Drug clearance in pediatric patients with renal impairment

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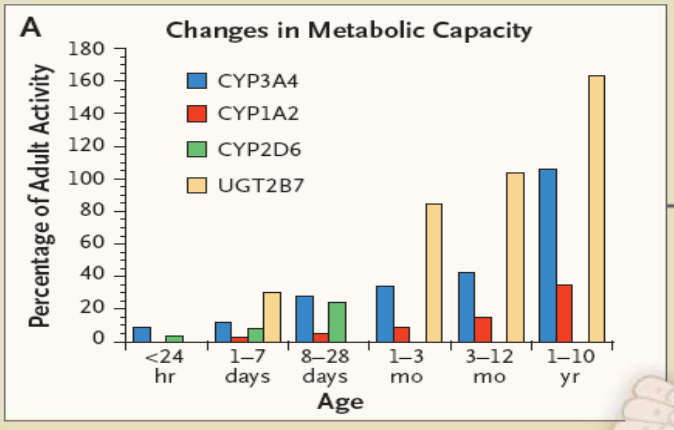
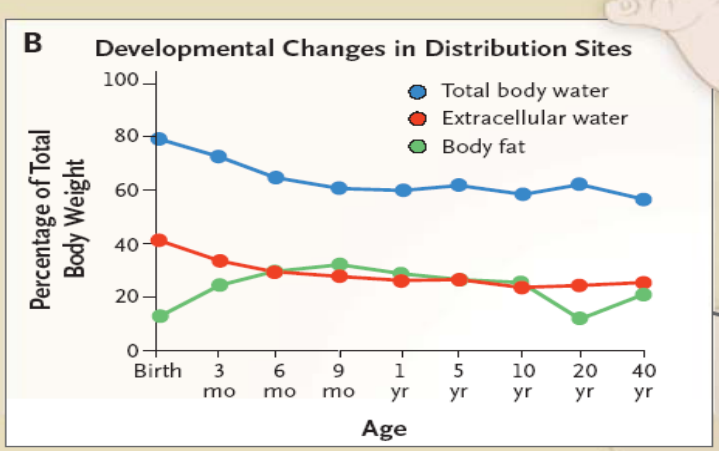
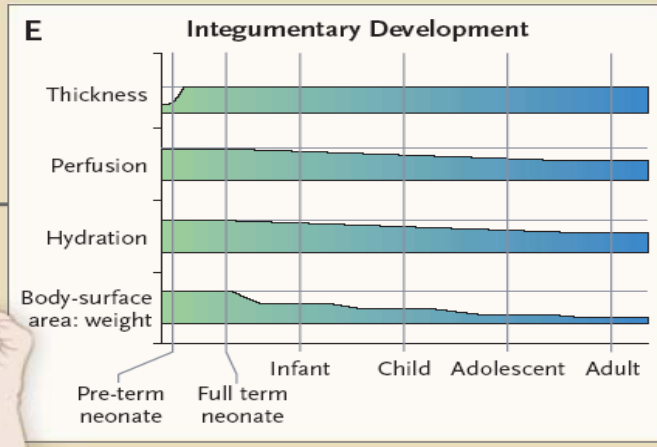
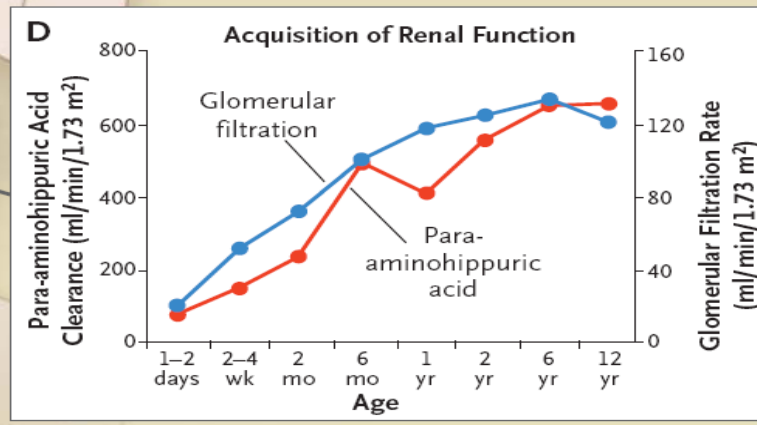
Presentation overview

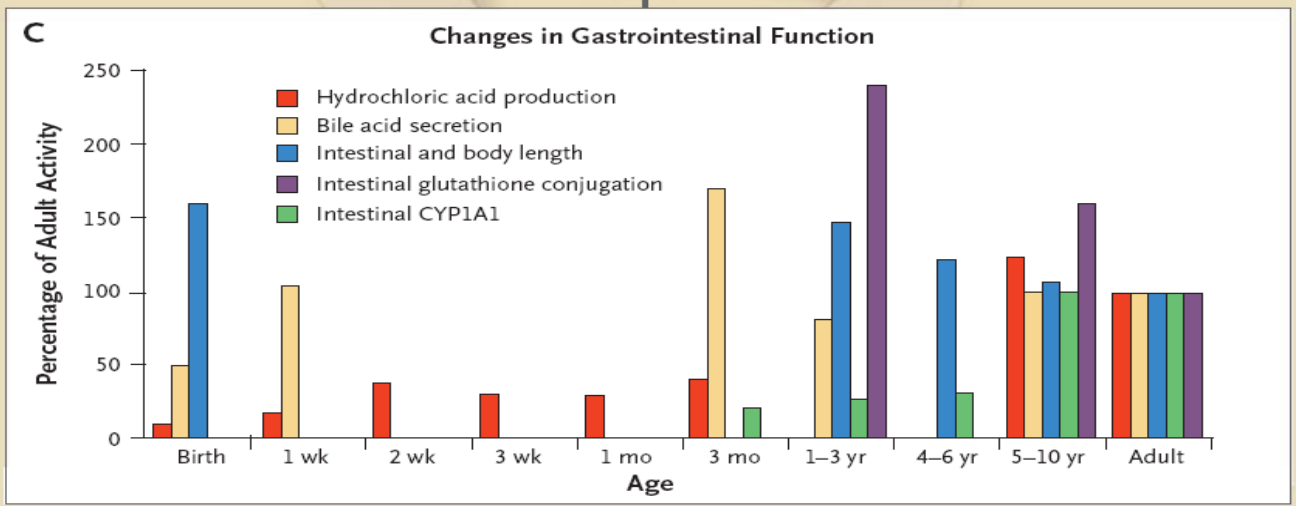
- Maturation of renal function
- Interplay of age and renal impairment
- What do we know about PK in pediatric renal insufficiency?
- Real-life practice



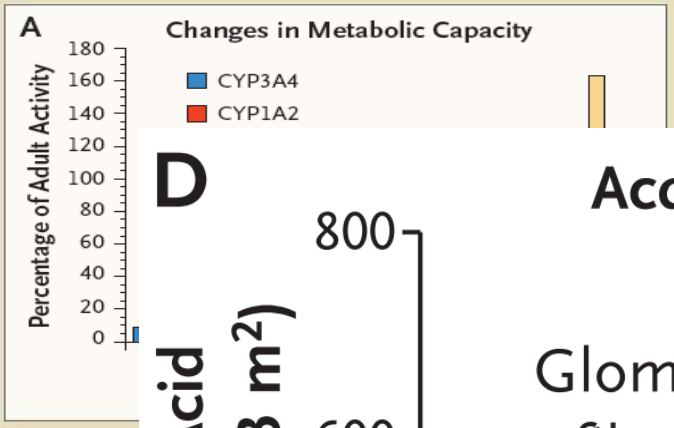


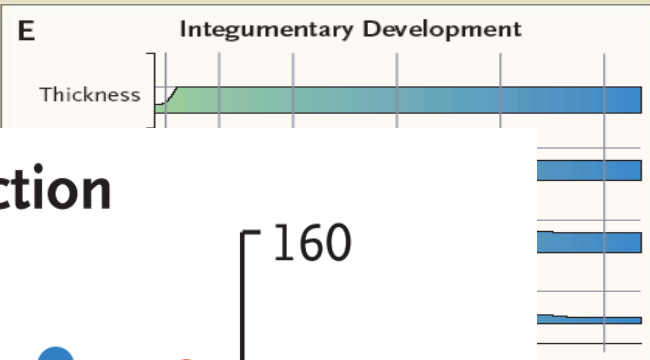


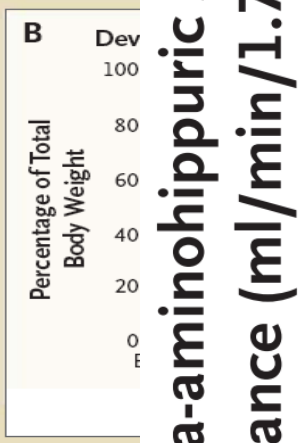


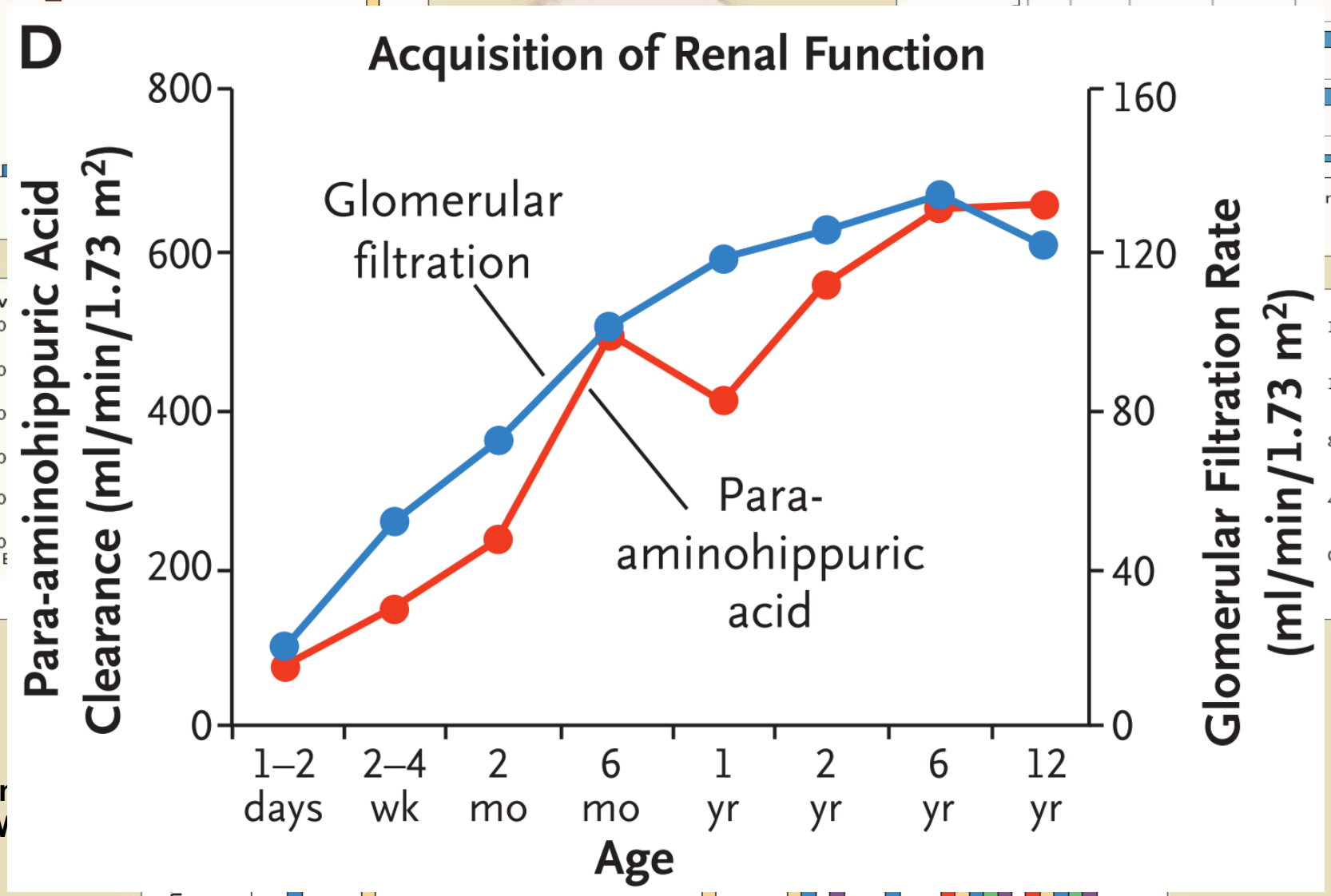


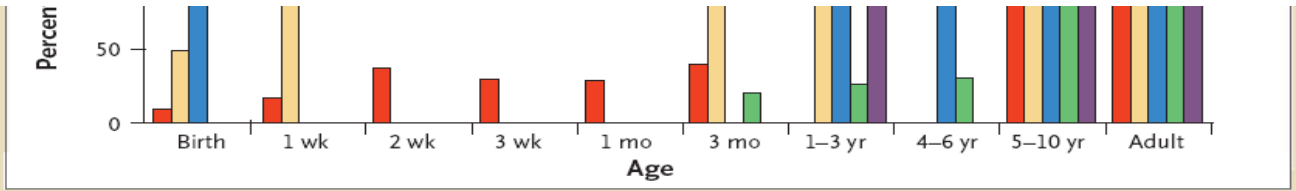
Kearns et al
NEJM, 2003


A
Changes in Metabolic Capacity
CYP3A4
CYP1A2
Percentage of Adult Activity
180
160
140
120
100
80
60
40
20
0


E
Integumentary Development
Thickness
nt
Adult

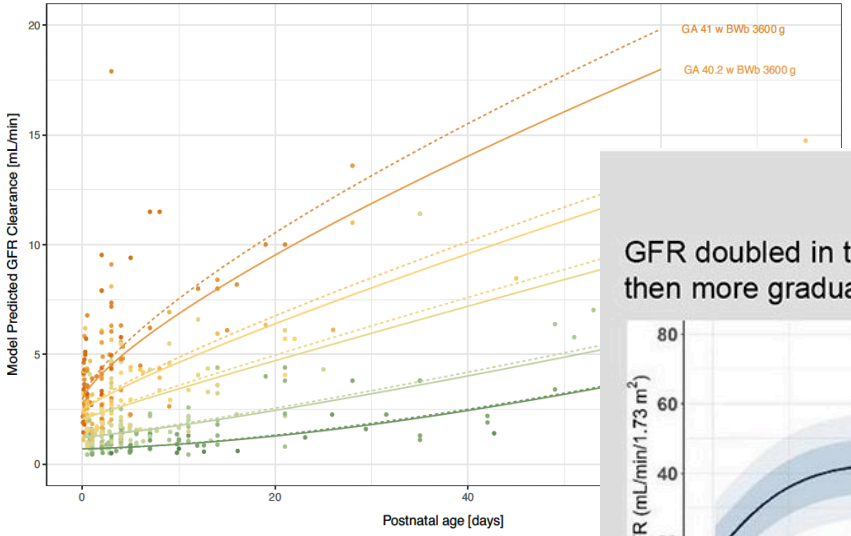

B
Dev
Percentage of Total Body Weight
100
80
60
40
20
0


D
Acquisition of Renal Function
Para-aminohippuric Acid Clearance (ml/min/1.73 m²)
800
600
400
200
0
Glomerular filtration
Para-aminohippuric acid
160
120
80
40
0
Glomerular Filtration Rate (ml/min/1.73 m²)
1–2 days
2–4 wk
2 mo
6 mo
1 yr
2 yr
6 yr
12 yr
Age


Percen
50
0
Birth
1 wk
2 wk
3 wk
1 mo
3 mo
1–3 yr
4–6 yr
5–10 yr
Adult
Age

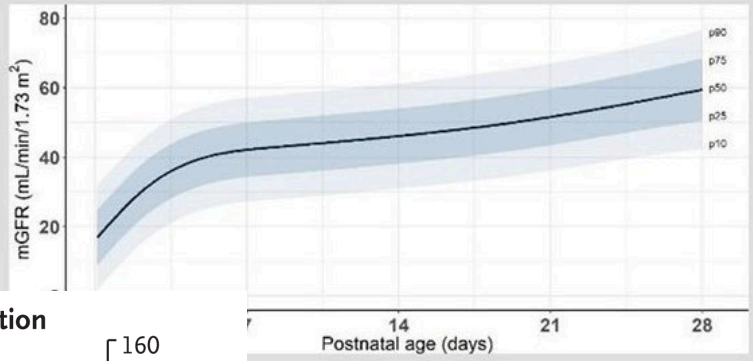
Kearn
NEJM

GFR maturation equation?

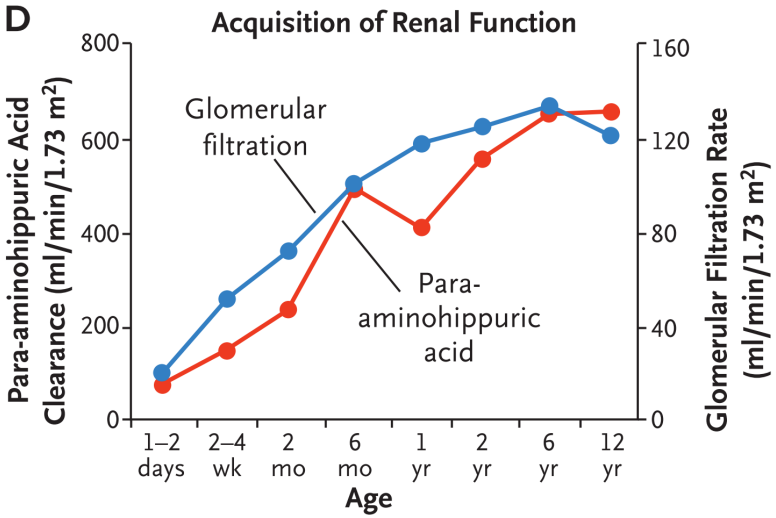


OUTCOME

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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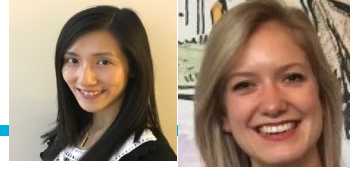
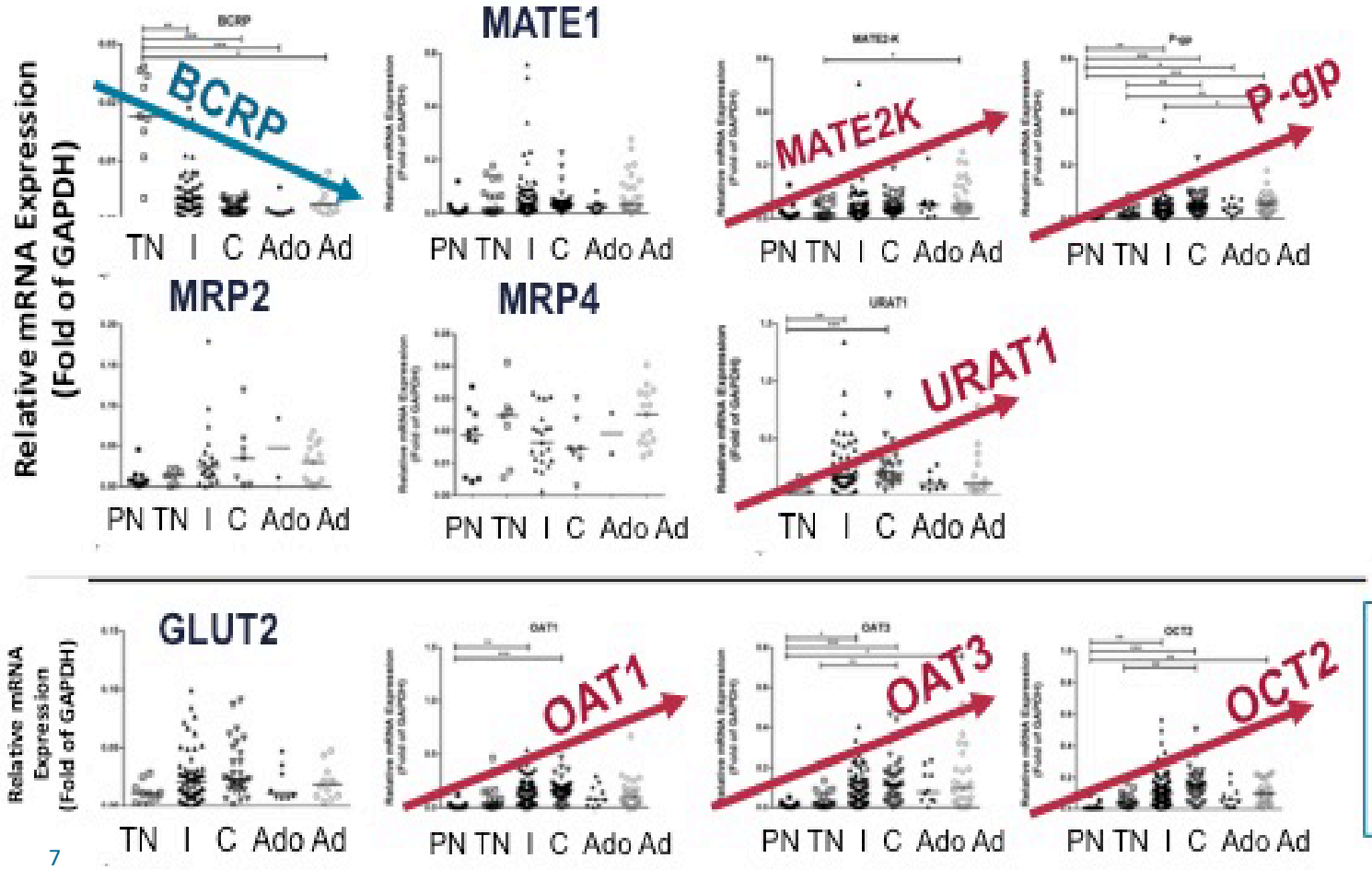
Smeets N et al, J Am Soc Nephrol. 2022 1277-1292, Wu et al, The AAPS Journal (2022) 24: 38

Renal transporter specific maturation

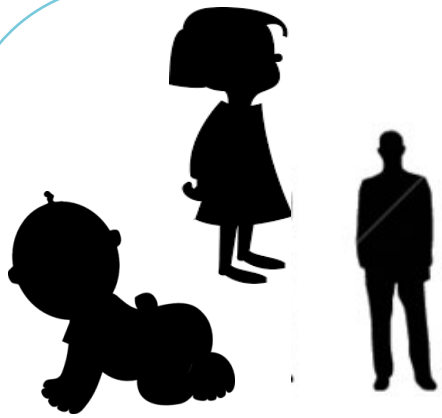


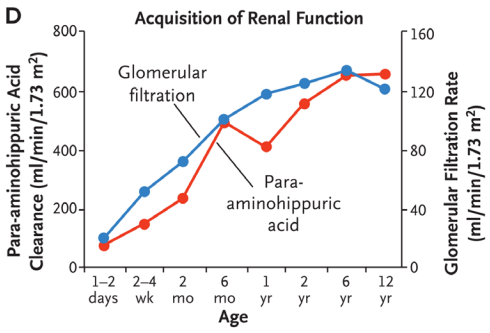
Transcript levels of 7 out of 11 transporters showed age-dependent changes

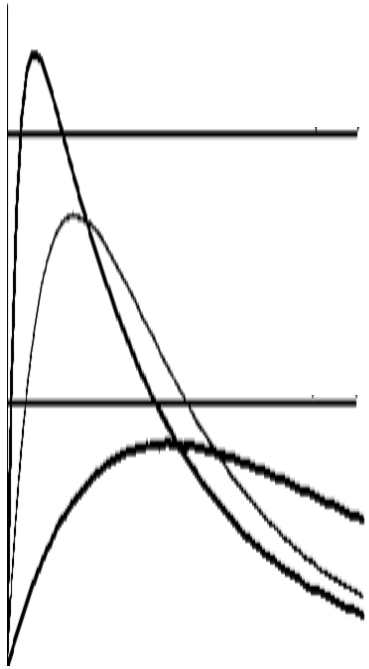


Cheung, van Groen et al, Clin Pharmacol Ther. 2019 Nov;106(5):1083-1092

Interplay of age and renal insufficiency?







NephroDose project

Aim: **provide pediatric drug doses for renal insufficiency**

Drug selection: if RI dosing information in Royal Dutch Pharmacy Association reference handboook + Listed in Dutch Pediatric Formulary (n=68)

Pubmed searches showed hardly any data

Adjusted pragmatic approach:
Elimination pathway similar?
Adjusted pediatric dosing proportional based on adult advice

www.kinderformularium.nl

Kinderformularium

Pharmacokinetics in children with CKD

Pediatric Nephrology (2020) 35:1153–1172
https://doi.org/10.1007/s00467-019-04304-9

REVIEW

Pharmacokinetics in children with chronic kidney disease

Anne M. Schijvens[1] · Saskia N. de Wildt[2,3] · Michiel F. Schreuder[1]

Received: 28 March 2019 / Revised: 26 June 2019 / Accepted: 2 July 2019 / Published online: 2 August 2019
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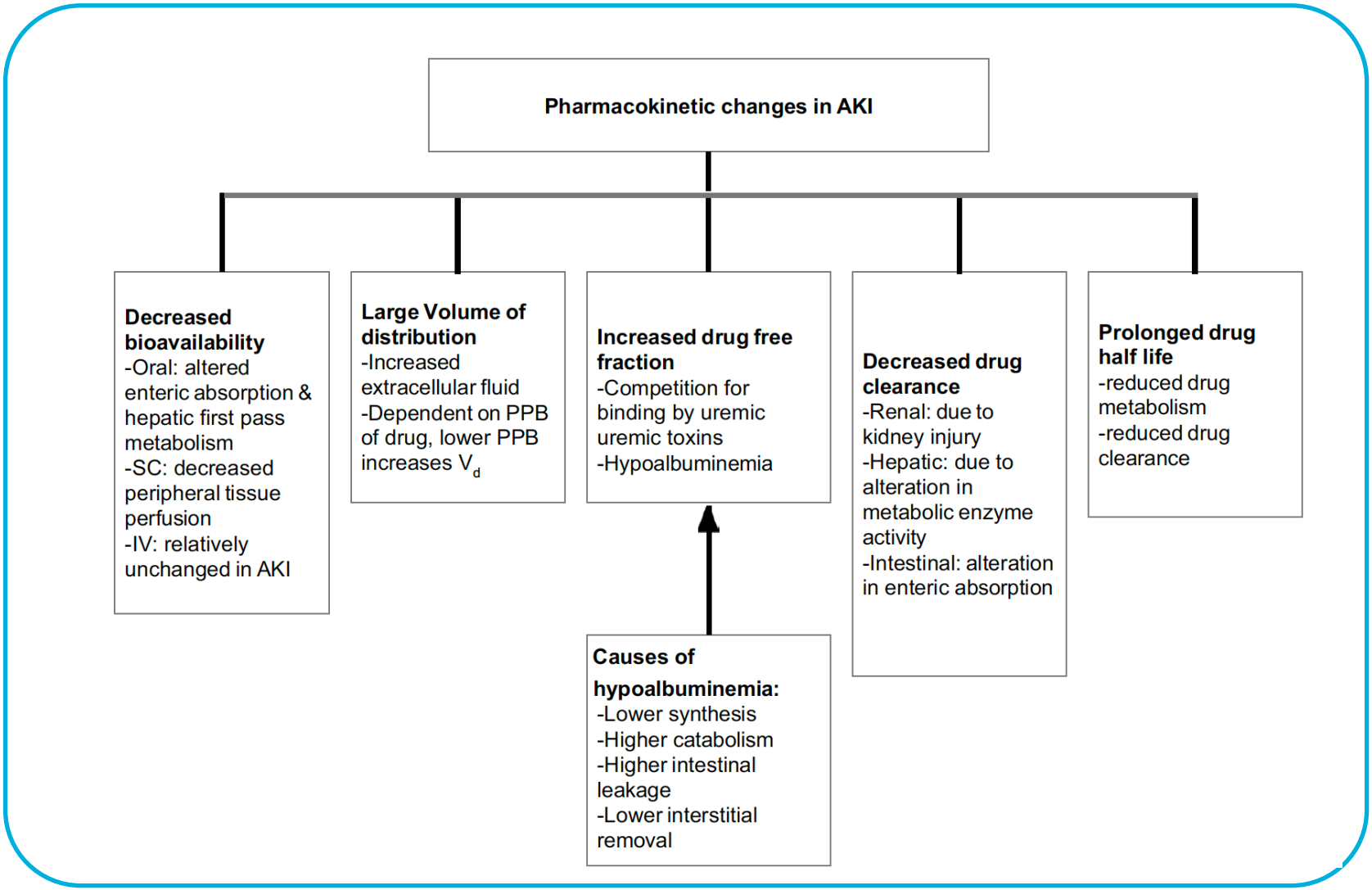
Abstract
In children, the main causes of chronic kidney disease (CKD) are congenital diseases and glomerular disorders. CKD is associated with multiple physiological changes and may therefore influence various pharmacokinetic (PK) parameters. A well-

Very limited PK data from children with CKD

Dose advice based on extrapolation from adults, taking RI associated PK mechanisms into account

Impact of AKI on PK



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Raina et al Ped Drugs 2023: 425-442

Pharmacokinetics in ICU children with AKI

Pediatric Drugs (2023) 25:425–442
https://doi.org/10.1007/s40272-023-00572-z

REVIEW ARTICLE

Check for updates

Pharmacokinetics in Critically Ill Children with Acute Kidney Injury

Manan Raina[1] · Amani Ashraf[2] · Anvitha Soundararajan[3] · Anusree Krishna Mandal[4] · Sidharth Kumar Sethi[5]

Renal insufficiency
Hemodialysis, Peritoneal dialysis, ECMO

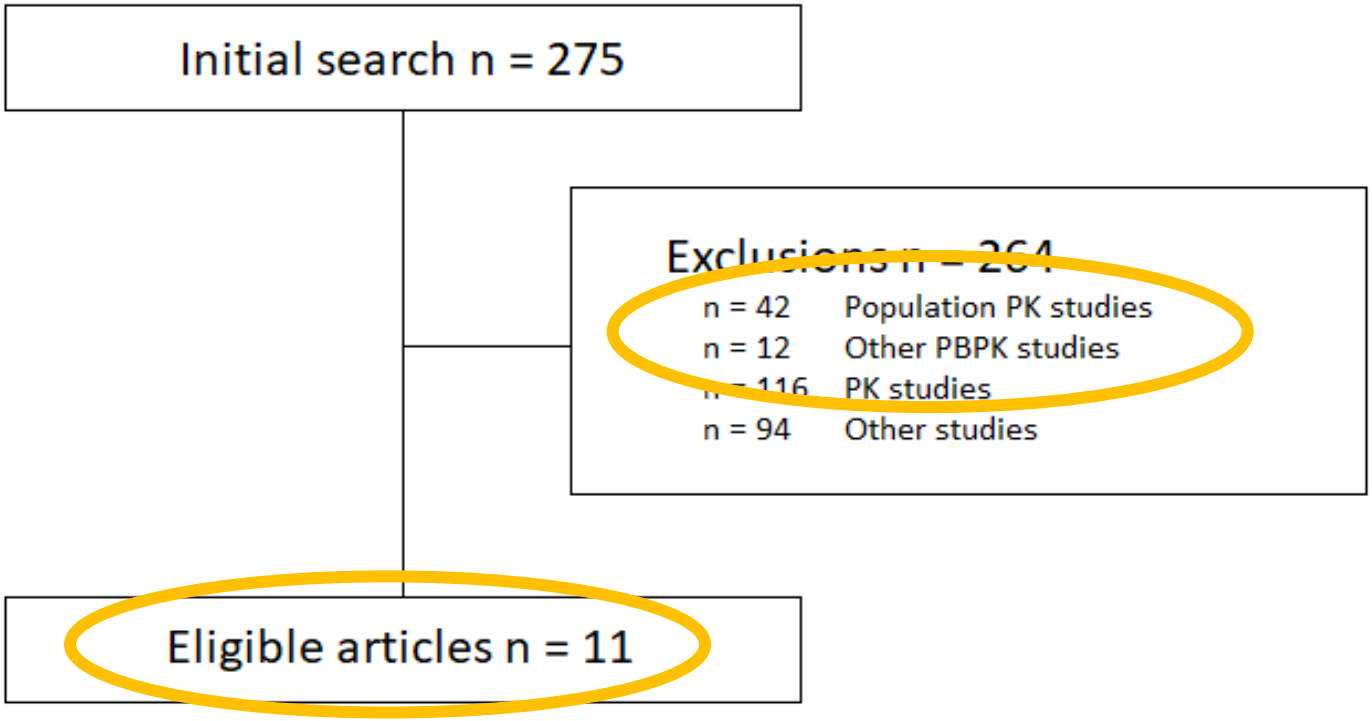
Very limited data on the impact of renal insuffiency and dialysis modalities on PK of drugs in critically ill children
Little dosing advices

Can we predict a dose with modeling?

Systems data	Trial design	Drug data
	Dose Administration route Frequency Co-administered drugs Populations No of male/female	

Physiologically-based pharmacokinetic model

Pediatric renal insufficiency PBPK papers?



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Manuscript in preparation

Take home message

- Age impacts drug disposition, but the interplay of age and renal insufficiency has not been elucidated
- Little dosing guidance available
- But: did we look close enough?
    - Role of popPK and PBPK studies?

Acknowledgements

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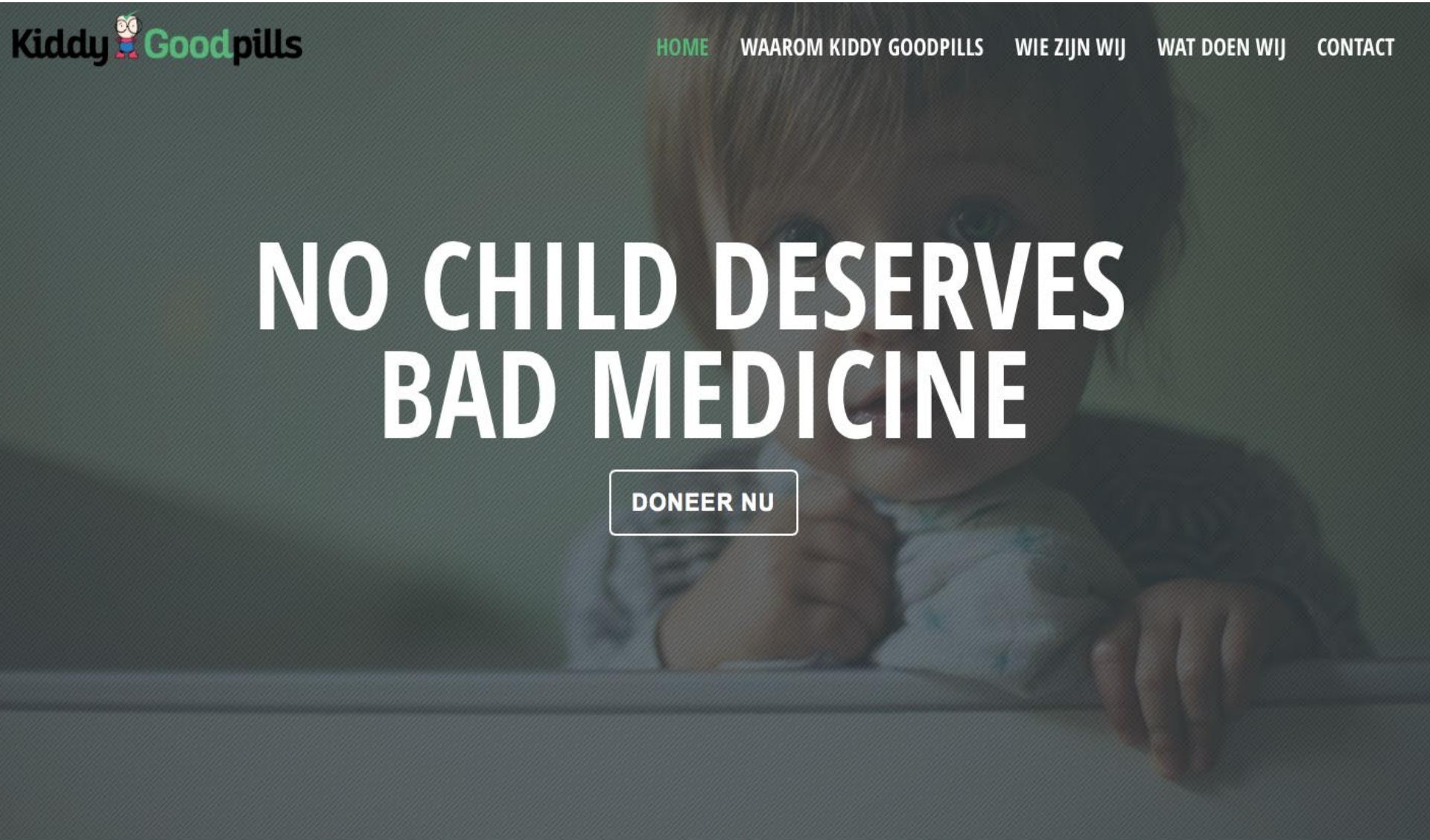
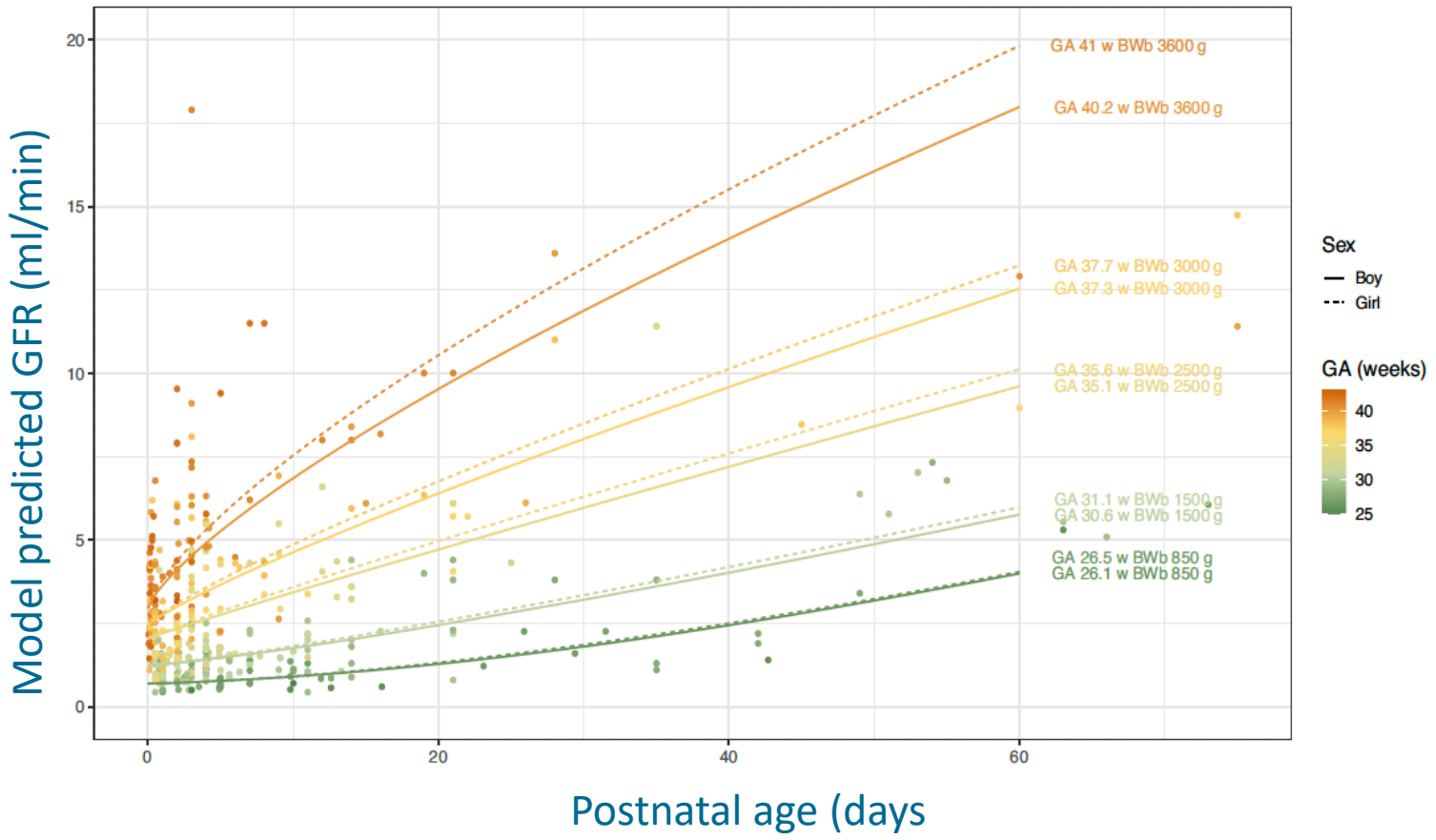
Kathy Cheung
Kathy Giacomini

FDA
Shu-Mei Huang

Questions?


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

GFR maturation using inulin in preterms



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Wu et al, The AAPS Journal (2022) 24: 38

What is GFR reference value in term infants?

Maturation of Glomerular Filtration Rate in Term-Born Neonates: An Individual Participant Data Meta-Analysis

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

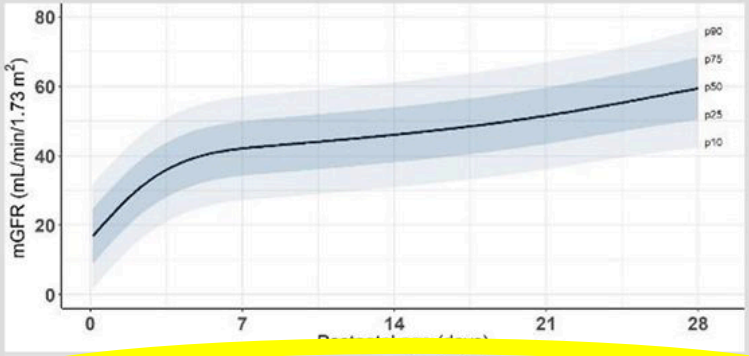
METHODS

- Individual participant data meta-analysis
- 48 studies, 881 neonates
- Definition of GFR reference values
- Update of Schwartz coefficient

eGFR(ml/min/1.73m2)=(k*height (cm))/serum creatinine(mg/dl)

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.



A coefficient of 0.31 led to accurate eGFR determination.

Conclusion
Our mGFR reference values and updated coefficient for the Schwartz equation can help to identify altered GFR in term-born neonates.

doi: 10.1681/ASN.2021101326

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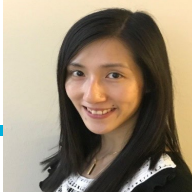
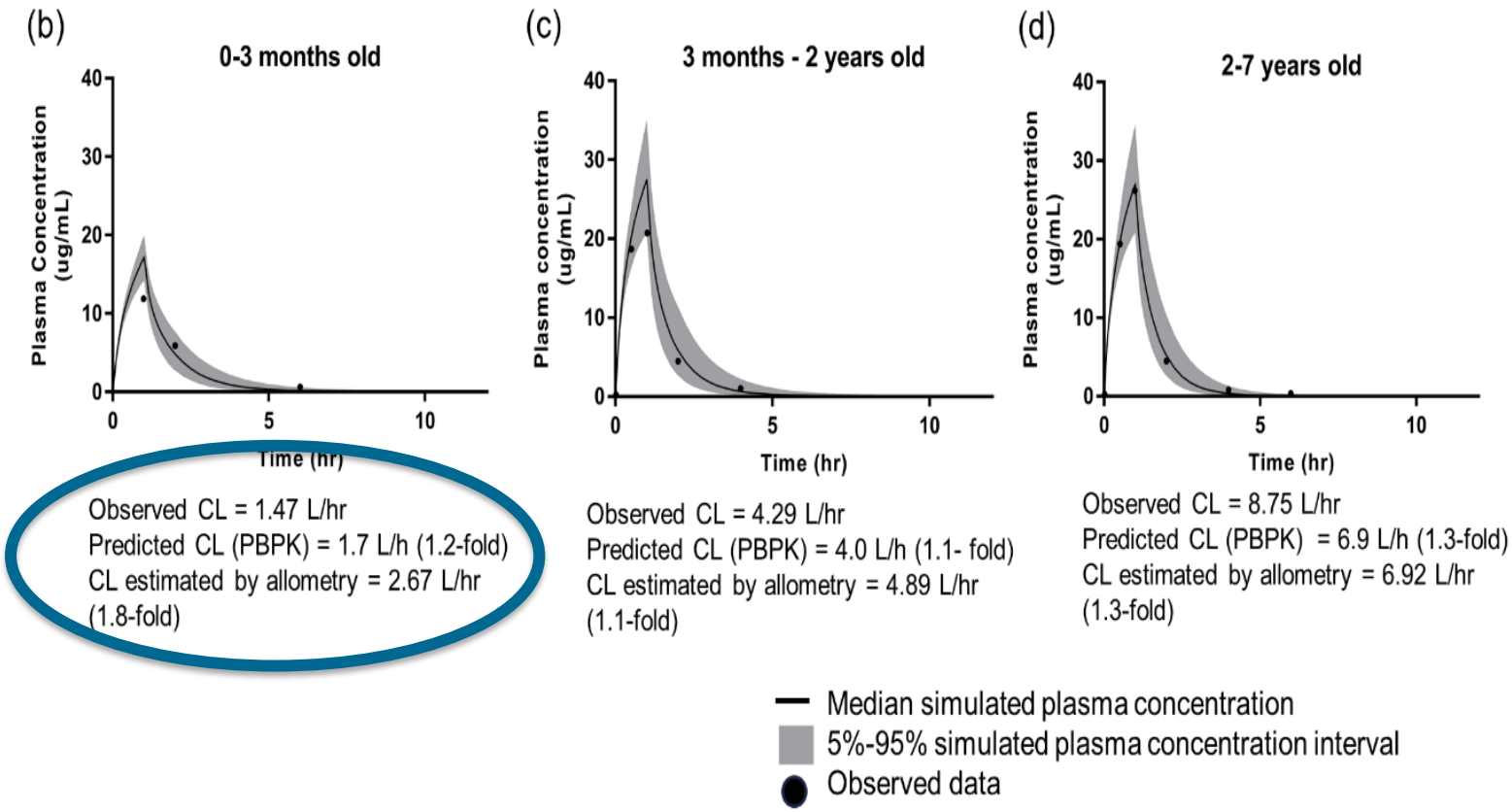
Smeets N et al, J Am Soc Nephrol. 2022 Jul;33(7):1277-1292

Pediatric kidney PBPK model - tazobactam





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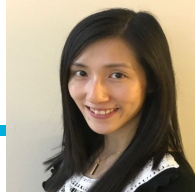
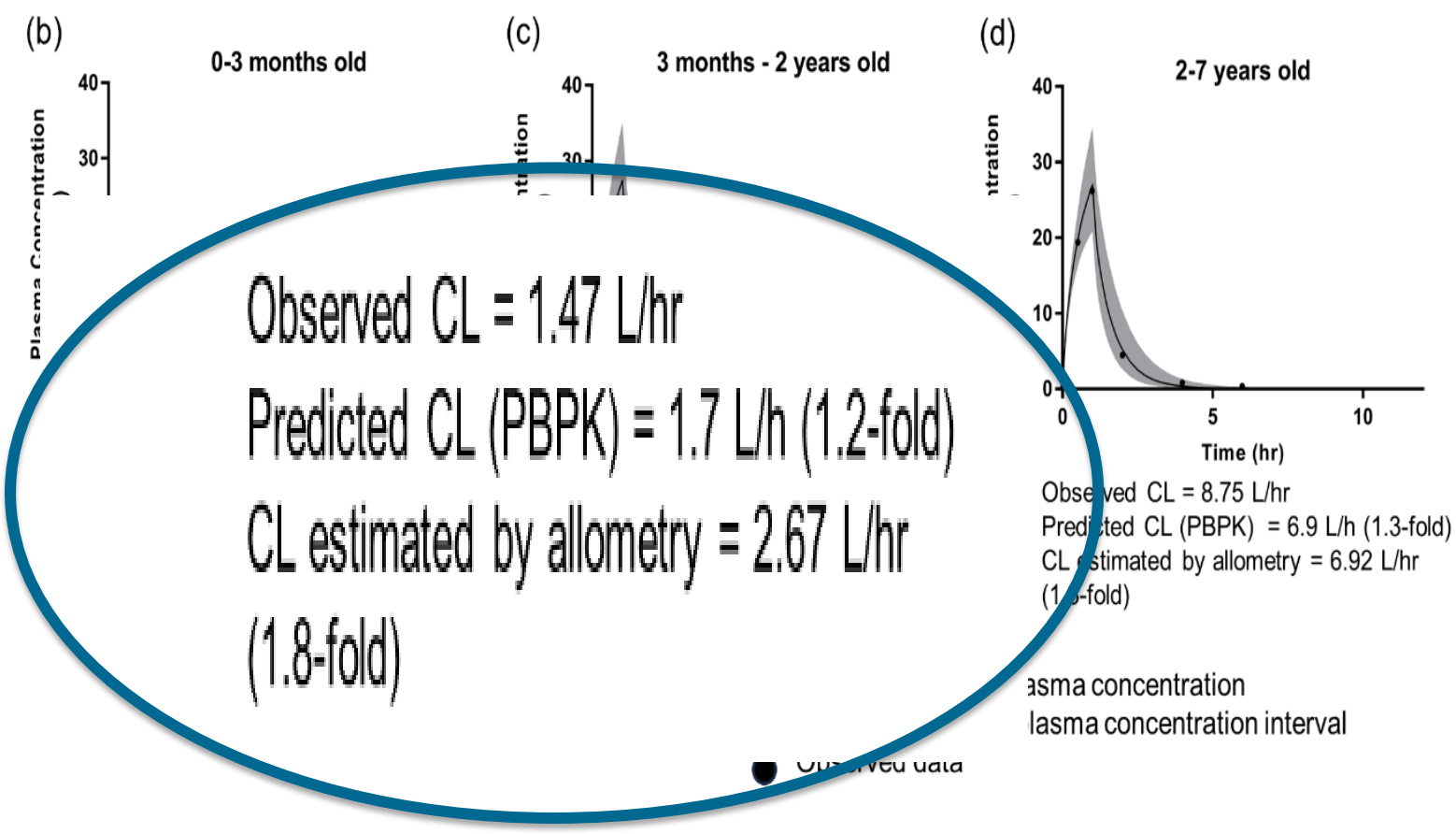
Cheung et al, J Clin Pharm, 2019 Sep;59 Suppl 1(Suppl 1):S56-S69

Pediatric kidney PBPK model - tazobactam





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Cheung et al, J Clin Pharm, 2019 Sep;59 Suppl 1(Suppl 1):S56-S69