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Considerations for Modeling & Simulation for Pediatric Renal Impairment

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Disclaimer & Disclosure

- The ideas presented represent the speaker's opinion. They do not represent official FDA policy or guidance.

- There are no financial conflicts of interest to disclose

Common Questions of Modeling & Applications for Renal Impairment

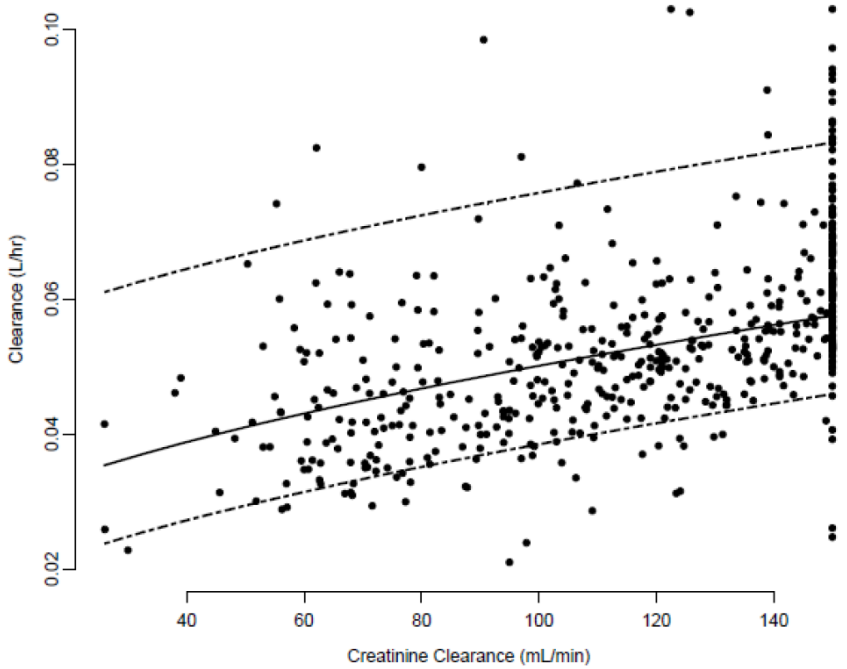
- What dose should we administer to the patient?
- Do we have CL for all the relevant populations characterized?
- Can we infer how CL or AUC will change for higher degress of renal insufficiency (e.g. moderate and severe renal impairment)?
- Do ontogeny considerations apply the same way in pediatric renal impairment?
- How do we label PK for the youngest kids who are not studied?
- Does Renal Impairment Impact Exposure-Response?

Population PK Estimation of Total Drug CL

$$CL_i = f\left(WT_i, GFR_i, PMA_i, \eta_i, \dots\right)$$

$$CL_i = \left(\frac{eGFR_i}{87.6}\right)^{\theta} \cdot e^{(\eta_i)}$$

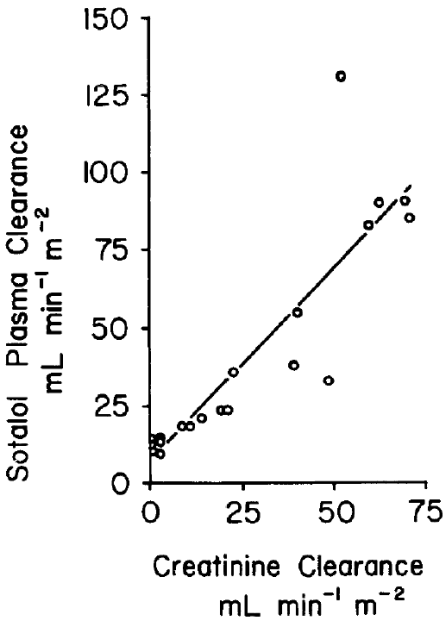
$$CL_i = (CL_{H+}CL_R) \cdot e^{(\eta_i)}$$



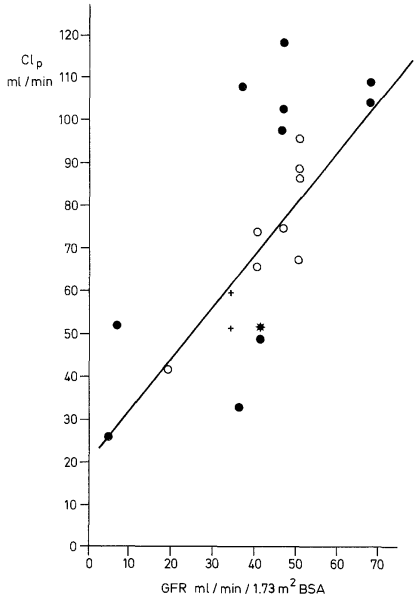
$$CL = \left(\theta_1 \cdot \frac{ALB}{3.6}^{\theta_8} \cdot \frac{BSA}{2.05}^{\theta_9} \cdot \theta_{10}^{SEX} + \theta_2 \cdot \frac{CRCL}{100}^{\theta_{11}}\right) \cdot \exp(\eta_1)$$

Is Clearance Linearly Related to eGFR?

Sotalol

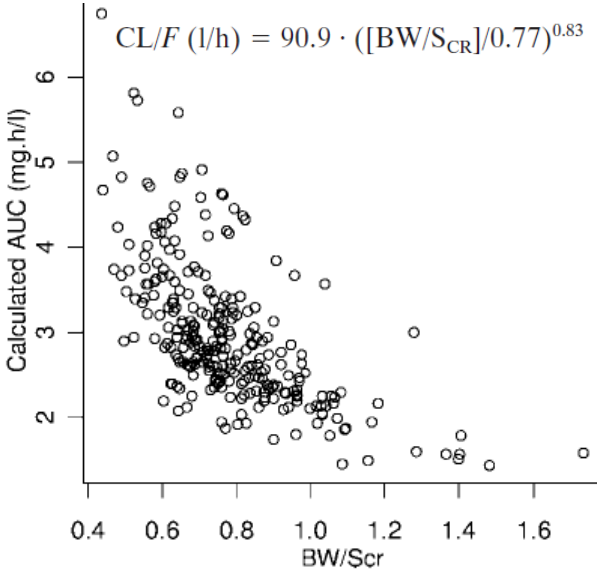


A.D. Blair (1981)



G. Berglund et al. Sotalol Kinetics in Renal Failure (1980)

Tenofovir



V. Jullien et al. (2005)

Guidance for Industry

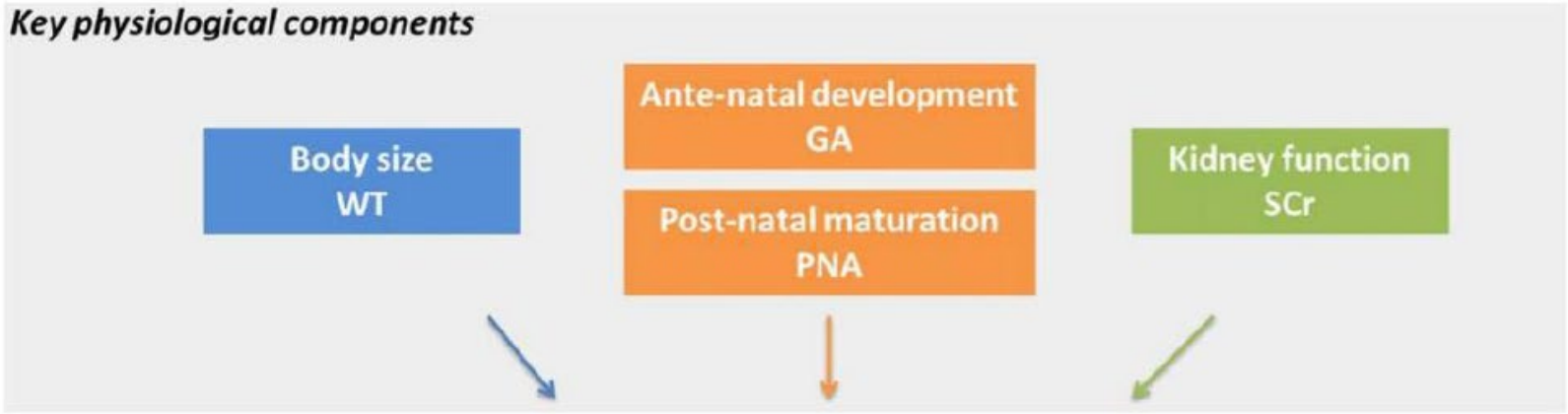
Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing

Considerations for Modeling

- Sufficient Data to Inform the Model:
  - Numbers of patients of range of renal function
  - Accurate dosing, dialysis, and sampling records
  - Sufficient samples per patient
  - Active Metabolite Concentrations
  - Common eGFR metric (across studies)
- What is the “best” equation for pediatric eGFR?

https://www.fda.gov/media/78573/download

Population PK for Pediatrics w Renal Elimination



$$CL = \mathrm{CL}_{\mathrm{standard}} \times F_{size} \times F_{maturation} \times F_{kidney}$$

???

$$F_{size} = \frac{WT}{WT_{std}}^{0.75}$$

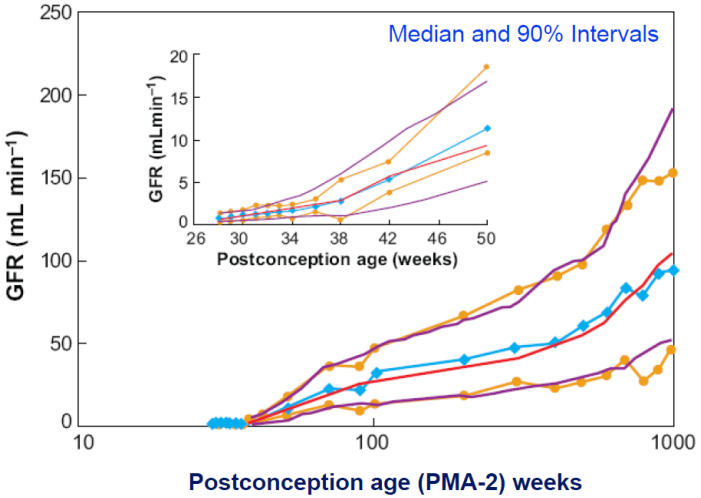
$$F_{maturation} = \frac{PMA^{Hill}}{TM50^{Hill} + PMA^{Hill}}$$

$$F_{kidney} = \frac{GFR_{actual}}{GFR_{std}}^{PWR}$$

Slide adapted from Jian Wang, PhD
https://www.fda.gov/media/128354/download

GFR Size & Maturation

Characteristics of the study	Study							
	1	2	3	4	5	6	7	8
Method	Cr-EDTA	Cr-EDTA	Mannitol	Inulin	Inulin	Cr-EDTA	Iohexol	Sinistrin
Number	185	347	63	39	56	111	85	37
Mean PMA (range)	384 weeks (87–1652)	655 weeks (48–1461)	144 weeks (40–608)	33 weeks (28–42)	32 weeks (27–42)	762 weeks (113–1226)	581 weeks (57–924)	30 weeks (26–36)



928 patients
26 weeks PMA to 32 y

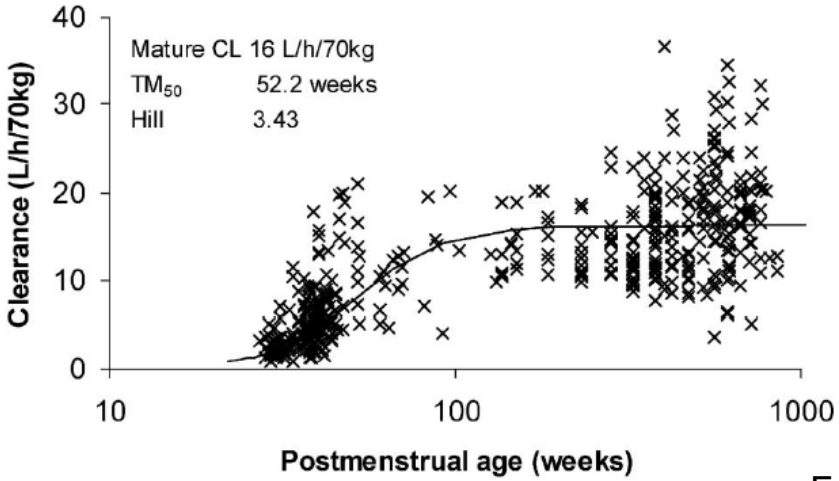
CLmax= 121 mL/min/70kg
TM50 = 48 weeks PMA
Hill = 3.4

PNWT > FFM > WT
to describe size and GFR

Rhodin MM et al. Pediatr Nephrol. 24 (1): 67–76 (2009).

Anderson Renal Maturation Model

$$CL = CL_{mat} \cdot \left(\frac{WT}{WT_{Std}} \right)^{\theta 1} \left(\frac{PMA^{HILL}}{TM50^{HILL} + PMA^{HILL}} \right)$$



Parameter	Separate Hill coefficient for GFR and paracetamol	95%CI*	Common Hill coefficient for GFR and paracetamol	95%CI*
Hill GFR	3.40	3.0–3.8		
Hill paracetamol	3.43	3.19–3.96	3.4	3.08–3.61
Hill morphine	3.92	3.25–4.40	3.83	3.43–4.17
TM_{50} GFR (weeks)	47.7	45.1–50.5	47.6	46.0–49.9
TM_{50} paracetamol (weeks)	52.2	49.8–54.1	50.1	49.4–54.5
TM_{50} morphine (weeks)	54.2	50.3–60.5	54.6	49.7–57.2

* = Confidence intervals from 250 non-parametric bootstrap runs

For Test Simulation Hill =3.4, TM_{50}=52 Weeks

Anderson BJ and Holford NHG, Drug Metab. Pharmacokinet. 24 (1): 25–36 (2009).

Estimating GFR for Children

Serum Creatinine Based Equations

Table 1. SCr-Based GFR-Estimating Equations Derived from Pediatric Patients*

References	Equations	Age Range, yr (No. of Patients)	Health Status	SCr Assay
Schwartz[19]	eGFR = 0.55 × Ht/SCr	0.5–20 (186)	CKD	Jaffe
Schwartz[20]	eGFR = 0.45 × Ht/SCr	PNA: 0.013–1 GA: term (137)	Healthy	Jaffe
Brion[21]	eGFR = k × Ht/SCr k = 0.33 (preterm), k = 0.45 (term infants)	PNA: 0–0.1 GA: 25–42 wks (202)	Well baby/ NICU	Jaffe
Modified ("bedside") Schwartz[22]	eGFR = k × Ht/SCr k = 0.413	1–16 (349)	CKD	Enzymatic
Counahan[23]	eGFR = k × Ht/SCr k = 0.43	0.167–14 (103)	CKD	Jaffe
Flanders metadata[24]	eGFR = k × Ht/SCr k = 0.0414 × ln[age] + 0.3018	0.083–14 (6734 SCr measurement)	Healthy	Enzymatic
Léger[26]	eGFR = (56.7 × Wt + 0.142 × Ht^2)/SCr	0.8–18 (64)	CKD/Tx	Jaffe
British Columbia Children's 1 (BCCH1)[27]	ln(eGFR) = 1.18 + (0.0016 × Wt) + (0.01 × Ht) + (149.5/SCr) − (2141/SCr^2)	1–19 (266)	CKD	Enzymatic
British Columbia Children's 2 (BCCH2)[27]	eGFR = −61.56 + [5886 × (1/ SCr)] + [4.83 × age (yr)] + 10.02 (if male)	1–19 (266)	CKD	Enzymatic

Cystatin C Based Equations

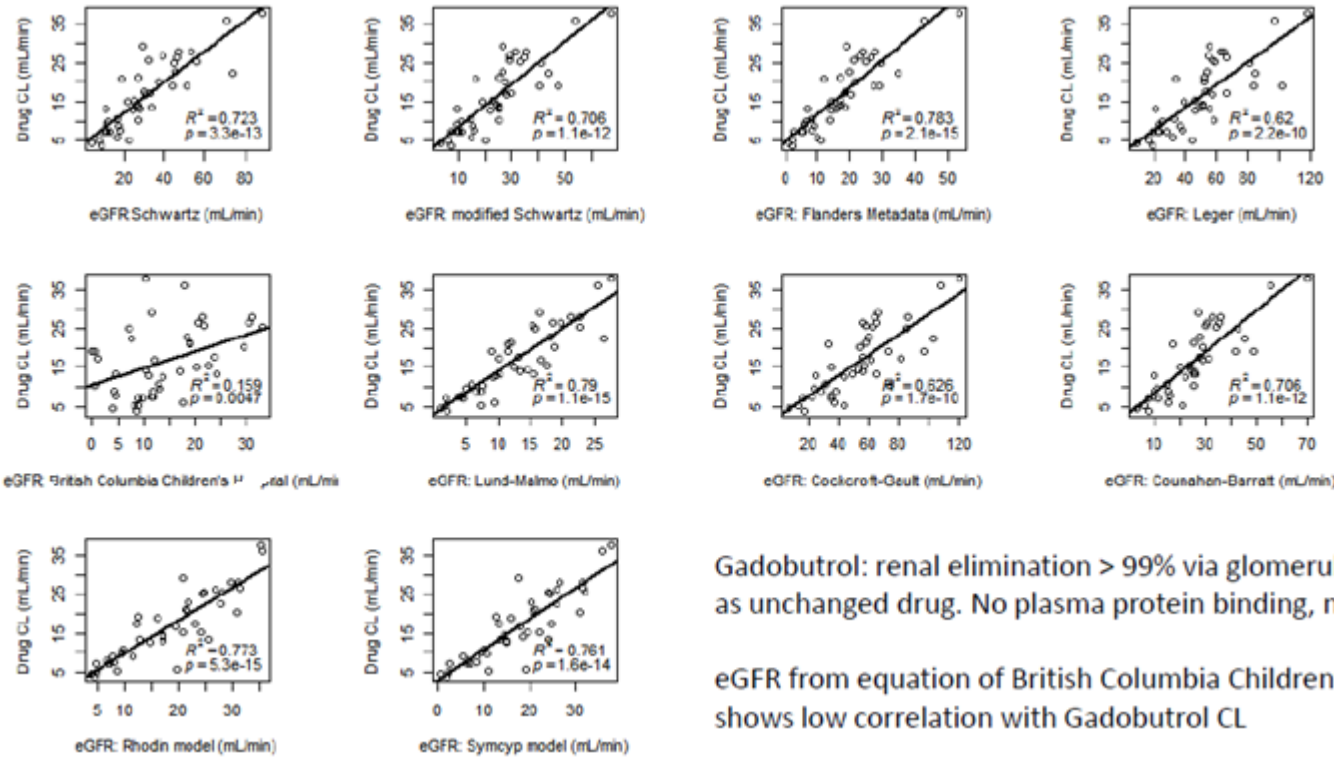
Table 2. CysC-Based GFR-Estimating Equations Derived from Pediatric Patients

References	Equations	Age (range, yr) Patient No.	Health Status	Assay
Filler[30]	$eGFR = 91.62 \times (CysC)^{-1.123}$	1–18 N = 536	CKD, Tx	Neph
Grubb[31]	$eGFR = 84.69 \times (CysC)^{-1.680} \times 1.384^{\text{if <14 yr}}$	0.3–18 N = 85	CKD	Turb
Zappitelli[32]	$eGFR = 75.94/(CysC)^{1.17} \times 1.2^{\text{if Tx}}$ $eGFR = (43.82 \times e^{0.003 \times Ht})/(CysC^{0.635} \times SCr^{0.547})$	8–17 N = 103	CKD, Tx, spina bifida	Neph (SCr enzymatic)
Bouvet[34]	$eGFR\ (mL/min) = 63.2 \times (SCr/1.086)^{-0.35} \times (CysC/1.2)^{-0.56} \times (Wt/45)^{0.30} \times (age/14)^{0.40}$	1.4–22.8 N = 100	CKD	Neph (SCr Jaffe)
Schwartz[35]	$eGFR = 39.8\ [Ht/SCr]^{0.456} \times [1.8/CysC]^{0.418} \times [30/BUN]^{0.079} \times [1.076]^{male} \times [Ht/1.4]^{0.179}$	1–16 N = 349	CKD	Neph

Muhari-Stark E, Burckart GJ. (2018)

Population PK Evaluation of eGFR Equations

Gadobutrol CL



Gadobutrol: renal elimination > 99% via glomerular filtration as unchanged drug. No plasma protein binding, no metabolism

eGFR from equation of British Columbia Children's Hospital shows low correlation with Gadobutrol CL

Slide adapted from Jian Wang, PhD

https://www.fda.gov/media/128354/download

Summary & Present Challenges

- Current approaches to labeling have leveraged off existing data, yet we are challenged with how to label for more severe populations
- Waiting for data gives a quantitative certainty, yet the remaining population suffers from lack of dosing recommendations in the meantime
- Surveys of eGFR methods such as those by Wang et al help give confidence in predictions for specific molecules
- The variety of eGFR models established in the context of pediatric CKD support use in this specific disease state. Other disease states would benefit from such methods applied for their corresponding data.
- Extrapolation of impairment effect on CL may be reasonable for products that are completely renally eliminated
- There is work being done towards PBPK and QSP for such evaluations of renal function. Entertaining these methods deserves consideration in light of the high unmet medical need for children with renal insufficiency and the mechanistic considerations these methods bring forward.

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