Conclusion The Bu MR on day 3 above 4.973 and 25.06 were associated with worse EFS in children undergoing HSCT and received Bu in QID and QD dosing schedules, respectively.

Disclosure(s) Nothing to disclose

P98

SEMI-QUANTIFICATION AND LOCALIZATION OF MEMBRANE TRANSPORTERS IN PAEDIATRIC KIDNEY TISSUE

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Background The kidney has a critical role in disposition, efficacy and toxicity of drugs and xenobiotics. Developmental changes of renal membrane transporters have the potential to explain population variability in paediatric pharmacokinetics and -dynamics of drugs but data are missing. We aimed to further delineate the expression of human renal tubular transporters multidrug resistance-associated protein (MRP) 4 and MRP2 and study localization in paediatric kidney samples.

Methods We planned to semi-quantify expression levels and to study the age-specific localization of the transporters MRP4 and MRP2 with immunohistochemistry on 44 human neonatal and paediatric kidney samples with age range of 24,00 - 40,00 weeks gestational age (GA) and 0,29 - 744 weeks post-natal age (PNA). The staining intensity was semi-quantitatively scored by two independent observers (MB and BG).

Results MRP4 is found to be localized at the apical membrane of the renal proximal tubules at 27 weeks of GA (n=3, 1,29- 4 weeks PNA) and no age-related changes of expression levels were detected. In a premature neonate of 24 weeks GA (n=1), no MRP4 was detected. The MRP2 staining did not meet the requirements to be scored and was rejected.

Conclusion MRP4 is expressed from at least 27 weeks GA onwards and does not show developmental changes. The localization was similar as in adults (Ritter et al., 2005). The half-life of the MRP4 substrate furosemide was found to be 6 to 20-fold longer in neonates than in adults (Pacifi, G.M., 2013). This could potentially be linked with the absence of MRP4 in a premature neonate with GA 24 weeks. However, these data should be confirmed as we only had 1 sample of $\pm$ 24 weeks GA available. Moreover, our data help us in understanding altered disposition of transporter substrates in paediatrics.

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P99

CLINICAL VALIDATION OF PUBLISHED VANCOMYCIN POPULATION PK MODELS IN CRITICALLY ILL NEONATES

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Background Vancomycin is commonly used for treatment of severe Gram+ neonatal infections. Currently, even with the use of optimized dosing regimens and therapeutic drug monitoring (TDM), target attainment rates are abominable, leaving patients at risk for therapeutic failure and toxicity. Model-informed precision dosing (MIPD) offers a large potential to improve therapy in the individual patient.

The aim of this study was to identify a suitable model for bedside MIPD by assessing the predictive performance of published population pharmacokinetic (popPK) models.

Methods A literature search was conducted to identify parametric popPK models. PK vancomycin data were retrospectively collected from NICU patients at the Radboud University Hospital, Nijmegen, The Netherlands. The model predictive performance was assessed by comparison of predictions to observations, calculation of bias (Mean Percentage Errors, MPE) and imprecision (Normalized Root Mean Squared Errors, NRMSE). Evaluations included both *a priori* (model covariate input) and *a posteriori* (model covariate and TDM concentration input) scenarios.

Results 265 TDM measurements from 65 neonates (median postmenstrual age:32 weeks [range:25–45 weeks]; median weight:1281g [range:597–5360g]; median serum creatinine:0,48 mg/dL [range:0,15–1,28 mg/dL]) were used for model evaluation. Six popPK models were evaluated^{1–6}. *A posteriori* predictions of all models were consistently more accurate and precise compared to the *a priori* (starting dose) predictions. PopPK models of Frymoyer *et al.* and Capparelli *et al.* consistently performed best through all evaluations in both the *a priori* and *a posteriori* scenario (MPE ranging from -18 to 6,4% in *a priori* scenario and -6,5 to -3,8% in *a posteriori* scenario; NRMSE ranging from 34 to 40% in *a priori* scenario and 23 to 24% in *a posteriori* scenario).

Conclusion Large differences in predictive performance of popPK models were observed. Repeated therapeutic drug monitoring remains necessary to increase target attainment rate. Best performing models for bedside MIPD were identified in our patient population.

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P100 A PRACTICAL FRAMEWORK FOR THE ASSESSMENT OF RISKS AND BENEFITS OF OFF-LABEL PRESCRIBING IN PAEDIATRICS (ARBOP-P)

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Background Guidelines for off-label prescribing are emerging.^{1–6} However, these guidelines do not provide practical guidance to assess the risk benefit balance and select the right paediatric dose. We, therefore, aimed to develop a practical framework to guide paediatric healthcare professionals to assess the risks and benefits of off-label use.

Methods We have reviewed available literature on the suggested criteria for appropriate off-label use and evaluated these criteria for relevance in paediatrics. For guidance on dose-selection we searched for regulatory guidance on paediatric drug development. Next, the literature was searched for strategies that can be applied to assess the risks and benefits of off-label use. Based on literature findings a framework was proposed to provide practical guidance to physicians for off-label prescribing. Finally, the framework was applied to a case.

Results The following conditions for appropriate off-label use were identified based on available literature: 1. *Medical need for off-label use*. 2. *Off-label use is based on ‘high quality evidence’*. As ‘high quality evidence’ in paediatrics is often lacking, we propose to replace the need for high quality evidence by a positive risk-benefit assessment based on available evidence. 3. *Parents and patients are informed*. This is not feasible for every single drug prescribed off-label, we propose a graded approach. 4. *The outcomes of off-label use are followed up*.

The PROACT-URL framework⁷ for decision-making as well as the FDA paediatric decision tree⁸ seem helpful tools to guide decisions in real-life practice.

Conclusion We identified important aspects and tools to develop a framework (ARBOP-P) to guide healthcare professionals on how to systematically assess and balance the benefits and risks for off-label use, including dose selection, to ultimately optimize efficacy and safety of paediatric off-label prescribing.

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P101 EXTENDING THE DUTCH PAEDIATRIC FORMULARY ACROSS EUROPE: SUCCESSFUL DEVELOPMENT OF COUNTRY SPECIFIC, PARALLEL, PAEDIATRIC DRUG FORMULARIES

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Backgrounds As many drugs in paediatrics are used of off-label, prescribers across Europe face a lack of evidence-based dosing guidelines. The Dutch Paediatric Formulary (DPF) was developed to provide dosing guidelines based on best available evidence from registration data, investigator-initiated research, clinical experience and consensus (1). The DPF has recently joined forces with Germany, Norway and Austria aiming to develop multi-language, parallel, paediatric drug formularies based on the DPF.

Methods

The DPF database and ICT framework were extended to a duplicate database for Germany. The dosing guidelines were translated to German and reviewed for fit with German practice. Relevant drugs and dosing recommendations were selected and country-specific information was added to address country-specific needs. Work-sharing on content development was studied in a small pilot.

Results The German Pediatric Formulary (www.kinderformulary.de) was launched on 1 October 2018 within a German paediatric medication safety project (KiDSafe). At that time 119 of 769 drugs were reviewed and published in the German formulary. The dosing recommendations of the DPF show a good fit with German practice; i.e. adaptations were needed in less than 10% of the cases caused by differences in licensing status, national guidelines or availability of formulations. There were no differences in interpretation of evidence. Nine drugs - highly relevant for German practice, but not listed in the DPF, were added to the German formulary based on SmPC. The content