predicted OATP1B1 phenotypes derived from genotyping of SLCO1B1 revealed the presence of about 40% low function alleles.

Conclusion:
In conclusion, the established procedures are applicable to determine CPI serum levels in healthy children and assess their association with genetic variants involved in its transport. Moreover, this study enables a direct comparison of pediatric CPI levels with the reference range derived from a meta-analysis of healthy adult volunteers.

37. Extravasation of vesicant and irritant drugs in pediatric patients- a literature review

Authors:
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Introduction:
Intravenous (IV) administration of drugs, fluids, and nutrients are crucial in pediatric healthcare for hospitalized children. However, a serious complication known as extravasation, which occurs when IV drugs leak into surrounding tissues, poses a risk of significant tissue damage, including necrosis. This risk is particularly pronounced in neonates and young children.

Methods:
Aim: This literature review seeks to gather and synthesize the latest information on managing drug extravasation in pediatric patients. The goal is to provide healthcare professionals with a practical clinical guideline for the management of extravasation.
Method: A literature review was conducted using multiple electronic bibliographic databases, including MEDLINE, Cochrane, CINAHL, Scopus, PubMed, and the Web of Science. Additional searches included examining references from key articles, consulting guidelines, and conducting general internet searches for relevant practices and recommendations. The vesicant/irritant drugs selected for this study are based on the drugs listed in the Swedish national formulary for children, ePed.

Results:
The search yielded a total of 905 hits, resulting in 24 studies and 21 guidelines that met the inclusion criteria. The findings reveal a lack of consensus on optimal management strategies, highlighting a reliance on clinical experience rather than evidence-based practice. The review suggests that preventive measures are the most effective management strategies. However, in the event of extravasation, early detection and immediate responses are essential. These responses include applying thermal compresses and administering hyaluronidase for substances with extreme pH or osmolarity, and phentolamine or terbutaline for those that induce vasoconstriction.

Conclusion:

This review emphasizes the importance of training healthcare professionals, ensuring rapid responses, and using specific antidotes based on the chemical properties of the extravasated drugs. Future research should concentrate on conducting randomized controlled trials to solidify the evidence base supporting these recommendations.

38. The reality of prescribing selected medications in the pediatric population: a single centre experience

Authors:
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Introduction:
Pharmacovigilance in the Czech Republic is managed by the State Institute for Drug Control. We have launched a project that deals with the most used drugs in hospitals. The primary objective was to evaluate the use of drugs in children, including off-label drugs, the methods of prescription and possible influencing factors.

Methods:
The project was implemented at the Department of Paediatrics and Inherited Metabolic Disorders, 1st Faculty of Medicine, Charles University and General Teaching Hospital in Prague from 2022 to 2024. In phase 1 of the descriptive cross-sectional study, data collection was performed on hospitalized paediatric patients treated with paracetamol, in phase 2, data were analysed according to the Summary of Product Characteristics (SmPC) and data collection was performed for ibuprofen and metamizol, only patients who had already taken paracetamol were included in the study (phase 3).

Results:
Paracetamol was used in 25 children, mean (SD) age 38 months, mean single prescribed dose 13.6 (2.7) mg/kg, mean cumulative daily dose 53.7 (11) mg/kg, number of prescriptions per patient 4.8 (1.9), for ibuprofen 18/25 children aged 36 months, meam single prescribed dose 7.42 (1.6) mg/kg, mean cumulative daily dose 28.8 (5.5) mg/kg, number of prescriptions per patient 3.9 (2.2), for metamizol 11/25 children aged 31 months received the drug, number of prescriptions per patient 3.0 (1.8), prescription accuracy was 63.6 % for paracetamol, only 13 % for ibuprofen and 9 % for metamizol.

Conclusion:
In the assessment of antipyretic prescriptions, updated according to the SmPC, the lowest level of variation was analysed for paracetamol. The most challenging of all drugs was the prescription of single and cumulative doses. There is an urgent need to introduce a systematic process of prescribing medications including evidence into daily clinical practice at various levels of care providers.

39. Personalized Immunomodulatory Drug Repurposing in Patients with Mucopolysaccharidosis

Authors:
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Introduction:
Mucopolysaccharidosis (MPS) are a group of rare, inherited metabolic disorders characterized by the accumulation of glycosaminoglycans, leading to progressive multi-systemic complications. Despite the substantial unmet clinical needs in MPS and the prospects of repurposing immunomodulatory drugs, reports on the clinical implementation of individual treatment trials (ITTs) remain scarce.

Methods:
To address this gap, we developed a decision-support tool that systematically appraises the best available evidence on immunomodulation in MPS. Our tool utilizes a decision analysis framework (DAF) with expert consensus, and input from patient representatives to enable personalized clinical decision-making. Through collaborating MPS centres, we provide individualized benefit-risk analyses, justification for ITTs involving off-label drug use, treatment recommendations, and analytical services to evaluate drug responses.

Results:
Here, we present the application of this platform in our first case—a female patient diagnosed with MPS type IV A (Morquio Syndrome). Adalimumab (20 mg, subcutaneous, biweekly) was identified as the optimal treatment, with a clearly positive benefit-risk profile. During 19 months of follow-up, the patient reported no adverse effects. Significant improvement in her primary symptoms (elbow and hip pain) was observed within 16 weeks, with complete resolution thereafter. Functional outcomes, including MPS-HAQ, MYMOP-II, ICR, and 6MWT scores, also improved. Results of inflammatory biomarker analysis are pending as of abstract submission.

Conclusion:
We demonstrate the practical application of an innovative DAF-based tool for immunomodulatory drug repurposing in MPS. The case outcomes will contribute to ongoing tool refinement. Currently, further MPS patients are being recruited at both national and international levels.

40. "Meet the Pain" is an educational multidisciplinary project to improve the pain assessment skills of neonatal intensive care unit nurses

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Introduction:
The "Meet the Pain" project aimed to develop an educational programme for neonatal intensive care unit nurses to achieve the highest possible consistency in pain assessment in premature neonates from 23 weeks of gestation by widely used COMFORTneo and Numeric rating scale (NRS). Scoring scales are the main tool for assessing pain in premature neonates. Therefore, nurses must be continuously educated and trained to use and interpret these tools correctly.

Methods:
The project was conducted at the Perinatology Centre in Prague from 2021 to 2024. In Phase I, 34 nurses scored premature neonates using the COMFORTneo and NRS pain scales on video recordings. We assessed inter-rater variability with Cohen's κ and used descriptive statistics to identify discrepancies in the COMFORTneo scale components, which resulted in the refined standardised pain assessment protocol. Then we conducted retraining for nurses (Phase II) and implementation in practice (Phase III). In Phase IV, we reassessed nurses' variability through video and bedside observations using the same statistics.

Results:
Median inter-rater variability (κ) in the COMFORTneo scaling significantly increased from 0.43 to 0.77 between Phase I and IV ($p<0.001$, Kruskal Wallis test), in the NRS pain scale from 0.49 to 1.0 ($p<0.001$, Kruskal Wallis test). Although improvement in individual COMFORTneo categories was negligible. Significant improvement in the total scores proved better recognition of details for distinguishing pain from general stress factors.

Conclusion:
Educating and practising nurses in pain and distress assessment improved scoring reliability, which is essential for personalized pain management in preterm neonates.

41. To re-dose or not? A decision-making flowchart after vomiting in the paediatric population

Authors:
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Introduction:
Vomiting is common in paediatrics. Oral drug administration followed by vomiting risks treatment efficacy. In these cases, health care professionals need to consider re-dosing. To date, no guideline on re-dosing is available. The aim was to develop an evidence-based yet practical flowchart on re-dosing after vomiting.

Methods:
We conducted a literature review in Pubmed, complemented by local (inter)national guidelines and expert opinions. We focused on paediatrics < 18 years who vomited oral drugs and studies on factors influencing gastric emptying. Various terms defining paediatrics, vomiting, and factors (e.g. dosage form, Tmax) were combined. The results were schematically depicted in a decision-making flowchart.

Results:
From the 60 study results, 18 were included, of which 12 were reviews. Additionally, 13 guidelines were analysed.
Re-dosing is needed if:
- the drug is visible in vomitus
- vomiting occurs ≤ 15 min post-ingestion or ≤ 30 min on a full stomach
Re-dosing is NOT needed if:
- vomiting occurs ≥ 4 hours post-ingestion or ≥ 1 hour/≥ Tmax on an empty stomach
Consider re-dosing on a case-by-case basis based on drug- and patient-related factors if:
- vomiting occurs < 1 hour/< Tmax on an empty stomach or 30 min-4 hours/< Tmax on a full stomach

Conclusion:
Different drug- and patient-related factors determine re-dosing after vomiting in paediatrics. Limited evidence makes it challenging to substantiate the flowchart in an evidence-based manner.

42. Causality, severity and avoidability of adverse drug reactions in children over an 11-year period

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Introduction:
Adverse Drug Reactions (ADRs) are a frequent cause of emergency admissions and extended hospital stays in children, leading to increased healthcare costs and patient morbidity. However, the causality, severity, and avoidability of ADRs in children remain underexplored.

Methods:
11-year retrospective cohort study of children aged 0-18 years who were either admitted to a paediatric hospital due to an ADR or who experienced such a reaction during their hospital stay. Those who presented with intentional drug misuse or overdose were excluded. Causality, severity and avoidability were assessed using the Naranjo criteria, Hartwig scale, and Modified Schumock and Thornton scale, respectively. ADRs were categorised as Type A (dose-related) or Type B (idiosyncratic).

Results:
Of 599 children with ADRs, the median age was 8.7 years (3 weeks-18 years). Most ADRs were mild (74%), with 25% moderate and 1% severe. The most commonly implicated drugs were antimicrobials (46%), analgesics (9%), antiepileptics (8%), and monoclonal antibodies. Type A reactions comprised 44%, with neurological symptoms being the most common. Type B reactions (56%) most commonly occurred with antimicrobials (63%). Overall, 15% of ADRs were potentially avoidable: 9% definitely and 6% probably avoidable. Most avoidable ADRs were due to failure to consider documented allergies, inappropriate dosing, drug interactions, or not applying preventative measures (e.g. premedication).

Conclusion:
Our study shows that 1 in 6 paediatric ADRs were potentially avoidable, highlighting the need for improved ADR documentation, pharmacovigilance, and clinician education.

43. Trends in paediatric hypnotic prescriptions in France, 2016-2023

Authors:
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Introduction:
To assess the rates and trends of hypnotic medication prescriptions for children and adolescents before and more than three years after the onset of the COVID-19 pandemic.

Methods:
Interrupted time-series analysis of national dispensing for children aged 6-17 years between January 1, 2016 and December 31, 2023 in France. Monthly rates of hypnotic prescriptions (hydroxyzine, alimemazine, melatonin, and Z-drugs) per 1,000 children were modelled before and after the start of the pandemic (March 2020). Rate Ratios (RR) were calculated between estimated and expected prescription rates.

Results:
A total of 2,675,142 prescriptions were dispensed to an average annual population of 9,963,497 children. In January 2016, the rate of hypnotic medications prescriptions was estimated at 1.9 per 1,000 children, and in December 2023 at 6.8 per 1,000. Prescription trends for all hypnotic medications increased from 0% (95% CI: -0.1; 0.1%) per month before the pandemic to +2.7% (95% CI: 2.5; 3.0%) after the pandemic onset. Post-pandemic prescription rates exceeded expected values by 131% (RR: 2.31, 95% CI: 2.08; 2.54).

Conclusion:
The substantial increase in hypnotic prescriptions for children may be related to a persistent deterioration in their mental health, changes in prescribing strategies and/or pre-existing unmet needs.

44. Patterns of paediatric methylphenidate users: a national time series analysis from 2016 to 2023

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Introduction:
Our study aimed to evaluate the trends and patterns of methylphenidate (MPH) use in children.

Methods:
Using the French General Health Insurance database, we included all MPH users aged 3 to 17 years from January 1, 2016 to December 31, 2024. Prevalence and incidence of MPH use per 1,000 children were analysed using joinpoint regression models. Time segments with distinct trends (monthly percent change; MPC) were identified over the study period. Further, analyses were stratified by age and sex categories (girls/boys; 3-5 years; 6-11 years; 12-17 years).

Results:
Joinpoint analysis of the monthly prevalence rate identified 5 periods with distinct trends: January 2016 – February 2020 (MPC: 0.58% [0.55;0.61%]); February – May 2020 (MPC: -8.07% [-8.70; -7.32%]); May – August 2020 (MPC: 9.17% [7.92;10.02%]); August 2020 – June 2023 (MPC: 1.27% [1.16;1.28%]); and June 2023 – Dec 2024 (MPC: 1.56% [1.44;1.79]). Analysis of the monthly incidence of MPH use identified similar segments and trends. Average monthly percent increase in of MPH use were substantial for adolescents compared to younger children and for girls compared to boys. Among new users, 15.4% presented concomitant use of other psychotropic medications in 2016 and 30.2% in 2024.

Conclusion:
Trends in MPH use accelerated after the COVID-19 pandemic and specifically in adolescents and girls. Also, concomitant use of other psychotropic medications among MPH users has increased.

45. Model-based blood pressure prediction for personalized medicine for people at any age

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Introduction:
High blood pressure is one of the major burdens worldwide. Easy and comfortable monitoring over several days and nights would help to identify people of risk and support also patients below 18 years of age. The aim was to develop and apply a model to enhance blood pressure monitoring.

Methods:
Based on cuffless blood pressure measurements taken at rest over a period of 14 days in six healthy volunteers, a model was developed to describe blood pressure profiles. To describe the rise and fall in systolic and diastolic blood pressure, exponential formulas were used in a non-linear regression model in R. The calculation formulas contained the following parameters: Baseline blood pressure, extent and rate of rise in blood pressure as well as wake time and bedtime.

Results:
All subjects showed a circadian pattern of both systolic and diastolic blood pressure over the 14-day period. The observed and predicted values show that nocturnal blood pressure was lower than daytime blood pressure in all volunteers. The blood pressure levels, fluctuations, and sleep times differed between individuals, indicating characteristic variations in the daily blood pressure curves.

Conclusion:
The developed model offers an innovative way to visualize blood pressure profiles over several days and allows the assessment of intra- and inter-individual blood pressure variability. This might be of interest for people of risk and to identify treatment failures also in patients below 18 years of age.

46. Maternal drug use and infant exposure during breastfeeding

Authors:
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Introduction:
Breast milk is the optimal infant nutrition; however, many infants may be ex-posed to prescription drugs if used by their mothers during breastfeeding. The aim was to eval-uate the prevalence of prescription drug use among breastfeed-ing mothers and to as-sess the availability of relative infant dose information for these drugs.

Methods:
This population-based cohort study was conducted using nationwide Danish register data from January 2006 to December 2022. All registered mother-infant pairs were included during periods of exclusive breastfeeding. The national health registers were used to identify live births, breastfeeding status, and pre-scription drug use by mothers during exclusive breastfeeding.

Results:
Among 534,080 exclusively breastfed infants, 290,845 (54.5%) were breastfed by mothers who used at least one prescription drug during the breastfeeding pe-riod. The drugs were primarily for haemorrhoids, contraception, infections, and pain manage-ment. During the exclusive breastfeeding period, a total of 573,108 distinct drug pre-scriptions were redeemed, of which 362,342 (63.2%) were for systemic use. Overall, 81.912 (22.6 %) of the redeemed prescriptions for system-ic drugs had an unknown infant dose. Among individual systemic drugs used during exclusive breastfeeding, 51.5% lacked information on infant dose.

Conclusion:
This large-scale cohort study reveals a high prevalence of prescription drug use during exclusive breastfeeding, often involving drugs with unknown safety pro-files regarding their transfer into human milk. These findings highlight the need for updated regulato-ry measures and increased efforts by pharmaceutical companies to ensure reliable in-fant safety data.

47. Effect of SARS-CoV-2 on psychotropic drug use in children: a population-based longitudinal study

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Introduction:
Several countries report higher prescription rates of psychotropic drugs during COVID-19 lockdown. However, the number of previously drug-naive children exposed to psychotropic drugs for the first time is an unstudied outcome. Our objective was to characterize first-time psychotropic drug users among children in the COVID-19 period.

Methods:
Children and adolescents (age: 0-19 years) in British Columbia (BC), with at least one dispensing for a psychotropic drug were assessed. Data source: BC pharmacy and medical visit data. Design&Analysis: New psychotropic users in the COVID-19 period (March 2020 - December 2023) and the precedent period (March 2016 – December 2019) were identified by their first psychotropic drug dispensing since birth. The total number of patients were analyzed across four age ranges (0–4, 5–9, 10–14, 15–19 years) and by sex. Chi-square test and logistic regression models were used for comparison between the time windows.

Results:
The number of children starting their first psychotropic drug increased in the COVID-19 period by 22.4% compared to the precedent period. The surge was twice as large in females (29.1%) as compared to males (15%). The age range 10-14 years shows the highest increase by 46.2%, followed by age range 5-9 years (24.2%).
Among the drug classes, stimulants for treatment of ADHD increased most in the COVID-19 period (55.5%). When divided by sex and age range, increases of stimulant users were highest in: girls 15-19 years (194%); girls 10-14 years (121.8%); boys 15-19 years (62.9%).

Conclusion:
Prescribing of psychotropic drugs to previously psychotropic drug-naïve children during the COVID-19 lockdown was significantly higher than in the period before the lockdown. This raises an important question of whether lockdowns which restricted social interactions is a trigger factor for psychotropic drug use for conditions like ADHD.

48. Predictive performance, and model refinement, of physiologically based pharmacokinetic (PBPK) models for CYP3A inhibitors clarithromycin and fluconazole in a virtual paediatric population

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Introduction:
Regulators are beginning to accept the use of physiologically based pharmacokinetic (PBPK) modelling to extrapolate drug-drug interactions from adult to paediatric individuals but require evidence that perpetrator and victim models are fit for purpose. This investigation assessed the performance of clarithromycin and fluconazole models to predict pharmacokinetics in paediatric populations.

Methods:
Predictive performance was assessed by comparing published pharmacokinetic (PK) data with PK simulations generated by Simcyp V23R2, using default perpetrator and population files. The performance of the compound models was assessed through visual predictive checks and by the ratio of predicted-to-observed PK parameter values (2-fold acceptance range). Following initial model assessment, refinement of default models to improve predictions was investigated using more mechanistic distribution and absorption (clarithromycin), and metabolism (fluconazole).

Results:
The default clarithromycin and fluconazole PBPK models predicted PK parameters within 2-fold of observed clinical data for single and multiple dose scenarios across the paediatric age range. However, the standard 2-fold criterion may not be sufficient for paediatric drug-drug interaction (DDI) assessment as it can yield less certainty in predictions. Incorporation of model refinements improved the predictive performance by up to 20% for clarithromycin and fluconazole.

Conclusion:
Clarithromycin and fluconazole PBPK models developed for use in adult, reasonably predict exposure in paediatric subjects. Through incorporation of more mechanistic descriptions of absorption, distribution, and metabolism, the performance improved allowing greater confidence with using them for DDI prediction in populations where there is less data, e.g. neonates and preterm.

49. Integrated, multimodal collaboration to support paediatric pharmacology and drug development: the conect4children (c4c) project and c4c stichting

Authors:
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Introduction:
Paediatric pharmacology and drug development needs collaboration. The aim of this submission is to describe collaborations built by the IMI2-funded conect4children (c4c) project.

Methods:
Collaboration was co-created between industry and academia, implemented, and described using structured approaches. National Hubs (NH) were identified and mapped using a maturity matrix and hub standards. Experts were selected following a competitive international call; Expert Groups developed quality improvement plans. European Reference Networks (ERNs) were contacted and a heat map of sites shared with c4c was prepared. Learned societies were contacted and collaboration was explored. Education and Training developed courses in a pedagogic framework. Data standards for paediatric research were developed using CDISC methods.

Results:
19 NH were identified and and tracked across 8 maturity domains. of maturity. All NH progressed at national level and in international collaboration. NH have contacts with more than> 250 sites and. NH have been involved in 20 industry and 3 non-industry trials. Experts, current total over >460, were identified and grouped in 24 groups which followed quality improvement plans and wrote 13 White Papers. Expert Advice has been given 42 times. 20 ERNs are active in paediatrics. The , extent of overlap in sites between ERNs and c4c varied between ERNs and countries. Learned societies, including ESDPPP, collaborated on White Papers and Education. 22 courses were developed. A CDISC Paediatric User Guide was developed.

Conclusion:
The results achieved within c4c project form the basis of c4c Stichting. c4c Stichting will continuing the work of the c4c project and provides a wide-ranging network for collaboration about paediatric pharmacology and drug development.

50. Comparison of maternal and fetal exposure to escitalopram, sertraline, and paroxetine during pregnancy combining human ex vivo placental perfusion data and physiologically-based pharmacokinetic modeling

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Introduction:
Selective serotonin reuptake inhibitors (SSRIs) are commonly used antidepressants during pregnancy. Here we aimed to predict maternal and fetal exposure to three widely used SSRIs - sertraline, escitalopram, and paroxetine - across pregnancy, using physiologically based pharmacokinetic (PBPK) models combined with ex vivo data.

Methods:
PBPK models for the 3 antidepressants were first developed with Simcyp v22 and evaluated for non-pregnant population. Estimated transplacental transfer parameters from ex-vivo human placenta perfusion experiments were then incorporated into a pregnancy PBPK model (p-PBPK) to predict maternal and fetal concentrations for each SSRI. Transplacental parameters were estimated through mixed-effects modeling with a physiologically-based mechanistic placenta (PBMP) model, using Monolix 2023R1. P-PBPK models were evaluated by comparing observed maternal and cord blood concentrations to predicted concentrations. The p-PBPK model was then used to simulate maternal pharmacokinetic profiles and fetal exposure across pregnancy.

Results:
PBMP model satisfactorily described ex vivo data from 28 placentas. The p-PBPK models accurately predicted maternal and fetal SSRIs concentration time-courses. A decrease in exposure during pregnancy relative to non-pregnant period should be expected. In the third trimester, residual concentrations were predicted to decrease by 56% and 43% for sertraline, 55% and 49% for escitalopram, and 90% and 88% for paroxetine, for total and unbound concentrations respectively. Cord blood-to-maternal plasma area-under-curve (fm AUC) ratios over 24 hours were calculated based on model predictions. By late pregnancy, fm AUC ratios were 0.45 for sertraline, 0.91 for escitalopram, and 0.58 for paroxetine.

Conclusion:

Three p-PBPK models have been developed to quantitatively predict sertraline, escitalopram and paroxetine exposure during pregnancy. This work confirms the benefit of integrating ex vivo data into PBPK modeling and provides a good overview of maternal and fetal exposure trends throughout pregnancy, and may help in clinical decision-making.

51. Comparative analysis of breast milk and infant formulas: microbiome and health implications

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Introduction:
The early-life microbiome is crucial for immune development. Breast milk, rich in bioactive agents, supports infants' gut, immune system, and brain. When breastfeeding isn't possible, formulas are effective alternatives. Studies compare breast milk and formulas to identify bacterial differences, enhancing formula efficacy and understanding their implications in medical conditions.

Methods:
We applied a methodology that integrates a DADA2-based script to process raw 16s rRNA data and the recursive ensemble feature selection (REFS) algorithm for robust biomarker discovery in three datasets. The datasets contain microbiome samples from both breastfed and formula-fed infants. One dataset (PRJNA633365) was used as the discovery dataset, while the other two (PRJDB7295 and PRJNA562650) were used for external validation of the resulting taxa set. Additionally, we used a web-based platform for comprehensive microbiome analysis called MicrobiomeAnalyst to identify taxonomic signatures and relate them to different diseases and diet/lifestyle.

Results:
The analysis linked resulting taxa signatures to long-term diseases like cardiovascular disease, type 2 diabetes, and asthma to specific microbiota changes. In cardiovascular disease, there was an increased abundance of Firmicutes, Bifidobacterium, Peptostreptococcaceae, and Streptococcus. Allergic diseases like eczema had decreased Bifidobacterium, Dialister, and Streptococcus. Asthma in infants under one year showed decreased Bifidobacterium and Streptococcus. In diet/lifestyle analysis, fructose and glucose, found in breast milk, increased Clostridiaceae, Enterobacteriaceae, and Lactobacillales. These sugars, along with lactose, are naturally present in breast milk. Fructose was detectable in both breast milk and the infant's gut at six months.

Conclusion:
Our analysis links microbiota changes to diseases like cardiovascular disease, type 2 diabetes, allergies, and asthma. Diet and lifestyle factors, such as fructose and glucose in breast milk, influence bacterial abundance. Understanding early-life microbiota is crucial for long-term health. Future research should explore these bacterial signatures to enhance formula efficacy.

52. Sedative antipsychotic use by children and adolescents in the Netherlands: dosages, duration and prescribers

Authors:
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Introduction:
The increasing global prescription of sedating antipsychotics in children and adolescents raises concerns about appropriate usage and safety in the Netherlands. This study aims to fill this critical gap by examining the patterns of sedating antipsychotic prescriptions, focusing on quetiapine, olanzapine, and pipamperone.

Methods:
Data from the IADB.nl pharmacy dispensing database, covering approximately 120 community pharmacies in the Netherlands, was analysed to assess sedating antipsychotic prescription patterns in children and adolescents, aged between 0-19 from 2017 to 2022. The study compared dosages, durations, and prescription rates of these antipsychotics, considering gender-based differences and the types of prescribers involved.

Results:
Our analysis revealed a significant rise in prescription rates for quetiapine (0.33 to 0.63 per 1000) and olanzapine (0.16 to 0.23), alongside a decline in pipamperone prescriptions (0.54 to 0.33) from 2017 to 2022. Quetiapine was predominantly prescribed in low doses (<100 mg), constituting 91.5% of all prescriptions and 95.8% of new prescriptions. Girls received lower quetiapine doses (43.37 mg) than boys (53.25 mg). Olanzapine had the highest average dosage, with quetiapine showing the shortest median usage duration (3 months) and pipamperone the longest (10 months). General practitioners initiated 26% of prescriptions, frequently prescribing quetiapine, whereas specialist-initiated prescriptions lasted longer.

Conclusion:
Rising prescriptions of low-dose quetiapine and olanzapine in youths raise safety concerns due to known adverse effects. Declining pipamperone use suggests shifting prescribing patterns. Sex differences in dosing highlight the need for personalized treatment approaches. Adherence to evidence-based guidelines and research into long-term pediatric effects remain critical.

53. Impact of discontinuing open-label doxapram use in neonates on informed consent rates in the DOXA-Trial

Authors:
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Introduction:
The DOXA-trial assesses the efficacy and safety of doxapram versus placebo in preterm infants. Initially, open-label doxapram remained available, potentially affecting parental consent. To improve low consent rates, 10 of 18 NICUs in the Netherlands and Belgium discontinued open-label use. This study evaluates the impact of this change on consent rates.

Methods:
We conducted a retrospective analysis of informed consent rates in the DOXA-trial across the 10 participating NICUs that modified their standard of care by discontinuing open-label doxapram use. Consent rates in the year preceding the discontinuation to those in the year following the change were compared using a two-sample Z-test for proportions.

Results:
Following the discontinuation of open-label doxapram, the consent rate increased significantly from 27.3% to 42.6% (CI 8.2% to 22.5%, $p<0.001$). This improvement could be attributed to multiple factors, including a shift in parental perception, potentially driven by the absence of an established treatment alternative, or by an improved ability of staff to effectively explain the trial without the complexity of open-label use. The improved consent rates eventually led to improved patient enrollment ($p=0.034$).

Conclusion:
The discontinuation of routine open-label doxapram use in NICUs significantly improved parental consent rates and patient enrollment in the DOXA-trial. In the design of future drug trials, one should consider to change the standard of care at start of the trial to optimize consent rates.

54. The CANDi project's first step: prioritization of off-label drug-indications warranting further assessment

Authors:
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Introduction:
Many drugs are used off-label in children, but the quality of underlying efficacy and safety data is remarkably low. Additionally, existing literature and real-world data are insufficiently used to support benefit-risk assessments. We propose leveraging these data to close the information gaps. Firstly, we need to identify and prioritize the drug-indication-age combinations that could benefit from this approach.

Methods:
Our prioritization method is based on literature review on prioritization methods used for research agendas and other related subjects, as well as input by the conect4children leads. The method was designed as a survey scoring the drug-indication-age group combinations which were based on the off-label drugs listed in the Dutch Paediatric Drug Formulary. An average score was calculated to generate top 10 lists. The top 10 lists were presented to the conect4children expert groups in live meetings to reach consensus on a top 3 for each subspecialty.

Results:
Our method scored efficacy, safety, population affected and disease severity on a scale of 0-10 with 10 meaning highest perceived efficacy, extreme safety concerns or no safety data available, high prevalence and/or incidence and high morbidity and/or mortality. Across fourteen paediatric subspecialties, 125 experts completed the survey. Only the intensive care group had the exact same top 3 chosen as was listed in the top 10 list. All other subspecialties had chosen 3 out of the 10 listed. Arguments for deviating from the initial top 3 were: clinical relevance of the drug, large population affected, the drug is widely used, high data availability, correct formulation, current dose variations and the possibility of extrapolation from adults or other indications.

Conclusion:
Using a newly developed prioritization method, paediatric off-label drugs were selected by subspecialty for evidence-generation using existing data. These results will aid in the next steps within project CANDi to improve off-label drug therapy in children.

55. Trends in hospitalizations for accidental poisoning in children in France, 2016-2023

Authors:
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Introduction:
The main objective of this study was to assess the trends of hospitalizations for accidental poisonings due to prescription drugs, opioids, and illicit substances (cannabis, cocaine, other) in children aged 6 months to 9 years in France before and more than 3 years after the COVID-19 pandemic.

Methods:
Cross-sectional study on national hospital data (PMSI) collected before the pandemic onset (Jan. 2016-March. 2020), the period of the pandemic mitigation measures (April 2020-June 2021) and the period after measures were lifted (July 2021-December 2023). Quarterly hospitalization rates per 100,000 children were modelled.

Results:
Overall, 21,715 hospitalizations for accidental poisonings were analysed: 81.4% related to prescription drugs, 6.4% to opioids, and 16.2% to illicit substances. Before the pandemic, only poisonings related to illicit substances were increasing by 1.9%/quarter (95% CI: 0.6-3.2%). During the mitigation measures, only poisonings related to prescription drugs exceeded expected rates by 7% (6-8%). After July 2021, trends increased significantly for poisonings related to opioids (+18.6%) and illicit substances (+1.5%), but rates exceeded the expected only for cocaine (+41%; 19-66%).

Conclusion:
Hospitalization rates for accidental intoxication in children increased during the pandemic mitigation measures for prescription drugs, but not for opioids or illicit substances. When the measures were lifted, an increase in accidental intoxications due to cocaine was observed.

56. Estimated glomerular filtration rates in neonates undergoing therapeutic hypothermia

Authors:
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Introduction:
As part of the I-PREDICT project(1), we collect data on (patho)physiological changes to inform a (patho)physiologically-based pharmacokinetic (PBPK) model in neonates undergoing therapeutic hypothermia (TH). Impaired postnatal renal function is a relevant aspect of these changes, while data comparing these patterns to healthy term cases are absent.

Methods:
We pooled mean serum creatinine data of estimated glomerular filtration rate (eGFR) in TH cases (2,3) over 10 days of life, with eGFR patterns in healthy term neonates (4,5,6). To calculate eGFR (2) or mGFR (3) in TH cases, we assumed a BSA of 0.25 m2, applying the Smeets k-value (0.31, mL/kg/1.73m2)(4).

Results:
In 3 control cohorts (4,5,6), the mean eGFR was 20/20/20, 26/25/22, 32/39/-, 35/34/33, 39/37/-, 41/38/-, 42/41/42, 42/43/-, 43/45/-, 44/47/- for the 10 consecutive postnatal days. In the TH cohorts (2,3), this was 16, 19/17, 24, 27, 28, 30, 33, 35, 38, 41 mL/kg/1.73m2. When expressed as % reduction, eGFR was 26% lower during TH, 25% on day 4-5, and still 20% on day 6-7. Consequently, all cohorts displayed a postnatal age-dependent maturation, but with significant differences in mean eGFR between TH cases and controls over the first week of life, so beyond the actual TH period of 72h.

Conclusion:
Conclusion: There are clinical meaningful differences in mean eGFR between the TH cohort and control cohorts over the first postnatal week, while both show postnatal maturation. This illustrates the complexity to detect renal impairment in early neonatal life, when fast maturation (eGFR doubles) should occur. These differences are instrumental to facilitate PBPK model development specific for the TH population, while interpatient variability in renal function is not difficult to cover.

References: (1) Smits et al., Front Pharmacol 2020 doi:10.3389/fphar.2020.00587.; (2) Krzyzanski et al., AAPS J 2023 doi:10.1208/s12248-023-00851-0; (3) Deferm et al., Clin Pharmacokinet 2021 doi: 10.1007/s40262-021-00991-6; (4) Smeets et al. DOI: 10.1681/ASN.2021101326; (5) Wu et al. Pharm Res 2024 doi: 10.1007/s11095-024-03677-3; (6) Munoz et al., doi: 10.1007/s00467-024-0663-y.

Funding: FWO senior clinical investigatorship (18E2H24N) FWO iPREDICT (G0D0520N), KU Leuven CELSA REPAIR-NEO (24/022).

57. Use of medication for gastroesophageal reflux during pregnancy and adverse birth outcomes

Authors:
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Introduction:
Symptoms of gastroesophageal reflux disease occur in approximately half of all pregnancies. Consequently, many pregnant people use over-the-counter medication, including antacids and proton pump inhibitors (PPIs), to treat these symptoms, but data on the safety of use during pregnancy are scarce. Therefore, we aimed to determine whether calcium-based antacid and PPI use during pregnancy is associated with selected adverse birth outcomes.

Methods:
In this prospective cohort study, we included 9,153 pregnancies enrolled in the PRIDE Study (2012-2019) and The Dutch Pregnancy Drug Register (2014-2019). Validated web-based questionnaires and obstetric records were used to collect data on exposures (use of calcium-based antacids and PPIs, including details on timing of use and dosage), outcomes (preterm birth, low birth weight, small-for-gestational-age [SGA], and low Ponderal Index), and confounders. We fitted crude and weighted modified Poisson regression models and Cox proportional hazard models for use of calcium-based antacids and PPIs before gestational day 161 and time-varying exposures after gestational day 160, respectively, using inverse probability of treatment weighting.

Results:
Calcium-based antacid use before gestational day 161 was not associated with any of the outcome measures, but use after gestational day 160 was associated with a decreased risk of low birth weight (hazard ratio [HR] 0.5, 95% confidence interval [CI] 0.3-0.9) and SGA (HR 0.6, 95% CI 0.4-0.8). We observed increased risks for use of high-dose PPIs before gestational day 161 and preterm birth (risk ratio [RR] 2.3, 95% CI 1.2-4.4) and low birth weight (RR 2.9, 95% CI 1.4-6.0), whereas any PPI use after gestational day 160 was associated with low birth weight (HR 2.0, 95% CI 1.2-3.6), SGA (HR 1.5, 95% CI 1.0-2.3), and low Ponderal Index (HR 2.3, 95% CI 1.3-4.2).

Conclusion:
Use of calcium-based antacids seemed safe during pregnancy with regard to birth outcomes, with associations that may be explained by reverse causation. PPI use in early and late pregnancy, however, was associated with multiple adverse birth outcomes including

preterm birth, low birth weight, SGA and low Ponderal Index, warranting restraint use of this over-the-counter medication during pregnancy.

Abstracts faculty: Tuesday 24 June 2025

Pharmacokinetics

Author: Prof. Pieter de Cock, Ghent University Hospital (BE)

Abstract:
Pharmacokinetics is pivotal in optimizing drug efficacy and safety across diverse patient populations. In this pre-conference workshop at ESDPPP 2025, attendees will engage in an insightful session dedicated to exploring current advances and challenges in pharmacokinetics, particularly emphasizing pediatric patient groups. This session will outline essential pharmacokinetic principles, discuss variability in drug absorption, distribution, metabolism, and excretion, and highlight recent developments in pharmacokinetic modeling and simulation. Participants will gain critical insights into how pharmacokinetic data can inform precise dosing strategies, improve clinical outcomes, and enhance patient safety. The session also aims to foster interdisciplinary collaboration among researchers, clinicians, and pharmacologists, reinforcing the importance of tailored pharmacotherapy in specialized populations.

Paediatric drug formulations

Author: Dr. Viviane Klingmann, Department of General Paediatrics, Neonatology and Paediatric Cardiology, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University, Düsseldorf, Germany

Abstract:
The focus of this presentation will be on the development of new paediatric galenic formulations for children and adolescentsto simplify the oral intake of medication and increase compliance. Nowadays, the most commonly developed dosage form is the mini-tablet. Our results of several clinical studies led to the acceptance of solid dosage forms already in young children in the EMA guidelines on paediatric galenic formulations and formed the basis for the acceptance of mini-tablets in Paediatric Investigation Plansfor different new medicines' development. In further studies,the team investigated the acceptability of other paediatric formulations like oblong tablets, mini-tablets in different sizes and orodispersible films. In addition, the research includes the development and validation of a methodology to define the level of acceptability of oral formulations, which was recognised by the EMA with a Letter of Support in 2023.

Workshop: Pharmacology for clinicians

Author: Dr. Robert Flint, Erasmus MC (NL)

Abstract:
Three important clinical pharmacological themes will be addressed during this hands on workshop. Each theme will use illustrative cases that will first be sorted out in small groups, followed by plenairy discussions.

The themes and goals are:

1. **Pregnancy & Lactation.** How to decide on the safety drugs used during pregnancy and lactation. Where to find the best evidence and information.
2. **Therapeutic Drug Monitoring & Applied Pharmacokinetics.** How to optimally use TDM in pediatric care, taking into account the impact of maturation on pharmacokinetic parameters and therewith drug exposure. This will be illustrated using interactive simulation software.
3. **Drug Drug Interactions and Side Effects.** How to interpret and act on the various types of drug drug interactions and side effects.

The diverse background of participants (e.g. physicians, pharmacists, researchers) will give different perspectives to the cases which will lead to fruitful discussions on the practical solutions.

Abstracts faculty: Wednesday 25 June 2025

Drug discovery, paediatric gastrointestinal disease as example

Author: Prof. Sven van IJzendoorn, University Medical Center Groningen (NL)

Abstract:
Microvillus inclusion disease (MVID) is a very rare and severe genetic bowel disorder that affects infants and young children. Degeneration of their small intestine causes the patients' inability to absorb nutrients from the diet and makes them life-long dependent on intravenous feeding. Unfortunately, most patients also die from the complications that accompany long-term intravenous feeding. Recently, we have found that the genetic defect in MVID causes intestinal cells to be hypersensitive to oxidative stress. This results in their premature death and degeneration of the small intestine. Importantly, this defect could be treated with an approved antioxidant in a mouse model of MVID. In this presentation, the challenges of translating these findings to a treatment for this disease are discussed.

Advancing patient-centric pediatric care using omics-derived biomarkers for predicting pharmacokinetic variability

Author: Prof. Bhagwat Prasad, Washington State University (USA)

Abstract:
Quantitative metabolomics and proteomics are emerging as powerful tools for predicting pharmacokinetic variability, particularly in vulnerable populations such as pediatrics, where developmental changes significantly influence drug disposition and response. By leveraging advanced mass spectrometry, these approaches enable precise quantification of drug-interacting proteins and endogenous metabolites, facilitating more accurate predictions of variability in drug metabolism, transport, and safety. In pediatric drug development, these methods offer critical insights into age-specific differences in drug disposition and help anticipate potential drug-drug interactions. Importantly, omics-guided pharmacokinetic prediction supports patient-centric, individualized dosing strategies by integrating factors such as developmental stage, genetic variation, and concomitant medications. This presentation will explore the transformative potential of quantitative omics in optimizing pediatric therapeutics through biomarker-driven, personalized pharmacokinetic prediction, illustrated with select case studies that highlight real-world clinical relevance.

Animal Models for In Vivo Lactation Studies

Author: Dr. Domenico Ventrella, Alma Mater Studiorum - Università di Bologna, (IT)

Abstract:
The importance of breastfeeding, well recognized both by the scientific world and public opinion, has put pressure on women under chronic pharmacological medication, due to the lack of data regarding offspring exposure via milk. Within the current pharmaceutical framework, only the ICH S5 (R3) guidelines mention lactation, stating that “Evidence of lactational excretion can be obtained, when warranted, by sampling milk or by demonstrating exposure in offspring during the pre-weaning period” and advising the use of rats. Despite milk collection being feasible in rats, quantitative data is not acceptable due to physiological differences. In such scenario, upon in-depth screening of existing literature, Göttingen Minipigs were proposed, setting up a dedicated study design allowing for repeated blood and milk samplings, also in piglets. The preliminary results, mainly in terms of milk/plasma ratios, seem to support the use of porcine species for lactation studies, leading to highresolution, translatable results.

Relative impact of CYP2D6 genotype phenotype on exposure of SSRIs during pregnancy: extrapolation approach using RWD and PBPK modelling

Author: Dr. Karen Rowland Yeo, SIMCYP, Sheffield (UK)

Abstract:
Pregnancy and associated physiological changes can affect the pharmacokinetics (PK) of selective serotonin reuptake inhibitors (SSRIs) which are first-line treatment for depression. Some SSRIs are metabolised extensively by CYP2D6, whose expression is increased significantly during pregnancy [1]. Almost 21% of SSRI-treated women remained depressed during pregnancy (14.4% genetically normal or ultrarapid metabolizers *versus* 6.1% poor or intermediate metabolizers) [1]. SSRI exposures measured during the 3 trimesters of pregnancy are available but CYP2D6 genotypes were not measured [2]. However, for metoprolol a model CYP2D6 substrate clinical data in CYP2D6-genotyped pregnant subjects across the trimesters are available [3]. In this presentation, I will discuss how PBPK modelling can be used to bridge across substrates with similar PK (metoprolol *versus* SSRIs) and ultimately, be used to predict appropriate doses for SSRIs during pregnancy based on CYP2D6 genotype to reduce the risk of antidepressant discontinuation due to inefficacious treatment.

[**References:**
[1] Bérard A *et al.* Front Pharmacol. 2017 Jul 17;8:402.

[2] Westin AA et al. PLoS One. 2017 Jul 14;12(7):e0181082.

[3] Ryu RJ *et al.* J Clin Pharmacol. 2016 May;56(5):581-9.

Abstracts faculty: Thursday 26 June 2025

Extrapolation in paediatrics

Author: Roberto de Lisa*, Dominik Karres*,

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Abstract:
Research involving children faces unique ethical and feasibility challenges and unnecessary enrolment in clinical trials should be avoided. Extrapolation, using prior knowledge (e.g., from adults) of efficacy data can address this. The ICH E11A guideline, effective as of January 2025, outlines two key aspects: the extrapolation concept and plan. The extrapolation concept summarizes existing evidence on disease similarity, drug pharmacology, and treatment response in adults and children, identifying knowledge gaps. The extrapolation plan addresses these gaps using quantitative methods like modelling and simulation, or Bayesian statistics and clinical trials as appropriate to addressing the uncertainties.

Extrapolation is a continuum, not a binary decision tree. It should consider the product's pharmacology and disease similarity, identifying and re-evaluating evidence gaps and uncertainties to inform the clinical development plan over time. It needs to be prospectively planed. Decisions must be based on scientific considerations and not retrofitted to suit benefit/risk assessments when development becomes challenging.

Providing evidence on use and safety of medications in pregnancy when randomized clinical trials are not feasible

Author: Dr. Marleen van Gelder, Radboud University Medical Center, Nijmegen (NL)

Abstract:
For ethical and medico-legal considerations, evidence on the use and safety of medications in pregnancy and lactation heavily relies on observational studies, facing numerous methodological challenges common to these designs. In this presentation, I will highlight the role of primary data collection and Real World Data to inform regulation of pharmaceuticals and clinical recommendations, advances in methodological approaches, and future directions. Examples include studies on the safety of commonly used medications in pregnancy and lactation (prescription and over-the-counter) using data from the PRIDE Study in The Netherlands, as well as Norwegian registry data.

Drug safety in Neonates

Author: Prof. Karel Allegaert, University Leuven (BE)

Karel Allegaert is a paediatrician (1999), neonatologist (2000) and clinical pharmacologist (2003), appointed at KU Leuven, departments of Development and Regeneration, and Pharmaceutical and Pharmacological Sciences as full professor, with an additional appointment as senior consultant (10%) at Erasmus MC, Rotterdam (Hospital Pharmacy). His research has its focus perinatal and paediatric clinical pharmacology.

Abstract:

Neonatal drug safety matters…

At the next ESDPPP conference, he will share a lecture on neonatal drug safety, since neonatal pharmacotherapy has it specific issues, related to - among others - to population specific pharmacoepidemiology, off label practices, polypharmacy, and the need to tailor causality or severity tools to the population. New approaches and tools have been developed to improve this scenery, and these will discuss during the Nijmegen meeting.

A joint presentation about the LENA project: From formulation to market authorization

Author: Prof. Jörg Breitkreutz, Prof. Stephanie Läer and Peter McBride

Abstract:
Orodispersible minitablets (ODMTs) were described in 2011 as a promising new dosage form [1]. The collaborative LENA project was initiated to develop Enalapril ODMTs and clinically investigate in newborns to adolescents.

Part 1 describes how enalapril maleate ODMTs (0.25 and 1 mg) were developed, manufactured and characterised. Dose recovery in food and from feeding tube materials was investigated.

Part 2 covers the clinical developmental concept and the clinical trials performed according to the Paediatric Investigation Plan (PIP). It also presents the main results of all studies, the results of the bioavailability study and the results of the three paediatric studies.

Part 3 decribes how the product was taken through the EU Regulatory framework to gain a Paediatric Use Marketing Authorisation (PUMA). It describes the Regulatory environment for paediatric medicines, dossier preparation, submission activities, PUMA approval and product launch.

[1] I. Stoltenberg, J. Breitkreutz. Eur. J. Pharm. Biopharm. 78: 462-469 (2011)

Benefit-risk in pregnancy and lactation, the regulator's view

Author: Charlotte Bakker, European Medicines Agency (EU)

Abstract:
The majority of pregnant women use medicines during pregnancy, ranging from inadvertent exposure to treatments for pregnancy-related conditions and chronic diseases requiring ongoing care. Assessing the benefit-risk balance of medicines in the pregnant population is complex, as it involves not only the health and safety of the mother, but also potential risks and benefits for the foetus. Despite the widespread use of medicines in pregnant and breastfeeding population, information on their safety remains limited. The European Medicines Agency is driving a shift in how data are generated and communicated, by identifying and implementing opportunities throughout the product life cycle. Multiple initiatives, including the development of the guideline ICH E21 on inclusion of pregnant and breastfeeding individuals in clinical trials, aim to support a better informed decision-making for medicine use during pregnancy and breastfeeding.

Abstracts faculty: Friday 27 June 2025

Antithrombotic therapy in pregnancy

Author: Prof. dr. Saskia Middeldorp, internist. Head Department of Medicine, Radboud university medical center, Nijmegen The Netherlands

Abstract:
Venous thromboembolism (VTE) during pregnancy and the postpartum period is a main cause of maternal mortality, and always associated with significant morbidity. Use of therapeutic anticoagulation during pregnancy, around delivery and in the postpartum period is associated with the burden of parenteral treatment, an increased risk of bleeding, and high costs. Women with pregnancy-related VTE suffer long-term consequences, such as postthrombotic syndrome, the need to avoid oral contraceptives, and the need for prevention during subsequent pregnancies.

Thrombophilia not only is associated with VTE, but, depending on the type of thrombophilia also with recurrent miscarriage and placenta-mediated pregnancy complications, such as preeclampsia and HELLP syndrome.

The optimal prevention of pregnancy-related VTE and the use of low-molecular-weight heparin to prevent recurrent miscarriage in specific populations was mainly based on very weak evidence. Saskia Middeldorp will discuss the results of the recently published international ALIFE2 en Highlow randomized controlled trials, focused on how these trials may impact clinical practice.

Pregnancy Formulary

Author: Anneke Passier, PhD, Teratology Information Service Lareb, 's-Hertogenbosch (NL)

Abstract:
Most pregnant women use medication. So far, pregnancy-specific PK data have been limited. Project **MADAM** (Model-Adjusted Doses for All Mothers) was set up to fill this gap and to provide evidence-based dose recommendations for pregnant women. PBPK models are used; computer models that combine the properties of a drug with the physiology of the pregnant body. This allows the simulation of plasma concentrations throughout pregnancy. The preliminary dose and the underlying evidence are assessed by a multidisciplinary working committee, focusing on maternal and fetal risks and benefits. If endorsed, the dose is published on the Dutch Lareb knowledge bank ('Moeders van Morgen') that provides information about medication safety during pregnancy and breastfeeding. Further international dissemination of the adjusted doses is planned, with future funding.
Prior experience with international dissemination of information by a free and publicly accessible knowledge bank, for countries lacking this information, was gained in the ConcePTION project.

The case of empagliflozin

Author: Dr. Terry Derks, University Medical Center Groningen (NL)

Abstract:
Since 2019, the wildly used SGLT2 inhibitors have been successfully repurposed in glycogen storage disease type Ib (GSD Ib) and Fanconi-Bickel syndrome (FBS). Off-label use of SGLT2 inhibitors targets extrahepatic complications in these ultra-rare inherited disorders of carbohydrate metabolism. In a relatively short period of time, hundreds of patients worldwide have started this treatment. These indications have been added to several national pediatric formularies and since August 2024 the treatment has been reimbursed by health insurers in the Netherlands.