The objective of this study was to develop a method to identify NFX metabolites in human samples, and apply it to the discovery of NFX metabolites in urine from pediatric patients undergoing treatment for Chagas disease.

Methods Urine was collected from 12 pediatric patients and 8 healthy volunteers (controls), and anonymized before analysis. Informed consent was obtained from all participants. Samples were aliquoted, deproteinized with ACN (BNZ as internal standard) and centrifuged in cold. 10% of supernatant in water was injected into a 1.8 μm C18 column and chromatographed in 3.5 min under a water/ACN gradient at 0.4 mL/min in a Shimadzu Nexera X2 UHPLC equipment. Species were positively ionized by a Turbo IonSpray source. Metabolites were identified and characterized by an ABSciex 6500 QTRAP spectrometer through Enhanced-Mass-Screening (EMS), Neutral-Loss (NL), Precursor-Ion (PREC), Enhanced-Product-Ion (EPI) and MS3 experiments. For chromatographic monitoring, parameters were optimized and the three most intense Multiple-Reaction-Monitoring (MRM) transitions were selected.

Results Denitrated NFX conjugated with cysteine (M1) and N-acetyl-cysteine (M2), as well as other phase I metabolites like saturated nitrile (M3), hydroxyamide (M4), carboxylic acid (M5) or aldehyde (M6) were identified in most samples. The final MS/MS detection method was high reproducible and sensitive for all metabolites.

Conclusions We found the main NFX metabolites in pediatric urine using a fast MS/MS method that can allow us to efficiently study the role of NFX and its metabolites in pediatric treatment response and the adverse drug reactions, and in combination with PK/PD experiments will facilitate future clinical trials, and possibly develop new therapeutic drug monitoring strategies.

REFERENCE

1. The research was carried out in the Translational Research Unit (IMIP-CONICET), located in the Buenos Aires Children’s Hospital ‘Dr. Ricardo Gutiérrez’, and financed by the Fund for Scientific and Technological Research (FONCyT, Project BID-PICT 2015–0168).

Disclosure(s) Nothing to disclose

P39 ESTABLISHMENT OF THE SWISS DATABASE FOR DOISING MEDICINAL PRODUCTS IN PEDIATRICS

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Background Drug therapy in children is challenging. Due to the lack of licensed drugs for paediatric use, off-label or unlicensed prescription is frequent. To improve quality and safety of prescription of medicinal products for children in Switzerland, the requirement to create and continuously run a national database was added in the revision of the therapeutic products act (TPA Art. 67a). The task of operating the database is given to SwissPedDose, an association representing eight Swiss children’s hospitals, the Swiss Society of Paediatrics (SGP) and the Swiss Association of Public Health Administration and Hospital Pharmacists (GSASA).

Methods Substances used in three therapeutic areas ‘general paediatrics’, ‘infectious diseases’ and ‘neonatology’ are selected according to their frequency of use in the eight participating hospitals. Dosage data of substance-indication pairs are requested from the hospital pharmacists. Based on these data and literature review a dosage suggestion consisting of substance, indication, route of administration, dose, daily repetitions and, if applicable, additional remarks is then elaborated by a specialised pharmacist of SwissPedDose. This suggestion is then discussed by experienced physicians delegated from the eight clinics. The elaboration, discussion and agreement on a national dosage recommendation takes place and is documented in an online platform specially programmed for this structured harmonisation process. Once an agreement has been achieved, the national dosage recommendation is sent to the eight participating clinics and published in a free accessible public database.

Results As of December 31st 2018, 195 dosage recommendations for children including 87 indications and 54 substances have been harmonised and published and are available for medical professionals on https://swisspeddose.ch/database.

Conclusion The goal of published recommendations for 100 substances by March 2021 is feasible to reach due to interprofessional collaboration. SwissPedDose may thus contribute to a more efficient and safe use of drugs prescribed to children in Switzerland.

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P40 COMPARISON OF ANTIBIOTIC CONSUMPTION BETWEEN PEDIATRIC HOSPITALS

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Background Antibiotic exposure and reduced microbiome diversity in early childhood are associated with the incidence of inflammatory bowel disease, asthma and type-1 diabetes later in life. Together with the emergence of microbial resistance, those adverse effects of antibiotics impacting on the individual and population levels.

Periodic monitoring of therapeutically used antibiotics in the framework of antimicrobial stewardship is required for their effective and restricted use in hospitals.

Children’s hospitals face two challenges for a meaningful quantification of antibiotic consumption:

§ Firstly, the algorithm DDD/inpatient days used in adult patients do not take into account the heterogeneity of the pediatric population. Up to date there is no global consensus on how to calculate and interpret the antibiotic consumption of wards and hospitals for children.

§ Second challenge is the relative scarcity of suitable pediatric hospitals as basis for comparison.

This study deals with the comparison and interpretation of antibiotic consumption between two similarly structured children’s hospitals in Austria.

Methodology The annual use of antibiotics was assessed in two large pediatric clinical settings at geographically distinct locations in Austria, encompassing all relevant wards, such as neonatology, internal medicine, surgery, pediatric oncology and PICU’s. The analysis discriminates among the wards and classes of antibiotics.
In addition to DDD and inpatient days, alternative parameters such as number of patient-admittances and number of used vials were included in the calculation.

**Result** Pediatric-specific pitfalls affecting the quantification and comparability were identified:

- Hospital guidelines concerning the multiple usage of dissolved and diluted antibiotics.
- Regional composition of the pediatric patient population in terms of pathology.
- Intramural allocations of wards sharing the drug deposit.

**Conclusion** Unexpected factors have severe impact on the reliability of annual antibiotic quantification and interpretation. Those factors need to be taken into account when comparing pediatric hospitals.

**REFERENCES**


**Disclosure(s)** Nothing to disclose

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**P41 PRENATAL EXPOSURE TO ANTIBIOTICS AND DEVELOPMENT OF EPILEPSY IN CHILDREN**

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**Background** Studies reported that prenatal exposure to antibiotics in general represents a risk factor for development of epilepsy and/or cerebral palsy in children. A pathophysiological relationship seemed improbable and required adjustment to possible confounders.

**Methods** In a retrospective cohort investigation, we enrolled children aged 3 to 18 years born between 1998 and 2012 at the single regional hospital, and their mothers, members of ‘Clalit’ (the largest Health Service Organization in the region). Computerized medications database was linked with hospital records of mothers and their children. The exposed group included all children whose mothers purchased one or more antibiotic medications during their pregnancy. Epilepsy was defined by Epilepsy diagnosis and/or by chronic dispensing of antiepileptic drugs. After applying inclusion and exclusion criteria for mothers and children, 88,899 children and their 74,416 mothers were selected for the study.

**Results** The group exposed prenatally to antibiotics comprised 36,622 (or 41.2%) children. Of them, 326 (0.9%) developed epilepsy compared to 370 (0.7%) in the unexposed group (p=0.002). Number Needed to Harm 500. Exposure during the first, second and third trimester was characterized by incidence of epilepsy in 0.8% (p=0.928), 0.9% (p=0.270) and 0.9% (p=0.094) of exposed children, respectively, compared to unexposed group. Based on Poison regression analysis, epilepsy was associated with male sex, maternal smoking and delivery by cesarean section. The possibility of confounding by indication was refuted by sensitivity analysis.

**Conclusion** We found an association of intrauterine exposure to antibiotics (particularly in late pregnancy) and development of epilepsy in children. Possible pathophysiological mechanisms are discussed. The effect of some undetermined confounder(s) cannot be ruled out.

**Disclosure(s)** Nothing to disclose

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**P42 EXTERNAL VALIDATION OF MODEL-BASED DOSING GUIDELINES FOR VANCOMYCIN, GENTAMICIN AND TOBRAMYCIN IN CRITICALLY ILL CHILDREN**

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**Background** Pharmacokinetic models are frequently used to simulate dosing strategies for special populations, including critically ill children. The Dutch Pediatric Formulary (DPF) partially bases its guidelines on these models. However, prospective validation of updated dosing regimens is rare. We aimed to identify target attainment and safety of vancomycin, gentamicin and tobramycin after a dose update in the DPF for critically ill neonates and children.

**Methods** Retrospective cohort study in PICU and NICU patients receiving vancomycin, gentamicin or tobramycin between January 2015 and March 2017 in 2 university hospitals. Demographic clinical laboratory and TDM-data were collected. Target (steady state) trough concentrations for vancomycin, gentamicin and tobramycin used were 10–15, ≤1 and ≤1 mg/l, respectively. Target gentamicin peak concentrations used were 8–12 mg/l.

**Results** 486 patients were included in total (165 vancomycin, 97 gentamicin and 224 tobramycin). Trough concentrations of vancomycin, gentamicin and tobramycin were within the target range in 37.5%, 85.3% and 77.2% of patients, respectively. Target attainment of gentamicin peak concentrations in NICU patients was 31%. Non-target trough concentrations were most prevalent in term NICU patients (vancomycin 70%, gentamicin 26% and tobramycin 36.8%). Gentamicin peak concentrations were subtherapeutic in 91% and 45.5% for term and preterm NICU patients, respectively. Creatinine concentrations correlated positively with antibiotic concentrations (correlation coefficient range 0.46–0.54, p≤0.01 in all cohorts).

**Conclusion** Despite recent model-based dosing alterations, sub- and supratherapeutic concentrations of vancomycin, gentamicin and tobramycin are still frequent in critically ill children. Linear dose alterations did offer improvements in target attainment, but did not fully address all relevant covariates that contribute to the large interindividual variation in clearance and/or volume of distribution in these patients. Creatinine clearance was consistently correlated with concentrations of all 3 drugs, but future research is needed to identify whether including this parameter in dosing can improve target attainment and safety.

**Disclosure(s)** Nothing to disclose