[O27-1] O27-1: Pharmacometrics (1)
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New population pharmacokinetic model that predicts the individual starting dose of tacrolimus following pediatric renal transplantation
Keywords: tacrolimus, renal transplantation, starting dose, pharmacokinetics, pediatrics

Background
Multiple clinical, demographic and genetic factors affect the pharmacokinetics (PK) of tacrolimus in children, yet in daily practice the starting dose is based solely on bodyweight. TDM limits the time a patient is exposed to concentrations outside the target range, but it can take two weeks to reach the target tacrolimus concentration. The aim of this study was to improve the starting dose of tacrolimus after pediatric renal transplantation.

Methods
Clinical, demographic, PK and genetic data were collected for the first six weeks after renal transplantation. All children were treated with basiliximab, tacrolimus, mycophenolic acid and glucocorticoids. Every child had at least one tacrolimus PK profile performed over 4h. A population PK analysis was conducted using NONMEM. Demographic, clinical and genetic parameters were evaluated as covariates for all PK parameters containing interpatient variability. The final model was internally and externally validated using visual predictive checks (VPC). Simulations were performed to determine the ideal starting dose.

Results
46 children with a median age of 9.1 years (range 2.4-17.9) were included. Population PK was best described by a two-compartment model with allometric scaling for bodyweight. Clearance (50.5 L/h) increased in CYP3A5 expressers, patients with an increase in eGFR, decrease in hematocrit and recipients of a kidney from a deceased donor. Together these covariates explained 41% of the variability in CL. The model was externally validated using VPCs. From the significant covariates, CYP3A5, bodyweight and donor type were useful to adjust the starting dose to reach the target predose level. For each combination of these covariates a new starting dose was calculated to reach a target level of 12.5 ug/L.

Conclusions
During the first 6 weeks after transplantation, the tacrolimus weight-normalized starting dose should be higher in patients with a lower bodyweight, who express CYP3A5 and those who receive a kidney from a deceased donor. Using these parameters an individualized guideline for the initial dosage was developed.