work sharing was piloted by the development of a new monograph and the periodic revision of a monograph complying to the Dutch standard operating procedure by Germany. This pilot has shown the feasibility of work-sharing in developing and updating drug monographs.

Conclusion The Dutch framework has successfully been extended to the German situation. Work-sharing on the development of dosing recommendations is feasible. Similar extension to Norwegian and Austrian nation-wide formularies has started.

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P102 ALTERNATIVE SPLICING OF THE *SLCO1B1* TRANSPORTER IN PAEDIATRIC LIVER

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Background Alternative mRNA transcripts occur in >90% of human genes and may be triggered by developmental signals. The hepatic transporter OATP1B1 (gene name *SLCO1B1*) traffics substrates across the hepatic membrane, and shows age-related changes in protein expression. We aimed to predict novel isoforms of OATP1B1 by studying alternative splicing of *SLCO1B1* in human paediatric post-mortem liver tissue, and the relationship of their mRNA expression with age.

Methods mRNA expression of *SLCO1B1* transcripts was determined using RNA sequencing (HISAT2/StringTie). Novel mRNA transcripts were considered of relevance when (1) the expression was >5% of the annotated isoform, (2) it was a *SLCO1B7* and *SLCO1B1* hybrid transcript, or (3) when the expression was associated with age. The software packages ORF-finder, TMpred and TOPO2 were used to predict the protein sequence and structure of the novel isoforms. Relationship of expression with age was studied with the Kruskal-Wallis test for age groups (fetal, 0–1.5 year, 1.5–6 year, 6–12 year and 12–18 year) and with Spearman correlation tests for age on continuous scale.

Results In 97 hepatic post-mortem tissues (gestational age median 16.4 [range 14.7–41.3] weeks, postnatal age 0.36 [0–17] years) 27 novel mRNA transcripts were detected. Of these, 13 were relevant: 2 isoforms are predicted to translate into amino acid sequences similar to the annotated isoform for OATP1B1, 9 isoforms may translate into truncated versions, and the expression of 8 isoforms was associated with age. None of the isoforms had an ORF that covered the *SLCO1B7* region.

Conclusion We showed that novel *SLCO1B1* mRNA isoforms potentially translate into OATP1B1 protein with unknown function, and that alternative splicing may well be a regulatory mechanism for *SLCO1B1* expression during development. This data provides a better understanding of age-related changes in

the expression of OATP1B1, and, with that, potentially improves prediction of disposition of endogenous and exogenous substrates.

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P103 TARGET ATTAINMENT OF AMIKACIN THERAPY IN CRITICALLY ILL CHILDREN

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Background Research regarding the optimal amikacin (AMI) dosing regimen in critically ill children is scarce.¹ Optimal AMI efficacy has been observed with plasma peak over minimal inhibitory concentration of the suspected pathogen (peak/MIC) ratios of 8 to 10. Plasma trough levels (C_{min}) >5mcg/ml are related to its toxicity.

The objectives of this pilot study were to: (1) evaluate target attainment rate and occurrence of supratherapeutic concentrations in early and assumed steady-state dose conditions, and (2) investigate the correlation between AMI clearance and estimated glomerular filtration (eGFR).

Methods Children admitted to the ICU receiving intravenous AMI (20 mg/kg once daily) were included. Serial blood samples were obtained from early (1st/2nd) and assumed steady-state (SS) doses. The evaluated target peak concentration range was 54–64 mcg/ml, assuming a *Pseudomonas aeruginosa* infection with Eucast MIC breakpoint of 8 mg/L, and a C_{min} threshold of 5 mcg/L. eGFR was estimated using the modified Schwartz formula. AMI clearance was calculated using non-compartmental PK analysis. Correlation was assessed by means of a scatter plot and Pearson Correlation Coefficient (r).

Results

Twenty-one patients (median age 1,5 years; range:0,5 months–14 year, median eGFR 162 ml/min/1,73m² (range:107–475 ml/min/1,73m²) were included. In early dose conditions, 69% of patients had therapeutic peak concentrations (median: 60 mcg/ml; range:26–73 mcg/ml). In SS conditions, 60% of patients had therapeutic peak concentrations (median: 59 mcg/ml; range:35–83 mcg/ml). Only one supratherapeutic C_{min} was observed. AMI clearance (median 0.08L/h/kg; range: 0.05–0.91 L/h/kg) was comparable to what has been previously reported but showed no correlation with eGFR (r=0.1; p=0,66) [1].

Conclusion This pilot study suggest that the current AMI dosing regimen may lead to subtherapeutic concentrations in patients infected with less susceptible pathogens. Supratherapeutic C_{min} were far less of a concern. Dose adjustments of