Translating adult renal impairment PK data—Academic/clinical perspective

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Presentation overview

- Extrapolation from adults
- Which scaling method?
- GFR and transporter maturation
- Extrapolation of adult CKD data
  - PK, popPK, PBPK data
- Take home message

Extrapolation from adults to children

Review > Expert Opin Drug Metab Toxicol. 2022 Feb;18(2):99-113.
doi: 10.1080/17425255.2021.2027907. Epub 2022 Feb 25.

An Update on the Use of Allometric and Other Scaling Methods to Scale Drug Clearance in Children: Towards Decision Tables

Anne van Rongen [1], Elke Hj Krekels [1], Elisa Am Calvier [2], Saskia N de Wildt [3 4], An Vermeulen [5 6], Catherijne Aj Knibbe [1 7]

Choice of method (linear, allometry or PBPK models) dependent on:
age, drug elimination route (GFR, active tubular transport, binding plasma protein, fraction unbound

Extrapolation from adults to children

Table 1. Decision table for pediatric scaling methods for renally cleared drugs through glomerular filtration (GF) and active tubular secretion (ATS) for typical children of different ages.

	1 day[1]	1 month[1]	6 months	1 year	2 years	5 years	15 years
GF of drugs binding to albumin	*If* $f_{u,adults} > 0.34$ PBPK	LinearBW	AS0.75	**AS0.75**	**AS0.75**	**AS0.75**	AS0.75
	If $f_{u,adults} \leq 0.34$ LinearBW		**LinearBW**	LinearBW	LinearBW	LinearBW	LinearBW
GF of drugs binding to AAG	*If* $f_{u,adults} < 0.23$ *OR* $f_{u,adults} > 0.78$ PBPK	*If* $f_{u,adults} \leq 0.45$ AS0.75	*All* $f_{u,adults}$ *values* AS0.75	*All* $f_{u,adults}$ *values* **AS0.75**	*All* $f_{u,adults}$ *values* **AS0.75**	**AS0.75**	AS0.75
	If $f_{u,adults}$ 0.23-0.78 LinearBW	*If* $f_{u,adults} \geq 0.34$ LinearBW	*If* $f_{u,adults} \geq 0.34$ LinearBW	*If* $f_{u,adults} \geq 0.34$ LinearBW	*If* $f_{u,adults} \geq 0.34$ LinearBW	LinearBW	LinearBW
ATS	OCT2	OCT2					
	OAT1	OAT1	OAT1				
	OAT3	OAT3	OAT3	OAT3			
	Pgp	Pgp					

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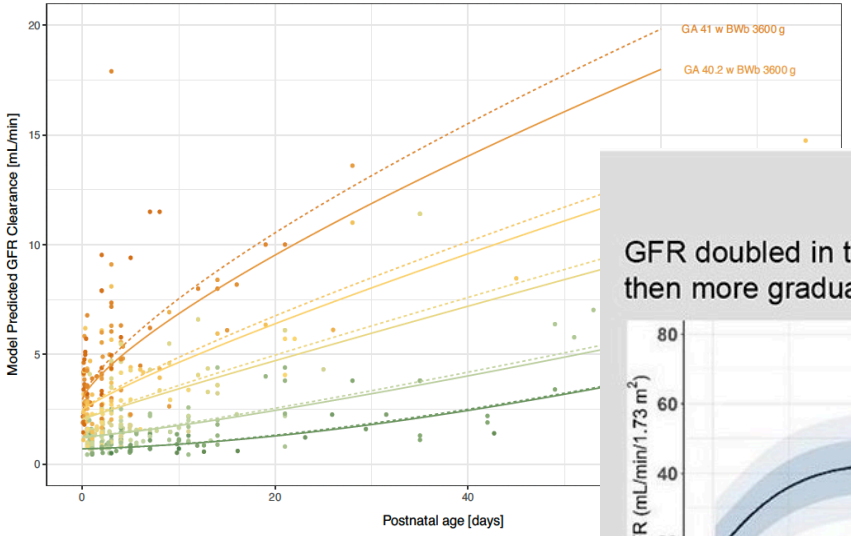
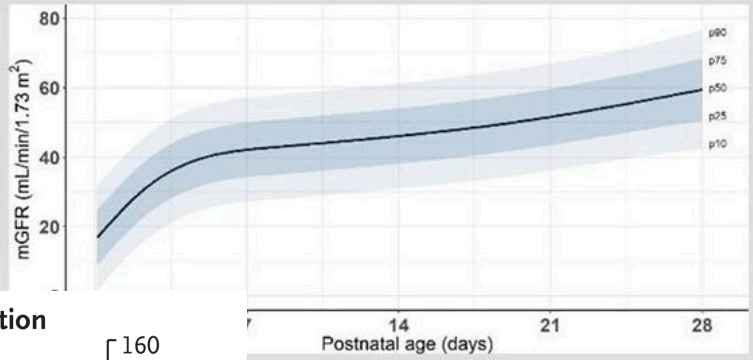
Van Rongen et al. Expert Opin Drug Metab Toxicol 2022 Feb;18(2):99-113

GFR maturation equation?

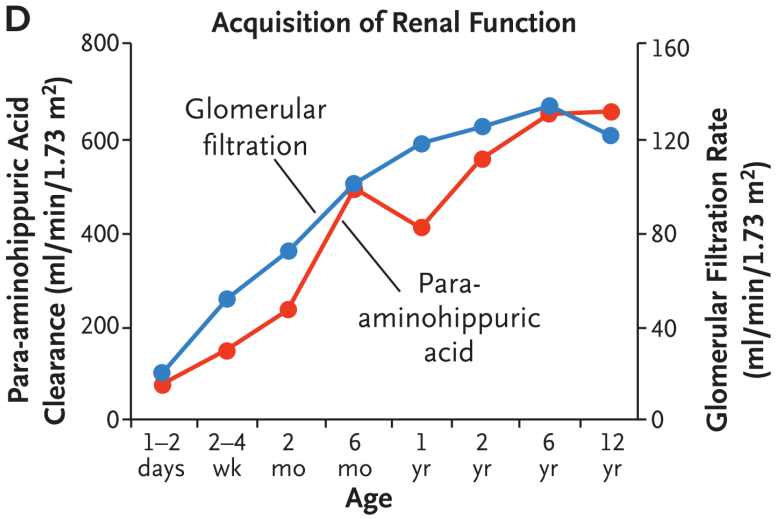


OUTCOME

GFR doubled in the first five days after birth from 20 to 41 ml/min/1.73m^2, then more gradually increased to 59 ml/min/1.73m^2 by four weeks of age.



31 led to accurate eGFR determination.



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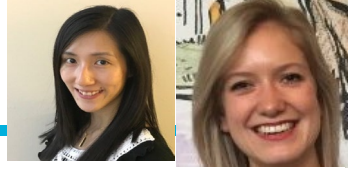
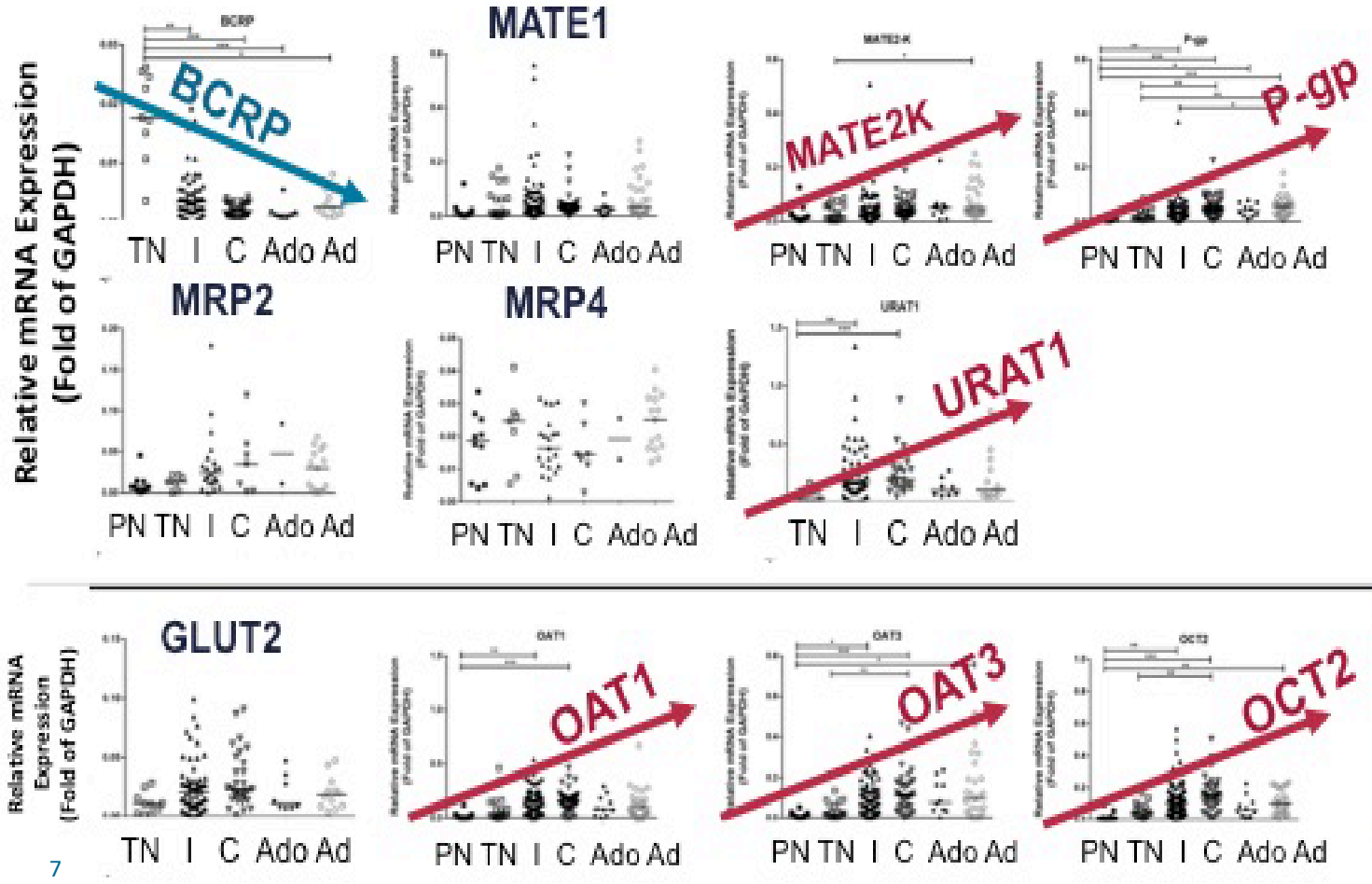
Renal transporter specific maturation

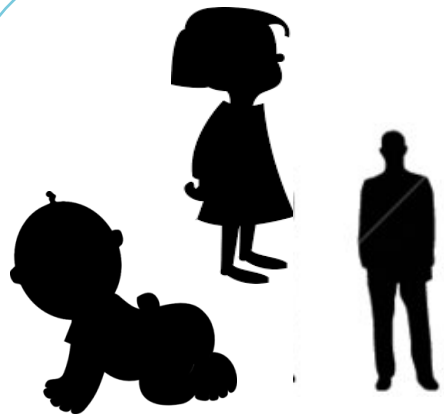


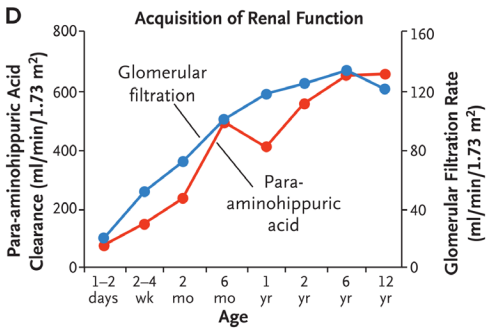
Transcript levels of 7 out of 11 transporters showed age-dependent changes

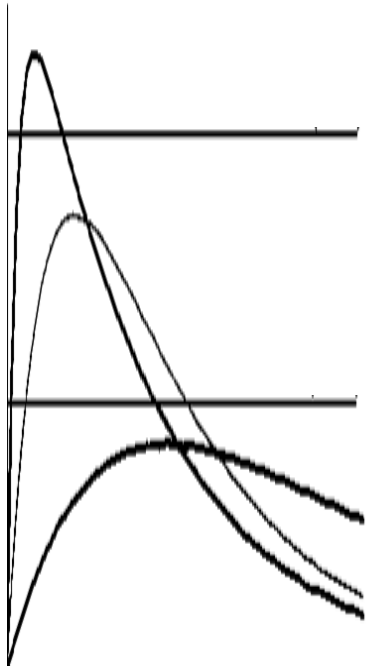


Cheung, van Groen et al, Clin Pharmacol Ther. 2019 Nov;106(5):1083-1092

Interplay of age and renal insufficiency?







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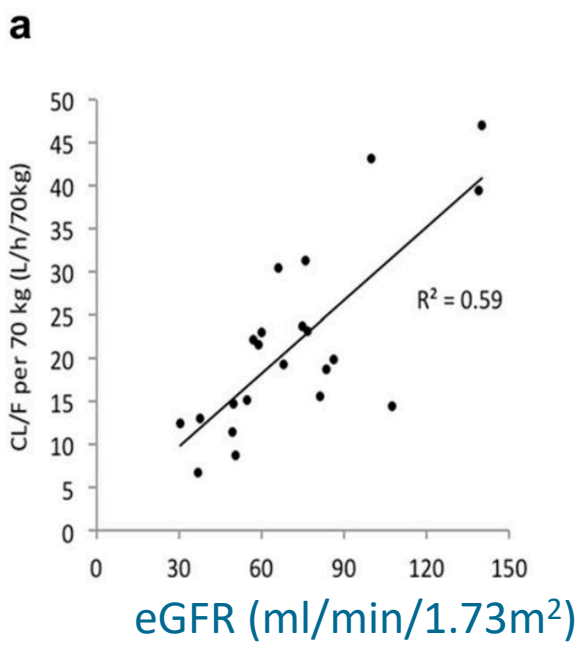
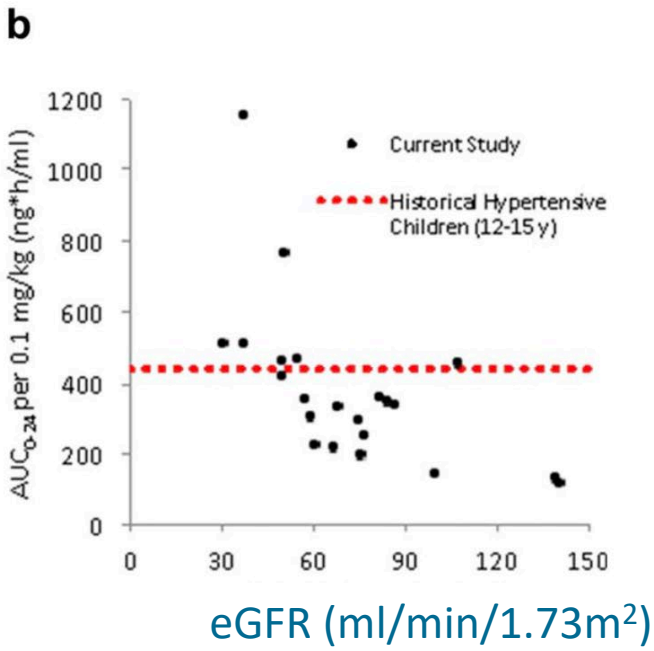
Lisinopril nonparametric PK in CKD patients

Allometrically scaled clearance (l/kg/70kg





Clearance related to GFR

No impact of age on clearance, BUT: only older children included

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Trachtman et al, Clin Pharm Ther 2015, 98(1)25-33

Pediatric popPK model of valganciclovir

American Journal of Transplantation 2009; 9: 636–643
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008

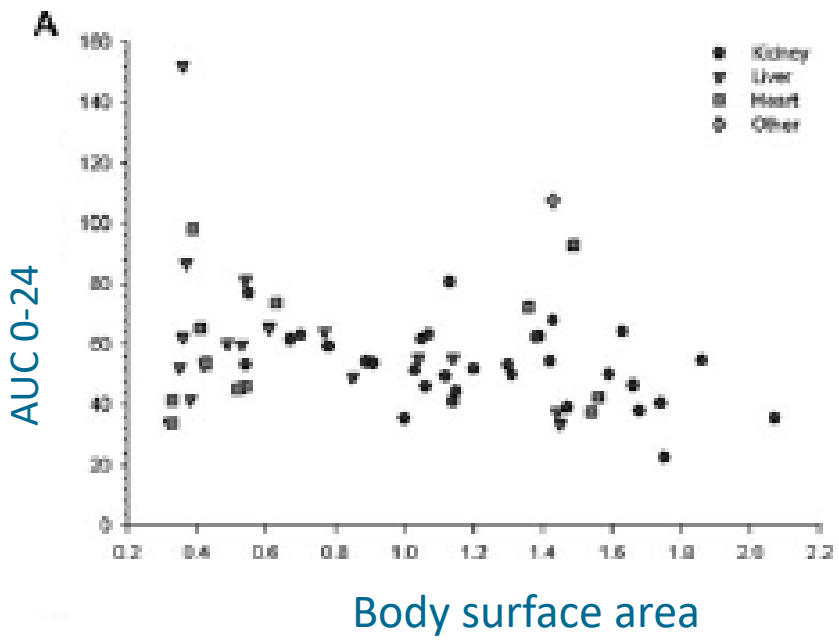
Valganciclovir Dosing According to Body Surface Area and Renal Function in Pediatric Solid Organ Transplant Recipients

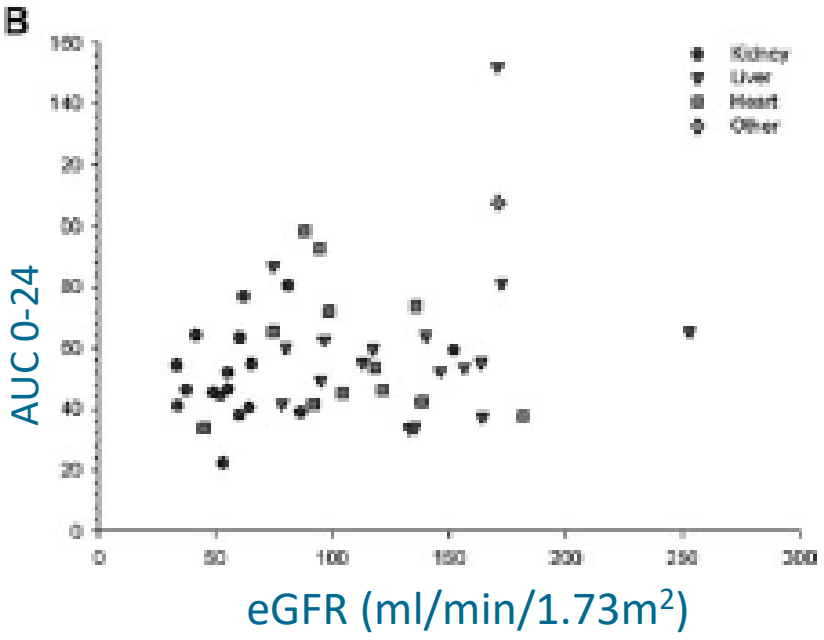
W. Vaudry[a,*], R. Ettenger[b], P. Jara[c], G. Varela-Fascinetto[d], M. R. Bouw[e], J. Ives[e] and R. Walker[f], on behalf of the Valcyte WV16726

Dose (mg) = 7 × BSA × CrCLS
CrCL using the Schwartz method, age and gender based

3 months – 16 yrs
eGFR > 35 ml/min/1.73m^2

Posthoc estimated valganciclovir AUC





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Vaudry et al. Am J Transpl 2009: 636-643

PopPK of milrinone in neonates with AKI

Clinical Trial > Clin Pharmacokinet. 2019 Jun;58(6):793-803.
doi: 10.1007/s40262-018-0729-3.

Developmental Pharmacokinetics and Age–Appropriate Dosing Design of Milrinone in Neonates and Infants with Acute Kidney Injury Following Cardiac Surgery

Tomoyuki Mizuno [1 2], Katja M Gist [3], Zhiqian Gao [4], Michael F Wempe [5], Jeffrey Alten [4 2], David S Cooper [4 2], Stuart L Goldstein [6 2], Alexander A Vinks [7 8]

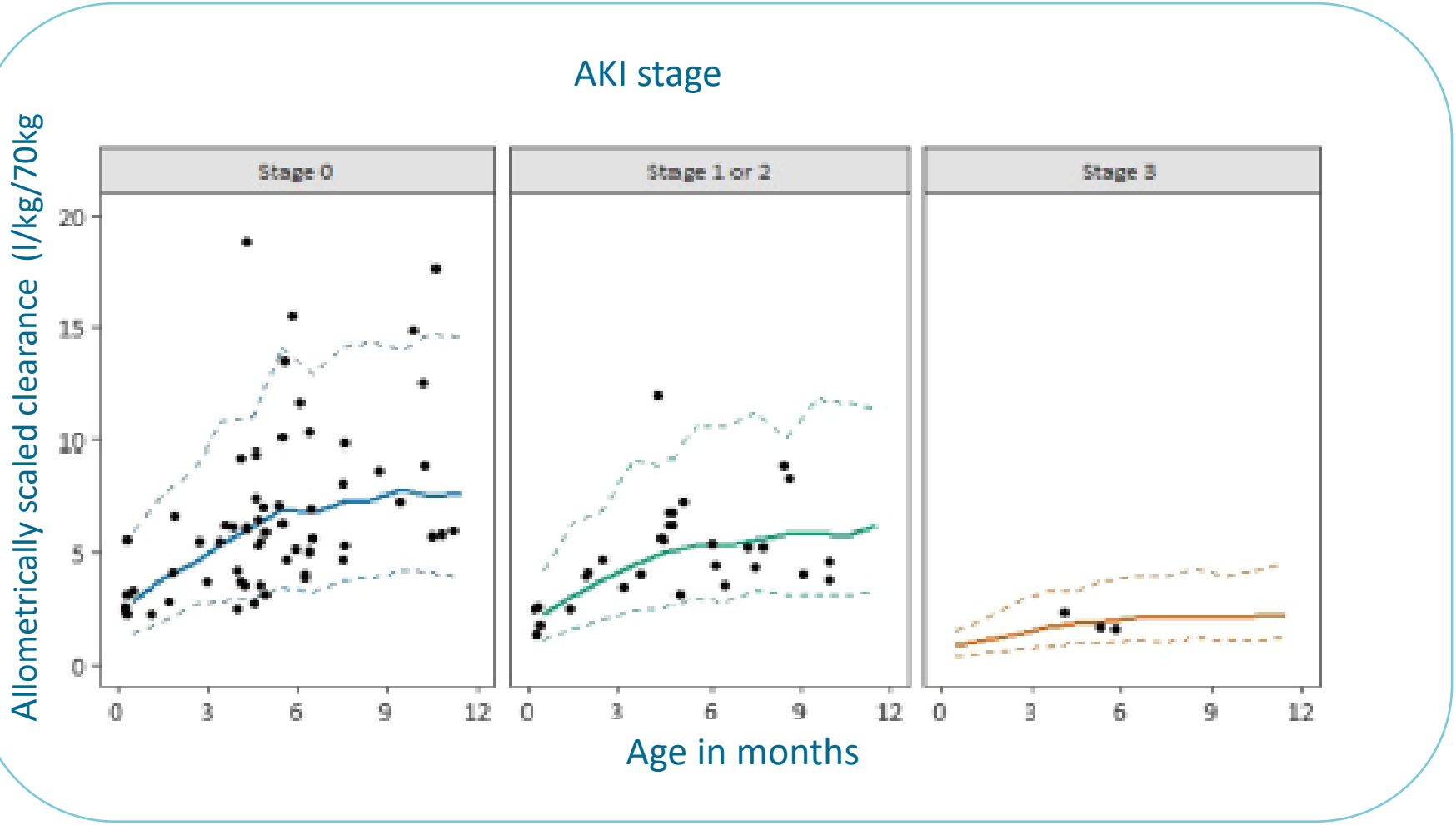
$$CL_{pediatric} = CL_{adult} \cdot \left(\frac{BW}{70}\right)^{Power} \cdot MF$$

$$MF = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$$

$$CL_i = CL_{pop} \times \left(\theta_{AKI1\ or\ 2}\right)^{power1} \times \left(\theta_{AKI3}\right)^{power2}$$

Pop PK model includes: size, maturation and AKI stage

PopPK of milrinone in neonates with AKI



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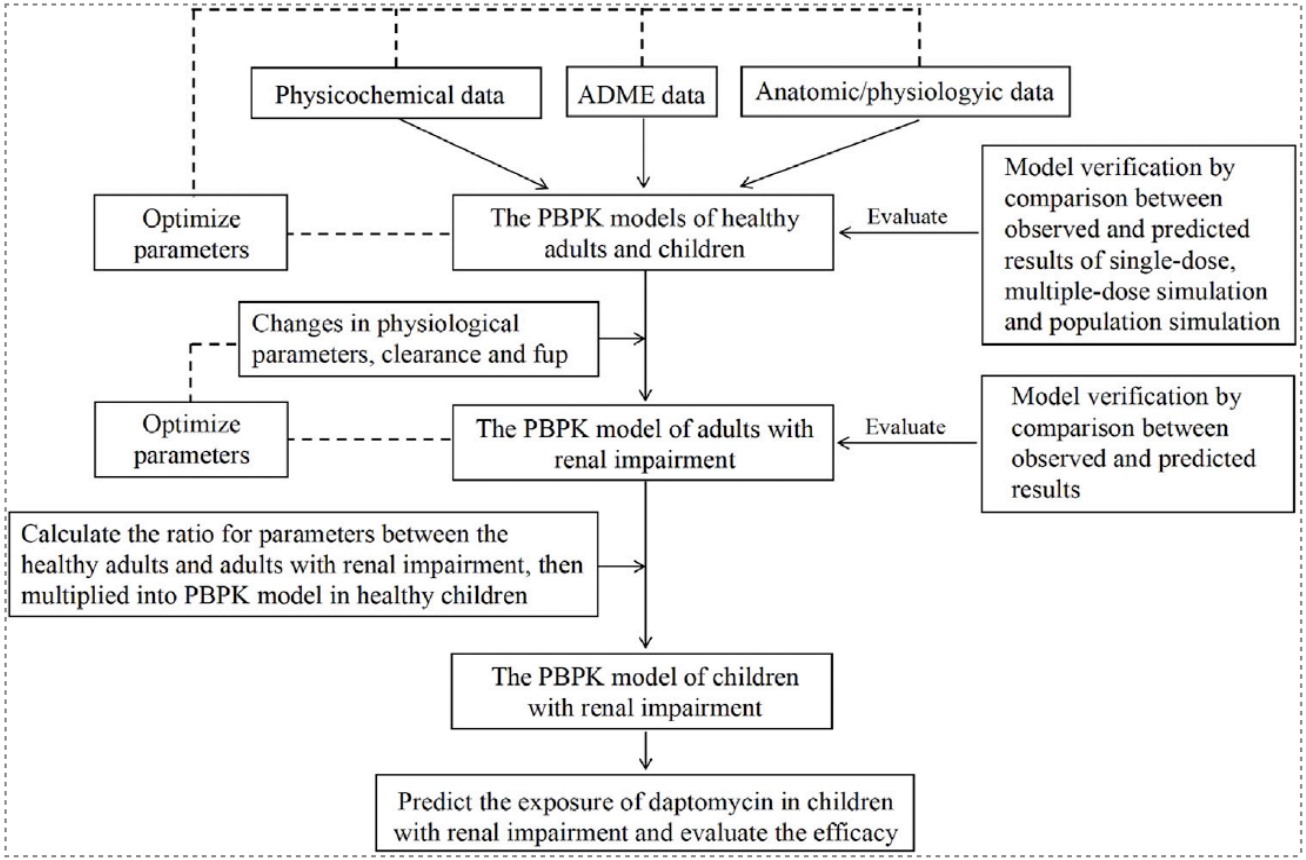
Mizuno et al, Clin Pharm Ther 2019; 793-803

PBPK model for pediatric and RI simulations



Limitation of presented model:
No verification data in children with RI!

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Ye et al 2022, Front. Pharmacol. 13:838599

Captopril PBPK Model pediatric and RI

› Sci Rep. 2023 Feb 15;13(1):2697. doi: 10.1038/s41598-023-29798-0.

Application of a physiologically based pharmacokinetic model in predicting captopril disposition in children with chronic kidney disease

Sundus Khalid [1], Muhammad Fawad Rasool [2], Imran Masood [3], Imran Imran [4], Hamid Saeed [5], Tanveer Ahmad [6], Nawaf Shalih Alqahtani [7], Fahad Ali Alshammari [7], Faleh Alqahtani [8]

PBPK model adult CKD scaled to pediatrics

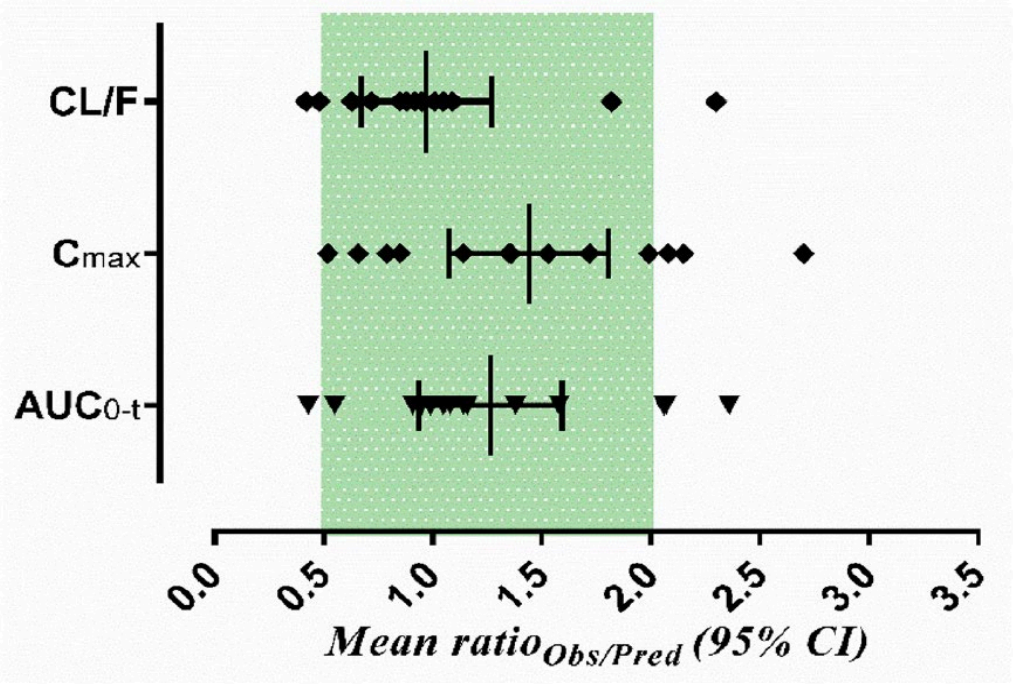
Including other CKD affected PK processes

Clearance scaled with BSA, not mechanistically

N=16, 3.5 - 18 yrs, GFR 20 – 200 ml/min/1.73m2

GFR = 98 – [(0.8)(age-20)]/ Scr, For women; GFR X 0.9

Captopril PBPK Model pediatric and CKD



'Limitation': only older children, with no expected interaction between maturation in GFR and renal insufficiency

Daptomycin PBPK model pediatric and RI

› Pharmaceutics. 2023 May 6;15(5):1424. doi: 10.3390/pharmaceutics15051424.

Lamivudine and Emtricitabine Dosing Proposal for Children with HIV and Chronic Kidney Disease, Supported by Physiologically Based Pharmacokinetic Modelling

Tom G Jacobs [1], Marika A de Hoop-Sommen [2], Thomas Nieuwenstein [1], Joyce E M van der Heijden [2], Saskia N de Wildt [2 3], David M Burger [1], Angela Colbers [1], Jolien J M Freriksen [2]

PBPK model adult CKD scaled to pediatrics

Including other CKD affected PK processes

allometric scaling and GFR/transporter maturation

Verification of pediatric CKD model with valganciclovir PK data

No verification with drugs of interest

Take home message

- Consider the age range of interest
- Interplay between maturation and renal insufficiency more pronounced in younger infants and neonates
- In PopPK models consider as separate co-variates
  - Age
  - Maturation
  - AKI stage
- In PBPK models
  - Allometry vs BSA vs mechanistich clearance model
  - Scaling other PK parameters
  - Use ’model’ drug with similar PK properties as surrogate
- Consider combining popPK and PBPK models

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University of Rochester, USA
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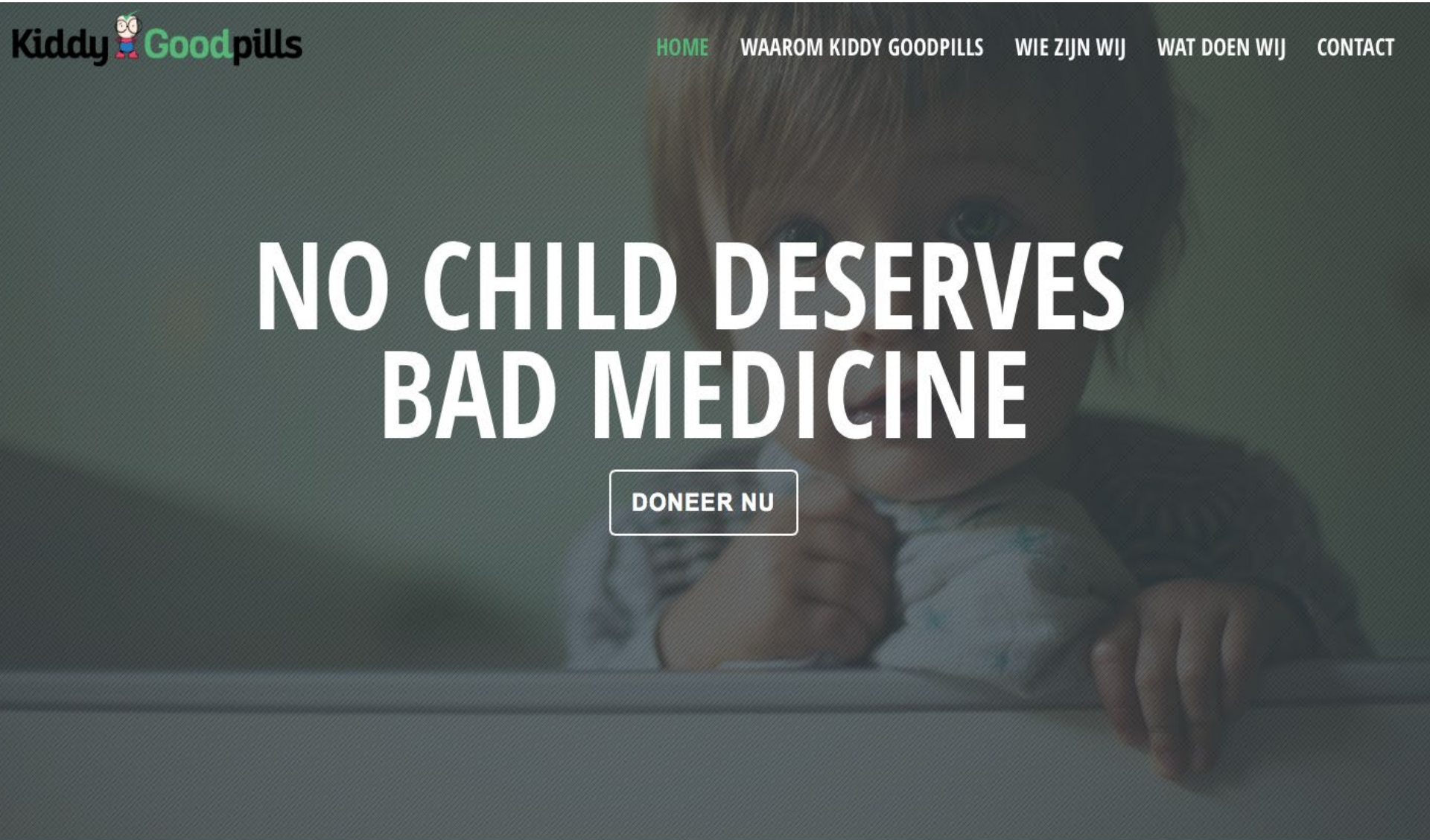
Questions?


Kiddy Goodpills
HOME
WAAROM KIDDY GOODPILLS
WIE ZIJN WIJ
WAT DOEN WIJ
CONTACT
NO CHILD DESERVES
BAD MEDICINE
DONEER NU