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Pharmacometrics for better dosing in children

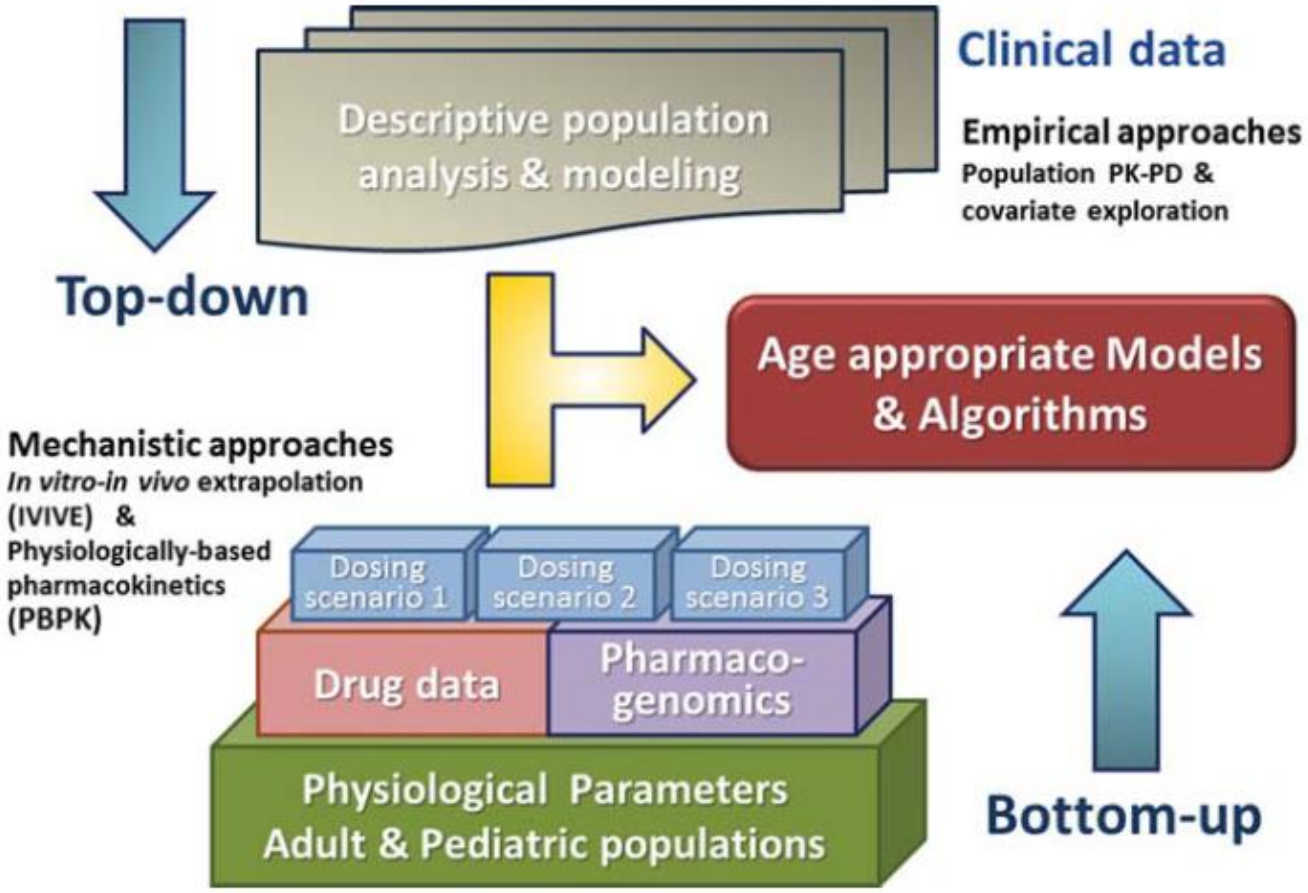
Pier Giorgio Cojutti

Alma Mater Studiorum – University of Bologna

Bologna, March 14th 2025

Modeling and Simulation in Pediatric Drug Therapy: Application of Pharmacometrics to Define the Right Dose for Children

Vinks AA et al. Clin Pharmacol Therap. 2015;98(3):298-308



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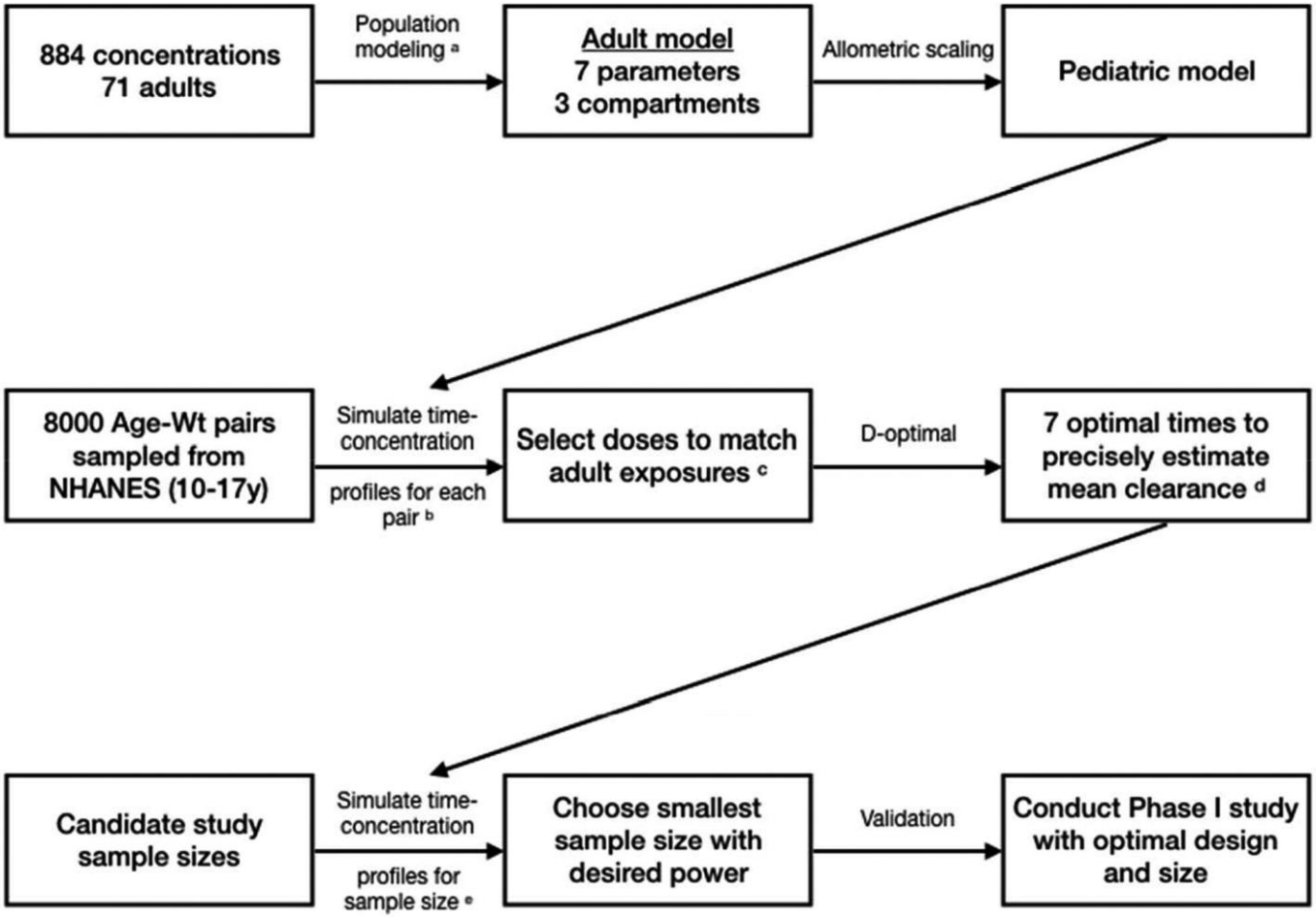
Modeling and Simulation Is Essential to Pediatric Clinical Pharmacology

Neely M et al. J Clin Pharmacol. 2018;58(S10):S73-85



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Selecting the proper pediatric dose: it is more than size that matters

Kearns GL. Clin Pharmacol Therp. 2015;98(3):238-40

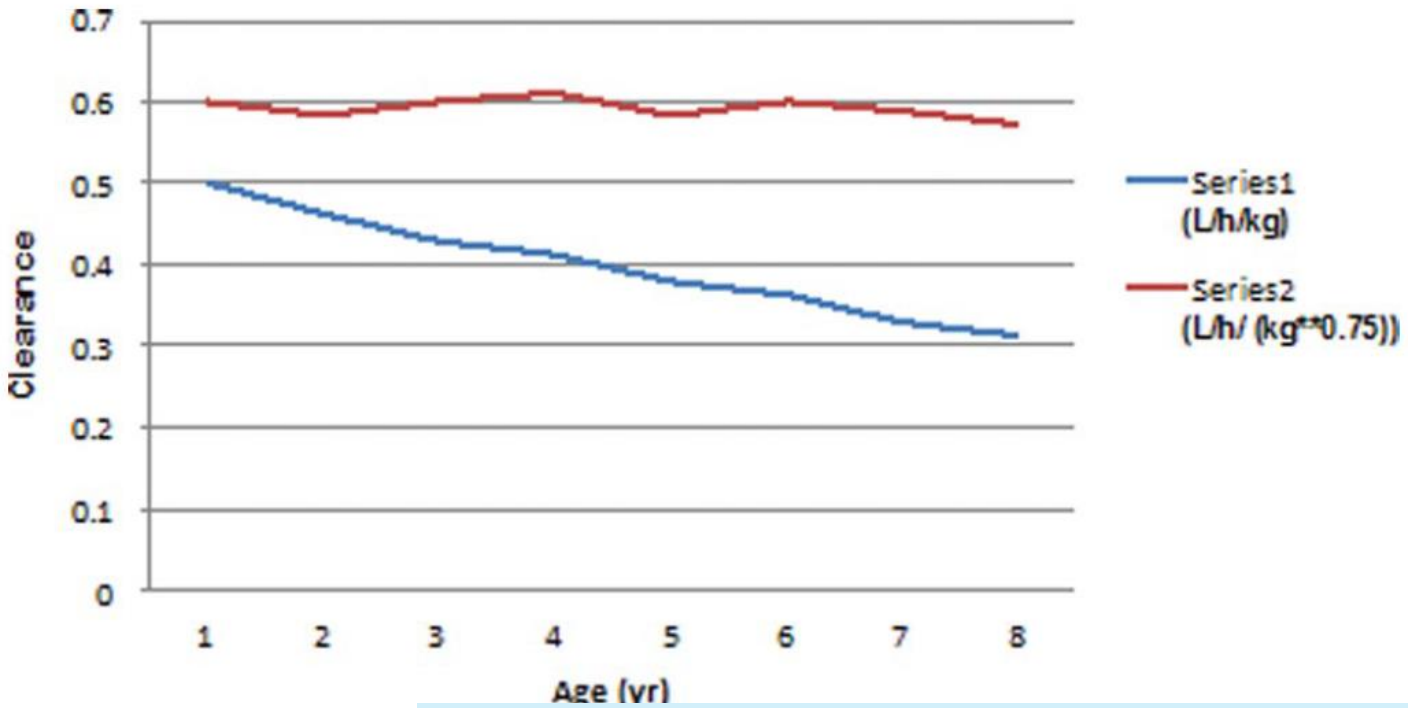
- THE CONUNDRUM OF AGE-APPROPRIATE DOSE SELECTION
  - drug action/response in sick children can be adequately predicted by data from adults
  - the pediatric population is homogenous

- ARE CHILDREN SIMPLY SMALL ADULTS? IT DEPENDS. . .
  - Allometric theory is true: the unit of ¾ (0.75) power of body weight (kg0.75) is a suitable unit of metabolic body size
  - Maturation factor+ organ function

Selecting the proper pediatric dose: it is more than size that matters

Kearns GL. Clin Pharmacol Therp. 2015;98(3):238-40

Impact of allometric scaling on the apparent relationship between oral clearance of a drug and age (when age is used as a developmental surrogate)



There are times, however, when the predictive accuracy of the best allometric model could be compromised.

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PK/PD evaluation of linezolid in hospitalized paediatric patients: a step toward dose optimization by means of therapeutic drug monitoring and Monte Carlo simulation

Cojutti P et al. J Antimicrob Chemother. 2015 Jan;70(1):198-206

Characteristics	Group 1 ($n=14$)	Group 2 ($n=9$)	P
General characteristics			
age (years), mean ± SD	4.9 ± 2.8	14.9 ± 1.3	<0.001
sex (male/female)	10/4	6/3	1.000
body weight (kg), mean ± SD	19.0 ± 9.5	57.2 ± 18.5	<0.001
body surface area (m^2), mean ± SD	0.71 ± 0.26	1.63 ± 0.30	<0.001
CL_{CR}[a] (mL/min), mean ± SD	3.38 ± 2.02	2.76 ± 1.69	0.223
Underlying disease, *n* (%)			
haematological malignancies	7 (50.0)	4 (44.4)	1.000
CNS neoplasia	4 (28.6)	0 (0.0)	0.127
cerebral abscess	1 (7.1)	0 (0.0)	1.000
hydrocephalus	1 (7.1)	1 (11.1)	1.000
cerebral venous thrombosis	1 (7.1)	0 (0.0)	1.000
polytrauma	0 (0.0)	3 (33.3)	0.047
cystic fibrosis	0 (0.0)	1 (11.1)	0.390
Main reason for linezolid, *n* (%)			
CNS infection	7 (50.0)	1 (11.1)	0.086
pneumonia	4 (28.6)	3 (33.3)	1.000
BSI	3 (21.4)	2 (22.2)	1.000
bone and joint infection	0 (0.0)	3 (33.3)	0.047
Microbiological isolate, *n* (%)			
MR-CoNS	5 (33.3)	5 (55.6)	0.403
MRSA	2 (13.3)	1 (11.1)	1.000
unidentified	8 (57.1)	3 (33.3)	0.423
Linezolid treatment			
duration of treatment (days), median (IQR)	15.7 (11–17.8)	11 (10–28)	0.975
dose/kg/day, median (IQR)	32.4 (30–36.4)	21.4 (15–28.6)	<0.001
route of administration (iv/os)	12/2	6/3	0.343
no. of instances of TDM, median (IQR)	2 (1–2.75)	2 (2–3)	0.570
C_{min} (mg/L), median (IQR)	2.57 (1.33–5.12)	2.90 (1.36–4.16)	0.759
AUC_{24} (mg·h/L), median (IQR)	240.35 (174.04–394.74)	298.68 (203.50–654.97)	0.106
Clinical outcome			
cured	9 (64.3)	5 (55.6)	1.000
improved	3 (21.4)	1 (11.1)	1.000
unchanged or failed	1 (7.1)	3 (33.3)	0.260
deceased for other causes	1 (7.1)	0 (0.0)	1.000

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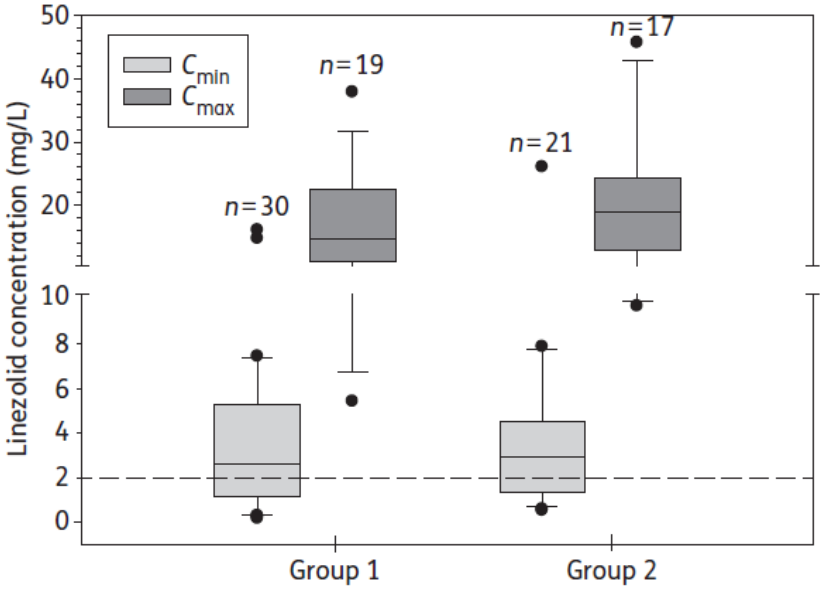
At first TDM (recommended age-based dosing regimens):

- Cmin was below the desired range in 50% of pts in Group1
- Cmin was below the desired range in 44% of pts in Group 2

- Cmin was above the desired range in only 1 pt in Group 2



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	Univariate analysis		Multivariate analysis	
Variable	unstandardized β-coefficient (95% CI)	*P*	unstandardized β-coefficient (95% CI)[a]	*P*
Age (years)	0.122 (−0.104, 0.348)	0.283		
Sex	−0.695 (−3.273, 1.883)	0.590		
Weight (kg)	0.001 (−0.055, 0.056)	0.983		
Body surface area (m^2)	0.293 (−2.117, 2.704)	0.808		
CL_{CR} (mL/min)[b]	−0.013 (−0.033, 0.007)	0.201		
Daily dose (mg/kg)	−0.045 (−0.183, 0.093)	0.518		
Co-treatment with:				
phenobarbital (6/51)	−2.384 (−6.275, 1.507)	0.200	−5.254 (−7.804, −2.704)	<0.001
dexamethasone (6/51)	−2.848 (−6.085, 0.389)	0.083		
rifampicin (1/51)	−3.461 (−12.587, 5.664)	0.450		
proton pump inhibitors (8/51)	3.137 (−0.244, 6.519)	0.068	5.695 (3.382, 8.008)	<0.001
calcium channel antagonists (6/51)	1.906 (−4.628, 8.440)	0.560		
amiodarone (2/51)	22.569 (16.066, 29.072)	<0.001	22.549 (17.462, 27.636)	<0.001

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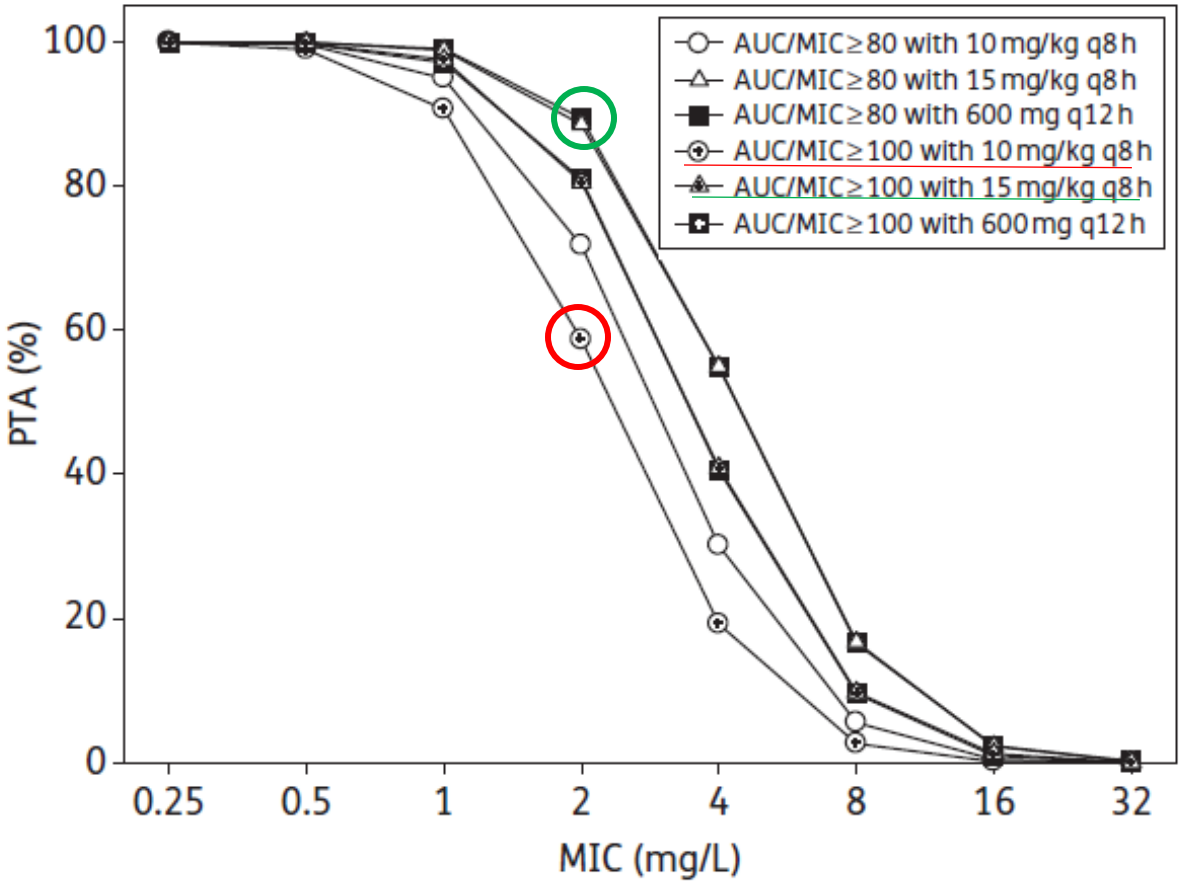

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Population pharmacokinetics of continuous-infusion ceftazidime in febrile neutropenic children undergoing HSCT: implications for target attainment for empirical treatment against *Pseudomonas aeruginosa*

Cojutti P et al. J Antimicrob Chemother. 2019;74(6):1648-55

Total number of patients	46
Age (years), median (IQR)	7.5 (4.0–12.0)
Male/female, *n*/*n*	29/17
Weight (kg), median (IQR)	25.0 (14.03–39.80)
Height (m), median (IQR)	1.20 (1.01–1.49)
Body surface area (m^2), median (IQR)	0.88 (0.64–1.34)
eGFR (mL/min/1.73 m^2), median (IQR)	200.0 (145.0–286.0)
Time from HSCT (days), median (IQR)	6.0 (1.0–11.75)
Type of haematological disease, *n* (%)	
ALL	22 (47.8)
AML	5 (10.9)
juvenile myelomonocytic leukaemia/CML	5 (10.9)
aplastic/Fanconi anaemia	4 (8.7)
neuroblastoma	3 (6.5)
congenital immunodeficiency disorders	3 (6.5)
sickle-cell anaemia	2 (4.35)
Ewing sarcoma	2 (4.35)
Ceftazidime treatment characteristics	
dose/kg/day (mg/kg), median (IQR)	145.98 (128.31–171.27)
C_{ss} (mg/L), median (IQR)	49.23 (36.81–62.88)
no. of TDM instances, median (IQR)	1.0 (1.0–2.0)
duration of treatment (days), median (IQR)	10.5 (7.0–16.0)
additional antibiotics, *n* (%)	
amikacin	38 (82.6)
teicoplanin	19 (41.3)
vancomycin	14 (30.4)
levofloxacin	13 (28.3)
tigecycline	5 (10.9)
metronidazole	3 (6.5)

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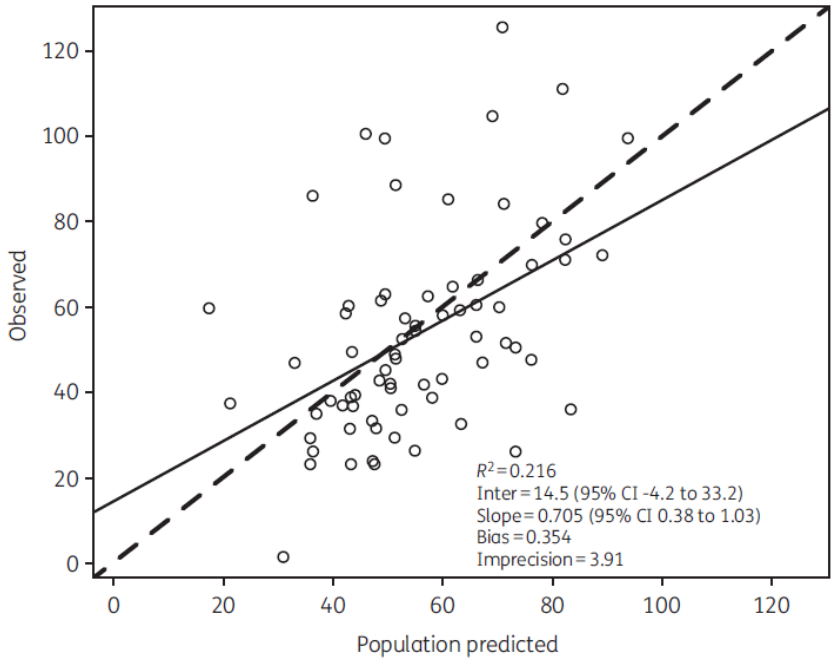

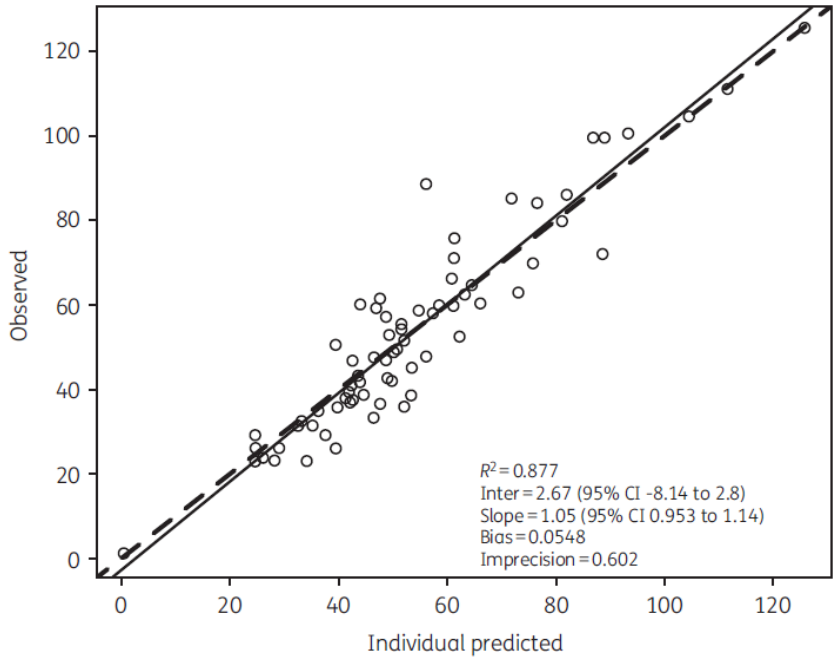

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Estimated glomerular filtration rate (eGFR) and body surface area were the covariates associated with drug clearance.

	Mean	Standard deviation	Coefficient of variation (%)	Median
$CL\ (L/h) = \theta_1 \cdot \left(\frac{\text{body surface area}}{0.88}\right)^{\theta_2} \cdot \left(\frac{\text{eGFR}}{200.5}\right)^{\theta_3}$				
θ_1	2.83	1.29	45.66	2.71
θ_2	0.68	0.37	54.31	0.84
θ_3	0.34	0.19	55.79	0.28
$V(L) = \theta_4 \cdot \left(\frac{\text{height}}{120}\right)^{\theta_5}$				
θ_4	33.95	32.09	94.52	25.89
θ_5	0.95	0.82	86.02	0.85
$k_{cp}\ (h^{-1})$	11.51	14.69	127.74	3.70
$k_{pc}\ (h^{-1})$	15.42	3.56	23.11	14.91

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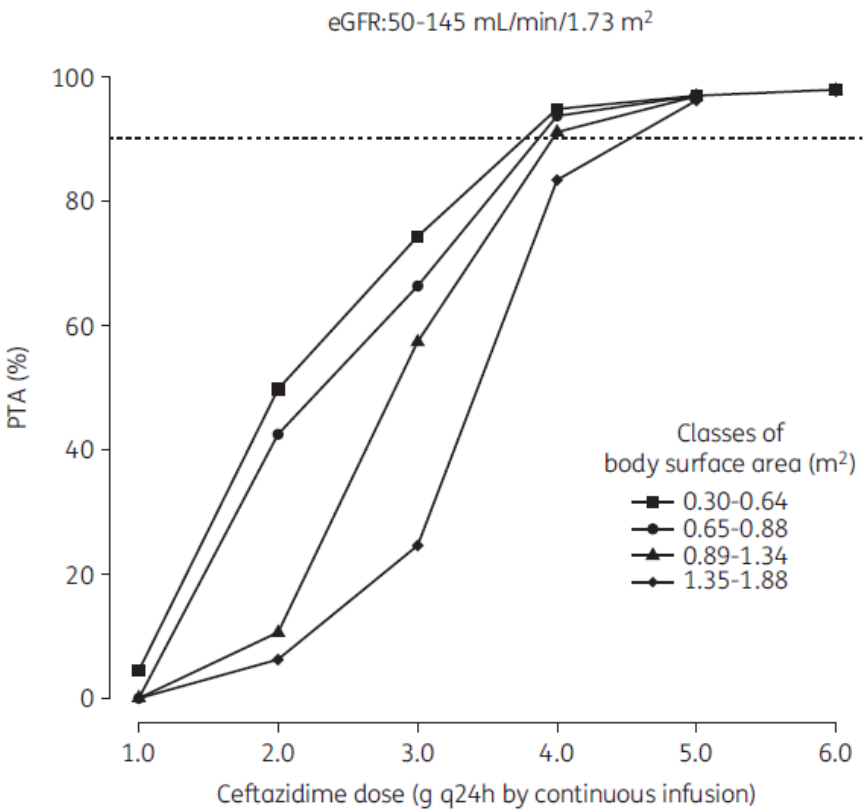

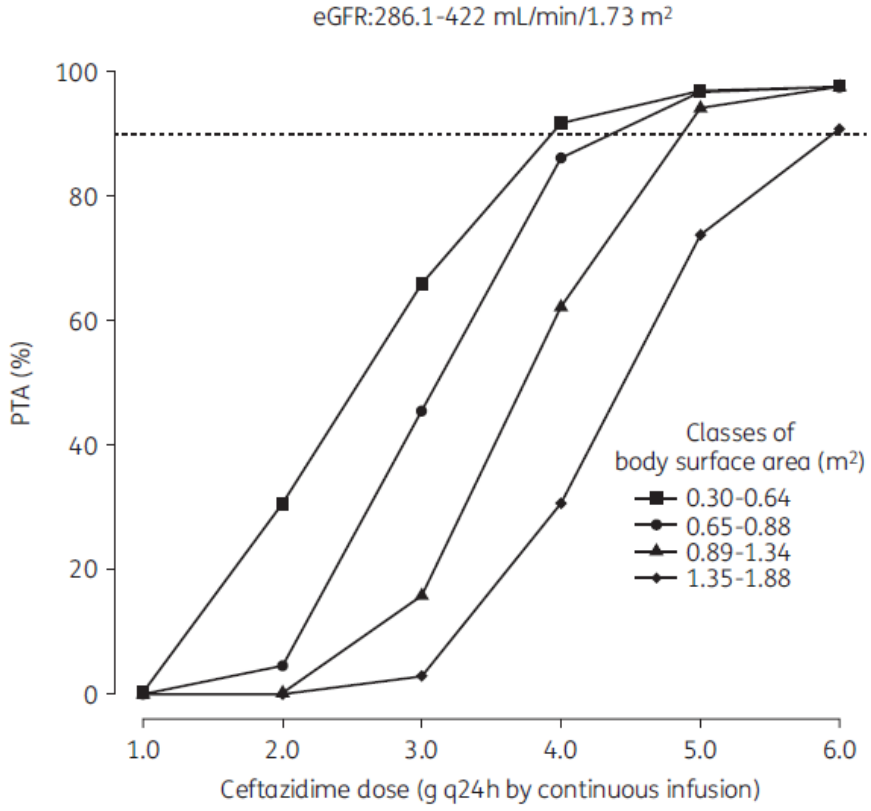

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	Body surface area (m^2)			
eGFR (mL/min/1.73 m^2)	0.30–0.64	0.65–0.88	0.89–1.34	1.35–1.84
50.0–145.0	3[a]	4	4	5
145.1–200.0	3[b]	4	5	5
200.1–286.0	4	4	5	6
286.1–422.0	4	5	5	6

Superscript letters identify suboptimal PTAs: [a]PTA <75% and [b]PTA <70%.

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EUCAST MIC Distribution

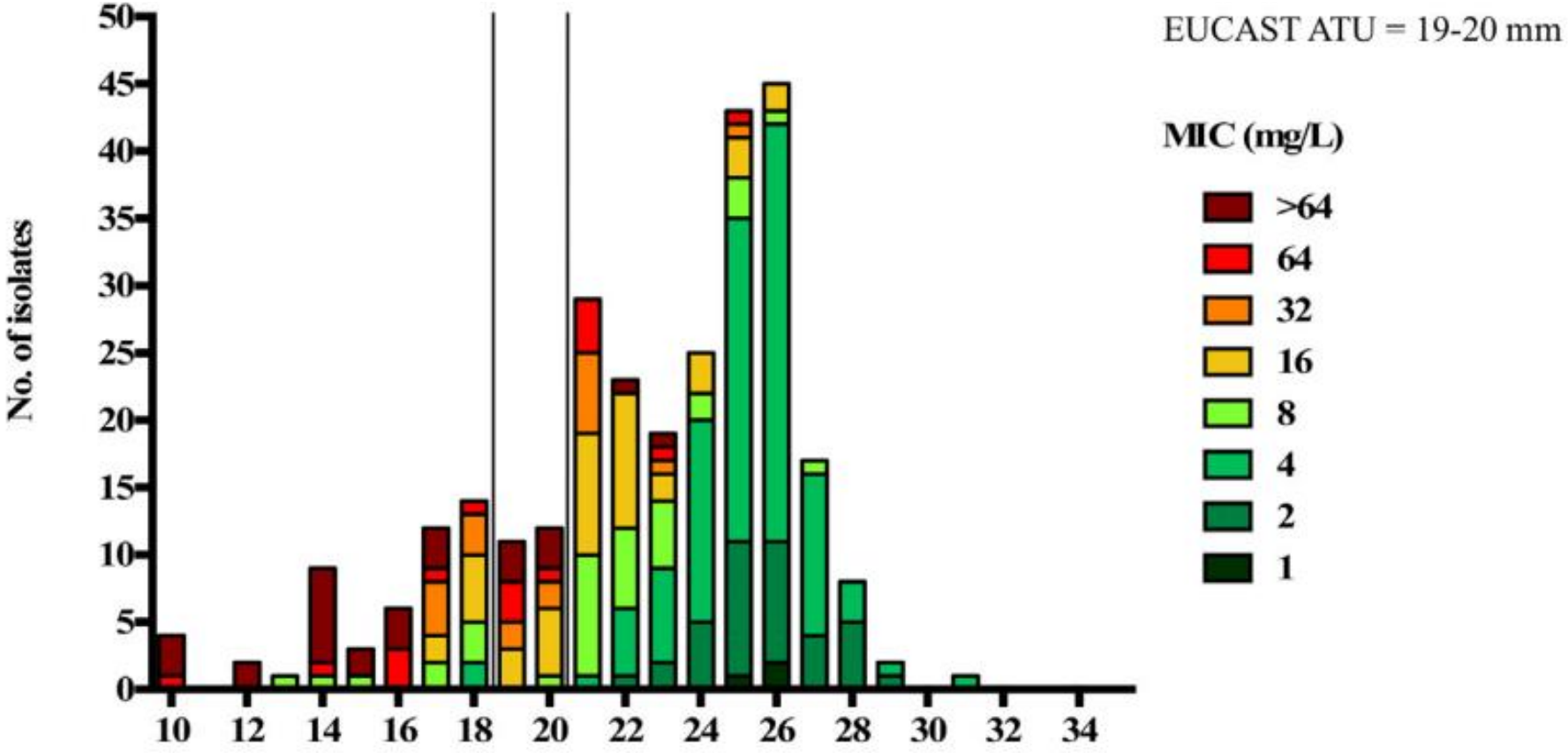

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Table 5. CFR with the advisable continuous-infusion ceftazidime dosages targeting C_{ss}/MIC ≥4 against *P. aeruginosa* in relation to the MIC distribution of EUCAST and that observed at our centre in HSCT children with high-risk FN in relation to classes of eGFR and body surface area

eGFR (mL/min/1.73 m^2)	Body surface area (m^2)	Ceftazidime dosage (g q24h)	CFR (%) according to EUCAST distribution	CFR (%) according to our local distribution
50.0–145.0	0.30–0.64	3	88.3	80.3
	0.65–0.88	4	90.2	81.8
	0.89–1.34	4	88.3	80.2
	1.35–1.84	5	88.9	80.7
145.1–200.0	0.30–0.64	3	87.1	79.4
	0.65–0.88	4	89.1	80.9
	0.89–1.34	5	89.2	80.9
	1.35–1.84	5	88.5	80.4
200.1–286.0	0.30–0.64	4	90.1	81.7
	0.65–0.88	4	88.2	80.2
	0.89–1.34	5	88.7	80.5
	1.35–1.84	6	88.8	80.6
286.1–422.0	0.30–0.64	4	89.4	81.2
	0.65–0.88	5	89.9	81.4
	0.89–1.34	5	88.3	80.2
	1.35–1.84	6	88.0	79.9

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Real-Life Population Pharmacokinetics of Recombinant Factor XIII and Dosing Considerations for Preventing the Risk of Bleeding in Patients with FXIII Congenital Deficiency

Cojutti P et al. Clin Pharmacokinet. 2022;61(4):505-13

Table 1 Demographic and clinical characteristics of the population ($n = 18$)

Patient characteristics	Median (minimum–maximum)
Age (years)	34.5 (6–74)
Weight (kg)	71.5 (19–98)
Body mass index (kg/m^2)	24.5 (13–33.5)
Creatinine clearance (mL/min)	112.2 (66.0–223.1)
Factor XIII deficiency status	
Minor	2
Moderate	2
Severe	14
Dose (IU/kg)	32.5 (25–50)
Number of samples per patient	5 (1–10)

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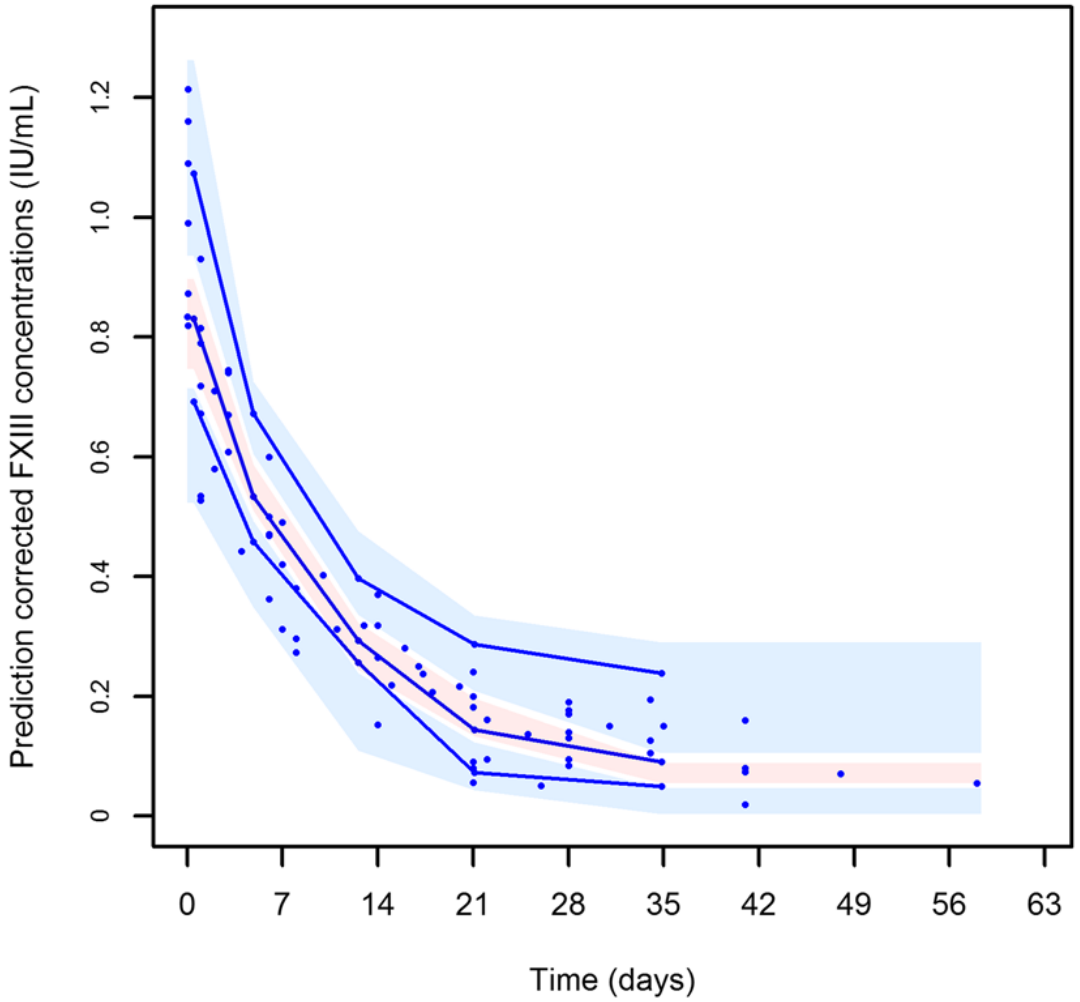

- 5-min intravenous infusion of rFXIII at 35 IU/kg
- Blood samples collected between 15-1392 h post-dose

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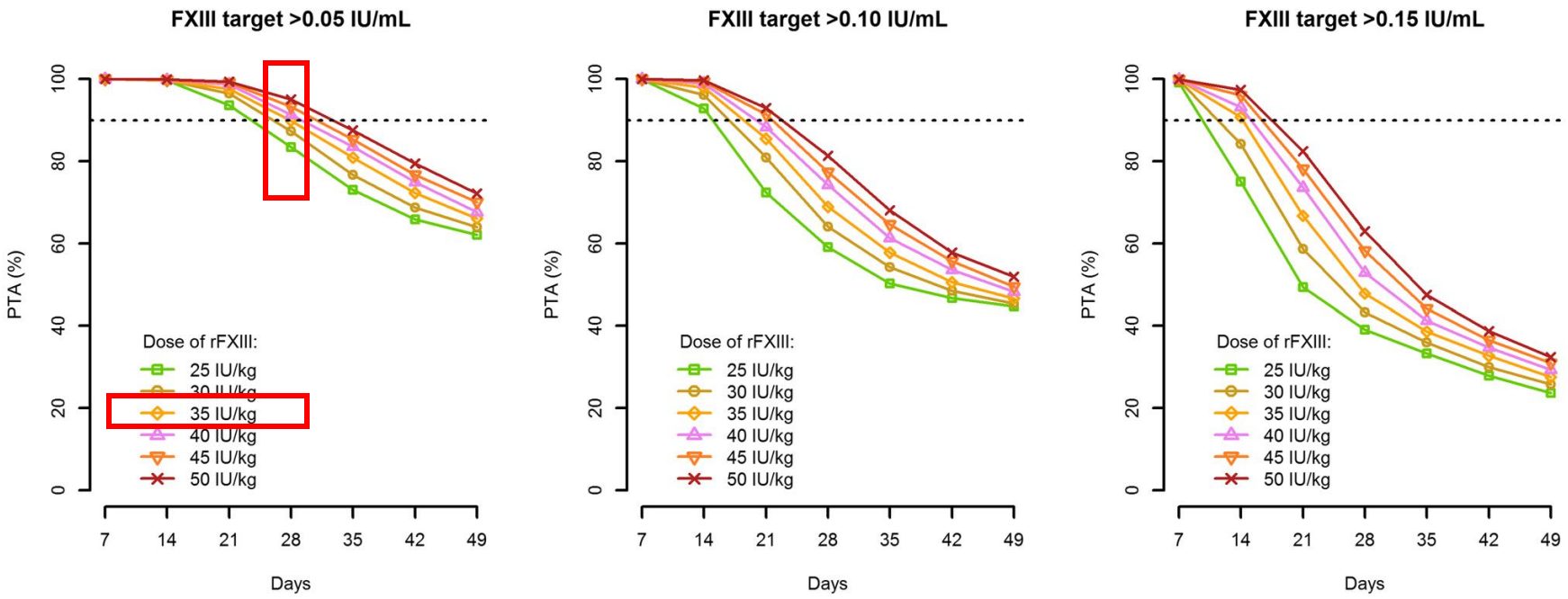

- Population pharmacokinetic analysis of data from real-life patients with FXIII deficiency treated with recombinant factor XIII (rFXIII) may help to better elucidate the pharmacokinetics of rFXIII and to assess the attainment of common FXIII thresholds to minimise the risk of bleeding.
- The standard rFXIII dosage of 35 IU/kg every 4 weeks is associated with a suboptimal attainment at day 28 of 89.9%, 68.9% and 47.8% in relation to the pharmacodynamic threshold of > 0.05, > 0.10 and > 0.15 IU/mL, respectively.
- Clinicians should consider alternative dosing regimens for rFXIII administration to minimise the risk of bleeding.

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Editorial: Therapeutic Drug Monitoring (TDM): A Useful Tool for Pediatric Pharmacology Applied to Routine Clinical Practice

Simeoli R et al. Front Pharmacol 2022;13:931843

- Pharmacometrics is useful

- TDM is optimal
  - Consider maturation, ontogeny, DDI
  - Application: antimicrobial, immunosuppressant, HSCT patients
  - Microsampling methods are increasing (VAMS, DBS etc.)