PBPK Simulation of the Effect of ABCC2 and ABCB1 Ontogeny on Ceftriaxone Pharmacokinetics
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Purpose
The ontogeny of transporters plays an integral role in the modulation of drug clearance during human development. The aim of the present study was to evaluate the differences in ceftriaxone disposition due to the ontogeny of ABCC2 and ABCB1 mediated biliary excretion from neonates throughout infancy and childhood to adults using a physiologically-based pharmacokinetic (PBPK) modeling approach.

Methods
A PBPK model for ceftriaxone disposition in adults was built using PK data following IV dosing using PKSim® (Bayer Technology Services, Leverkusen, Germany). This model was scaled to pediatric patients (1 month – 15 years) based on age-associated changes in anatomical, physiological and clearance parameters relevant for ceftriaxone disposition. In addition, we integrated data on the ontogeny of hepatic ABCC2 and ABCB1 protein expression inferred from 112 pediatric patients between 0 and 12 years of age previously described by our group (Clin Pharmacol Ther 2007, 81, S101). The PBPK model was used to explore by simulation age-associated changes in systemic exposure to ceftriaxone.

Results
In adults and pediatric patients older than 8 months, the clearance of ceftriaxone is dependent on both renal elimination and ABCC2 and ABCB1-mediated biliary secretion, with an allometrically weight adjusted clearance based on a 70 kg person (CL) of 28.0 mL/min. While hepatic ABCB1 expression was found to be relatively constant throughout childhood, infants under the age of 8 months have substantially reduced ABCC2 expression (Clin Pharmacol Ther 2007, 81, S101), which the model translated into a reduced biliary clearance. Consequently, renal elimination became the predominant elimination pathway and CL was reduced in this age group to 18.6 mL/min, with a corresponding increase in systemic exposure by 51%. The corresponding model predictions of systemic exposure in infants less than 8 months as well as older children could be confirmed by clinical case reports from the literature.

Conclusion
In children less than 8 months of age, the clearance of ceftriaxone is reduced due to the reduced ABCC2 expression resulting in a lower clearance that is dominated by renal excretion. The PBPK model can now be used to guide optimal dose selection in young pediatric patients.