Model-informed precision dosing of antibiotics: moving beyond one model-one target fits all

Hiie Soeorg

Research Fellow of Medical Microbiology

Department of Microbiology

Medical Faculty

University of Tartu

Estonia

Antibiotics in intensive care units

- Commonly used (55-67% of patients) (Versporten *et al*. 2018)
- Therapeutic drug monitooring (**TDM**) is recommended for beta-lactams, vancomycin, aminoglycosides, linezolid, teicoplanin, voriconazole (Abdul-Aziz *et al*. 2020)
- **Standard doses** perform poorly – meta-analysis of **beta-lactams** (Mangalore *et al*. 2022)

• Target attainment 26%		50%	RR 1.85 (95% CI 1.08 to 3.16)
• Clinical cure 57%	TDM →	69%	RR 1.17 (95% CI 1.04 to 1.31)
• Microbiological cure 68%		79%	RR 1.14 (95% CI 1.03 to 1.27)
• Mortality 21%		18%	RR 0.85 (95% CI 0.69 to 1.04)

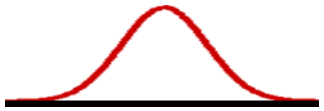
CI – confidence interval
RR – relative risk

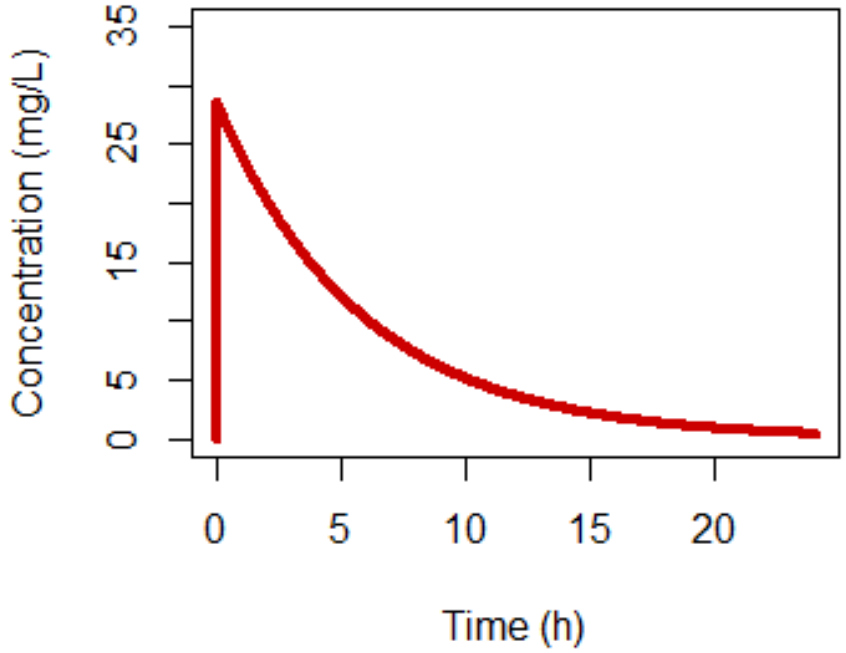
Dose recommendations

- Based on population PK models

$$C\,(t) = \frac{Dose}{V}\, e^{-\frac{CL}{V}\cdot t} + \varepsilon, \qquad \varepsilon \sim N(0, \sigma)$$

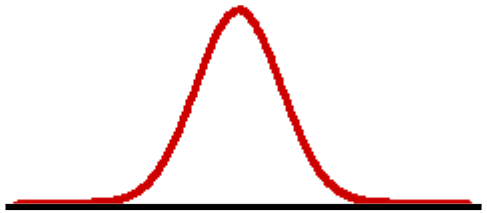
Error term





- Variability in CL and V, e.g.,

$$CL = \theta \cdot f(Patient\ characteristics) \cdot e^{\eta}, \qquad \eta \sim N(0, \omega)$$



CL – clearance
PK - pharmacokinetic
V – volume of distribution

PK models for dose recommendations

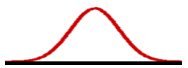
- Standard dose: dose that achieves the target in a population (with a range of chracteristics, e.g., weight, renal function)
- Repeat N times

Patient characteristics, e.g., weight 50…100 kg

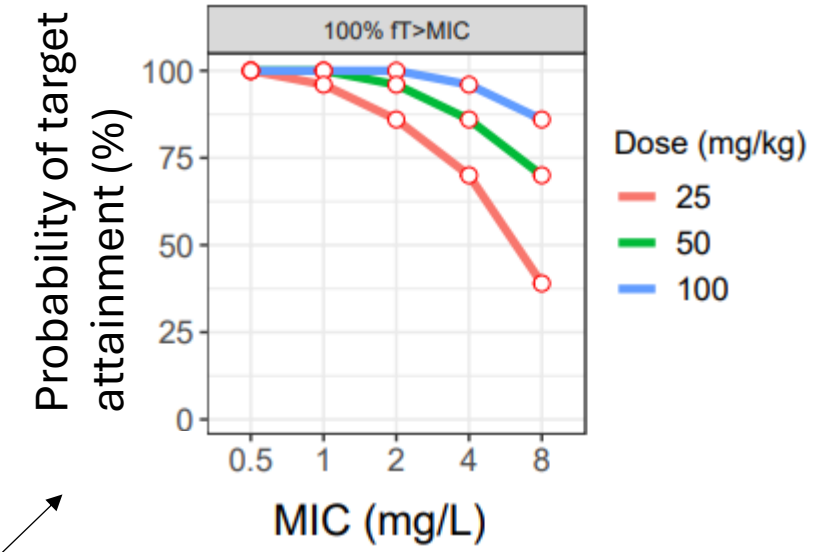
Randomly from 

$$CL = \theta \cdot f(Patient\ characteristics) \cdot e^{\eta}$$

$$C\ (t) = \frac{Dose}{V} e^{-\frac{CL}{V} \cdot t} + \varepsilon$$

Randomly from 

Attained target?



Padari *et al*. Pediatr Infect Dis J 2021

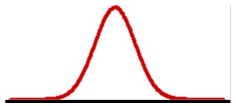
CL – clearance
MIC – miinimum inhibitory concentration
PK - pharmacokinetic
V – volume of distribution

PK models for dose recommendations

- We could use the same procedure for a particular patient

- Repeat N times

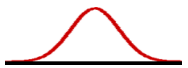
Patient characteristics

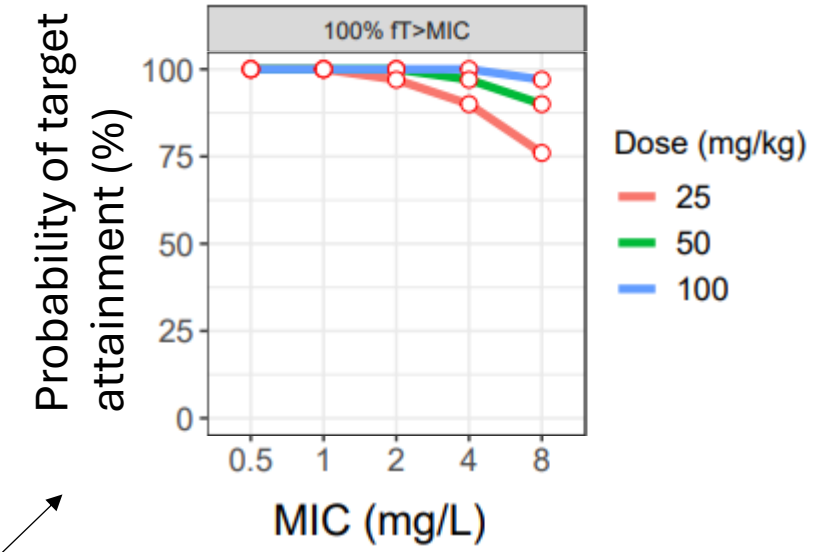
Randomly from 

$$CL = \theta \cdot f(Patient\ characteristics) \cdot e^{\eta}$$

$$C\ (t) = \frac{Dose}{V} e^{-\frac{CL}{V} \cdot t} + \varepsilon$$

Attained target?

Randomly from 



CL – clearance
MIC – miinimum inhibitory concentration
PK - pharmacokinetic
V – volume of distribution

PK models for dose recommendations

- After TDM we can estimate individuaal pharmacokinetic parameters

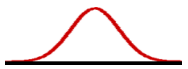
- Repeat N times

Patient characteristics

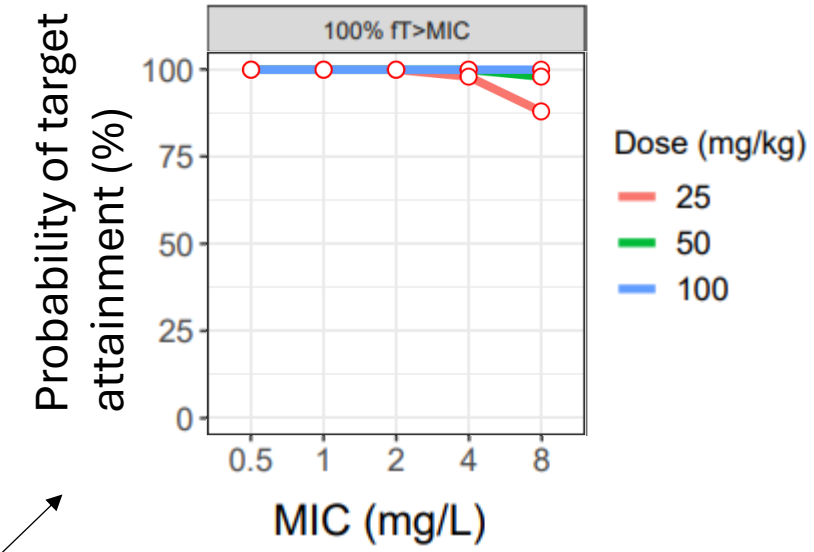
Estimated value

$$CL = \theta \cdot f(Patient\ characteristics) \cdot e^{\eta}$$

$$C\ (t) = \frac{Dose}{V} e^{-\frac{CL}{V} \cdot t} + \varepsilon$$

Randomly from 

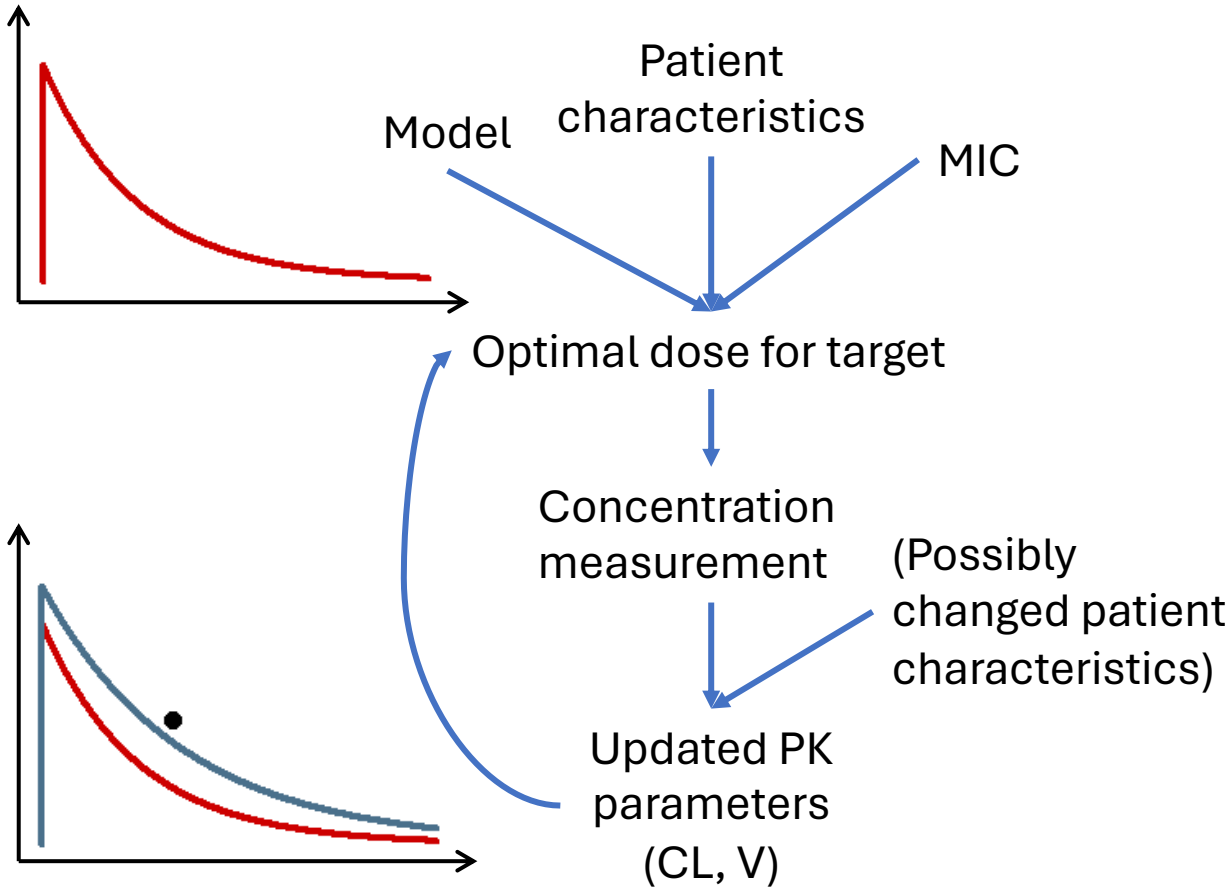
Attained target?



CL – clearance
MIC – miinimum inhibitory concentration
PK – pharmacokinetic
TDM – therapeutic drug monitoring
V – volume of distribution

Model-informed precision dosing

- Approach to maximize the efficacy and minimize toxicity
- Relevant
  - Highly variable PK
  - Narrow therapeutic window
- Use by physicians/pharmacistis (Williams *et al*. 2023)
  - Vancomycin: 11% (high-income countries 17%)
  - Beta-lactams: 3%



CL – clearance
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The benefit of individualized dosing

- Relative risks (95% confidence interval)

	MIPD* or TDM vs no dose adjustment of anti-infectives (Sanz Codina *et al*. 2023)	MIPD vs TDM or empiric dosing of vancomycin (He *et al*. 2020)
Target attainment rate ↑	1.41 (1.13-1.76)	1.59 (1.49-1.70)
Treatment failure ↓	0.70 (0.54-0.92)	
Nephrotoxicity ↓	0.55 (0.31-0.97)	0.57 (0.46-0.71)

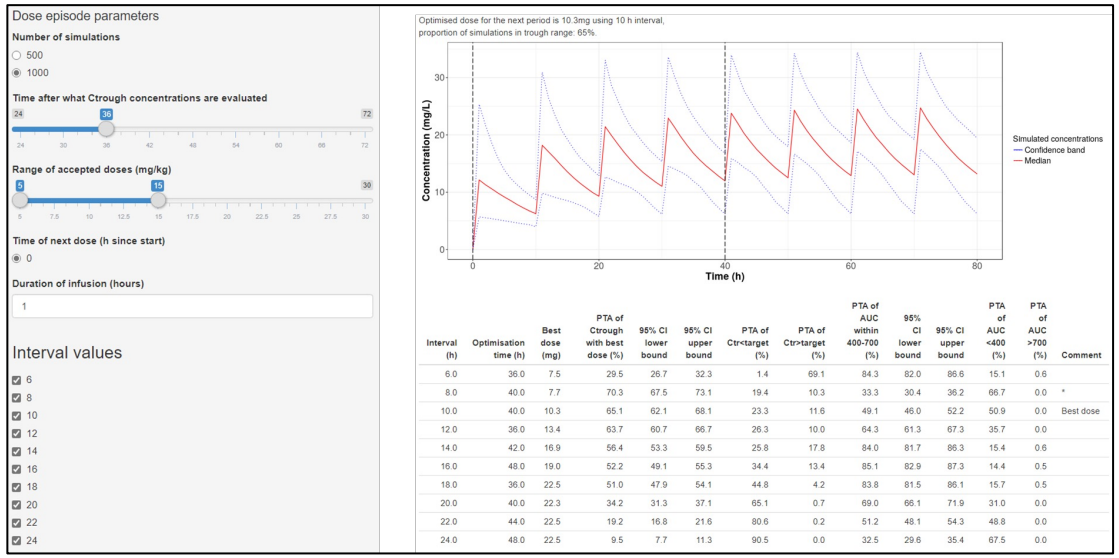
* Subgroup analysis based on the method of individualized dosing – no differences for mortality, treatment failure, clinical cure, treatment duration or nephrotoxicity.

- No difference in mortality, length of hospital stay
- **Cost-benefit**: AUC-guided vancomycin dosing using MIPD software may save up to **US$ 2065 per patient** (costs included vancomycin concentration measurements, MIPD software, acute kidney injury hospitalization costs) (Lee *et al*. 2021)

AUC – area under the curve
MIPD – model-informed precision dosing
TDM – therapeutic drug monitoring

Prospective validation of MIPD of vancomycin

- Neonates/infants (n=48)
- Historical control group (n=66) – standard doses + TDM-based dose adjustment



Interval (h)	Optimisation time (h)	Best dose (mg)	PTA of Ctrough with best dose (%)	95% CI lower bound	95% CI upper bound	PTA of Ctr<target (%)	PTA of Ctr>target (%)	PTA of AUC within 400-700 (%)	95% CI lower bound	95% CI upper bound	PTA of AUC <400 (%)	PTA of AUC >700 (%)	Comment
6.0	36.0	7.5	29.5	26.7	32.3	1.4	69.1	84.3	82.0	86.6	15.1	0.6	
8.0	40.0	7.7	70.3	67.5	73.1	19.4	10.3	33.3	30.4	36.2	66.7	0.0	*
10.0	40.0	10.3	65.1	62.1	68.1	23.3	11.6	49.1	46.0	52.2	50.9	0.0	Best dose
12.0	36.0	13.4	63.7	60.7	66.7	26.3	10.0	64.3	61.3	67.3	35.7	0.0	
14.0	42.0	16.9	56.4	53.3	59.5	25.8	17.8	84.0	81.7	86.3	15.4	0.6	
16.0	48.0	19.0	52.2	49.1	55.3	34.4	13.4	85.1	82.9	87.3	14.4	0.5	
18.0	36.0	22.5	51.0	47.9	54.1	44.8	4.2	83.8	81.5	86.1	15.7	0.5	
20.0	40.0	22.3	34.2	31.3	37.1	65.1	0.7	69.0	66.1	71.9	31.0	0.0	
22.0	44.0	22.5	19.2	16.8	21.6	80.6	0.2	51.2	48.1	54.3	48.8	0.0	
24.0	48.0	22.5	9.5	7.7	11.3	90.5	0.0	32.5	29.6	35.4	67.5	0.0	

Target (C_{trough} **10…15 mg/L**) attainment

	Control group	**Study group**	p-value
After the first optimized dose	20%	**50%**	0.002
After any adjusted dose	37%	**62%**	0.01

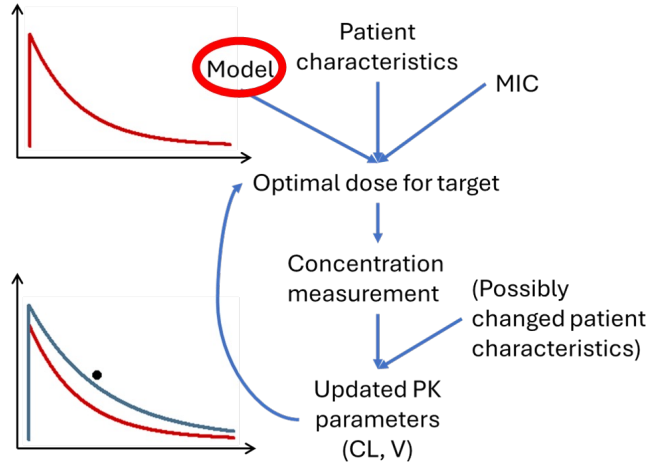
Kalamees *et al*. at ESPID 2023

C_{trough} 10…20 mg/L after any dose adjusted 56.1% in a study by Frymoyer *et al*. 2020.

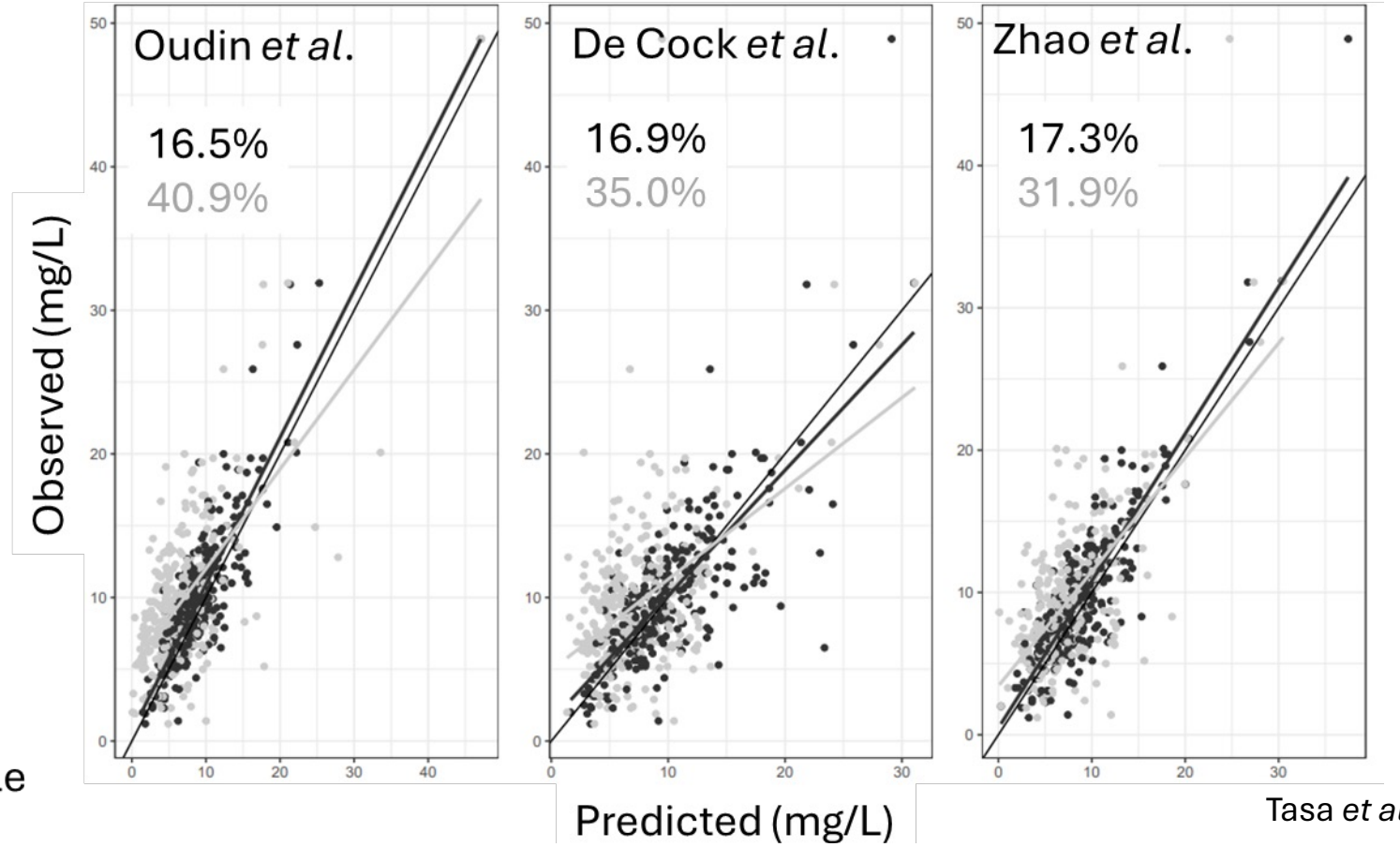
C_{trough} – trough concentration
MIPD – model-informed precision dosing
TDM – therapeutic drug monitoring

PK model for MIPD

- The PK model with the best predictive performance in a validation dataset



Median absolute percentage errors

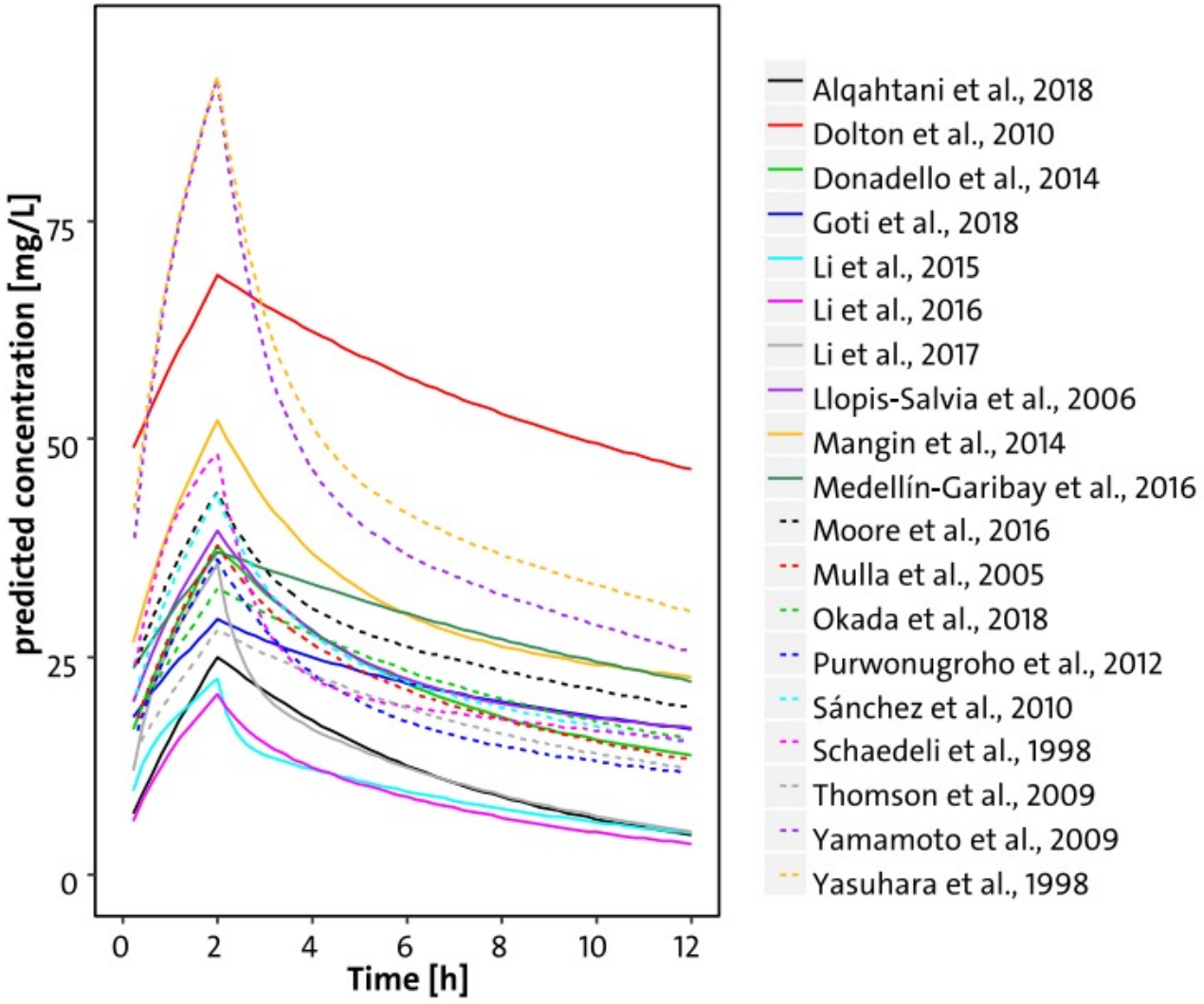


MIPD – model-informed precision dosing
PK - pharmacokinetic
TDM – therapeutic drug monitoring

Tasa *et al*. 2018

PK model for MIPD

- Different models may predict very different concentrations for a specific patient
- Heterogeneous patient population → one model for all could result in „incorrect model“ for some patients → inappropriate dose recommendations



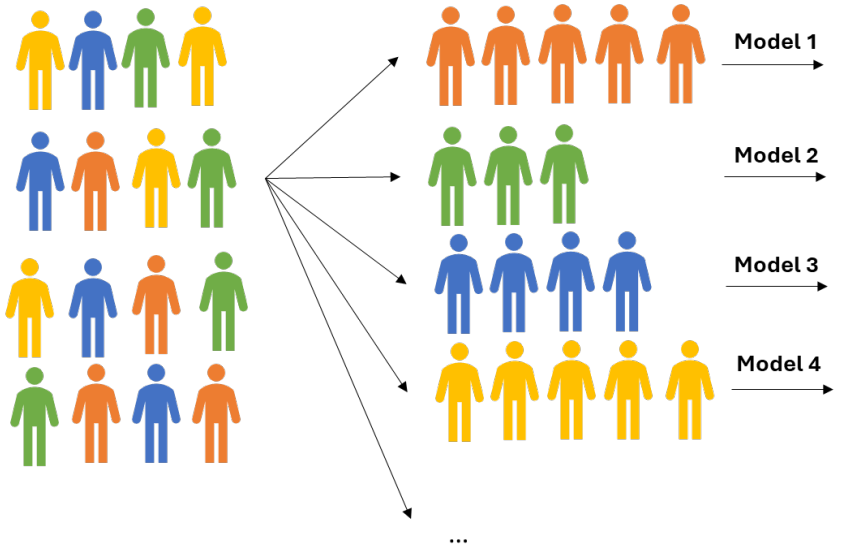
Simulated vancomycin pharmacokinetic profiles of a standard patient (male, 50 years old, body weight 75 kg, body height 1.7 m, serum creatinine 85 µmol/L, twice daily vancomycin dosing of 1000 mg with an infusion length of 2 h)

Broeker *et al*. 2019

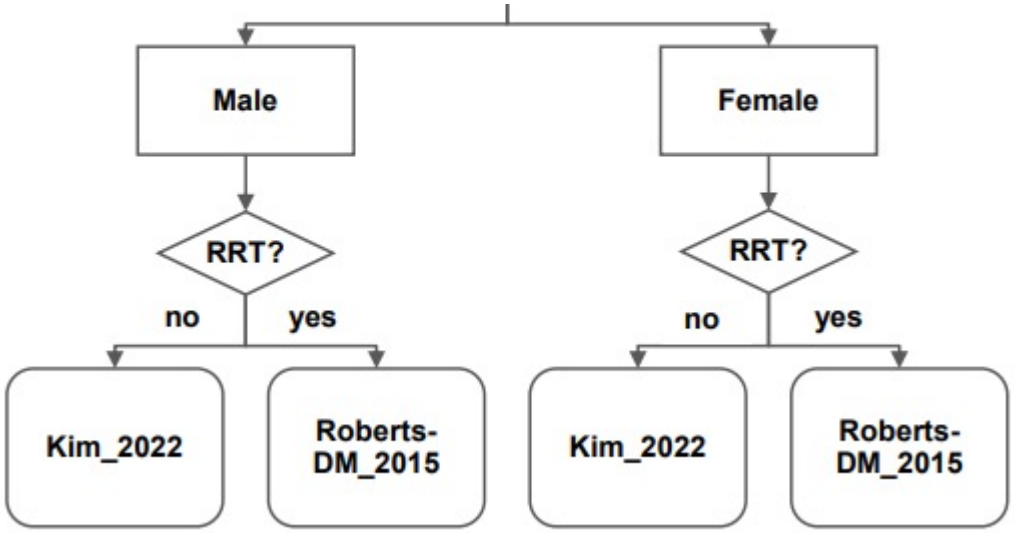
MIPD – model-informed precision dosing
PK - pharmacokinetic

Which model to choose?

- Some patients are considered to be more similar in terms of characteristics influencing PK, e.g., requiring RRT



Piperacillin PK models



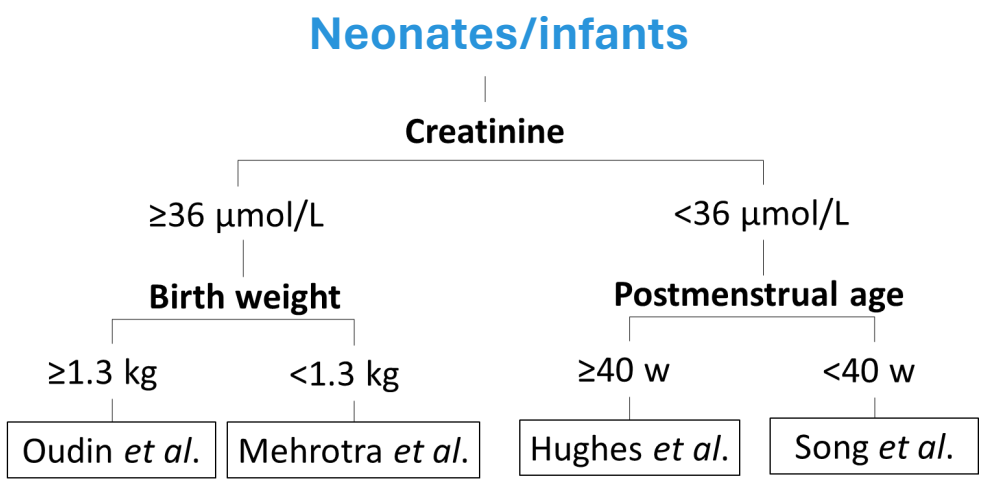
	One model for all	Kim_2022	Roberts-DM_2015	Kim_2022	Roberts-DM_2015
Median absolute percentage error	37.00%	33.90%	36.55%	31.96%	36.26%

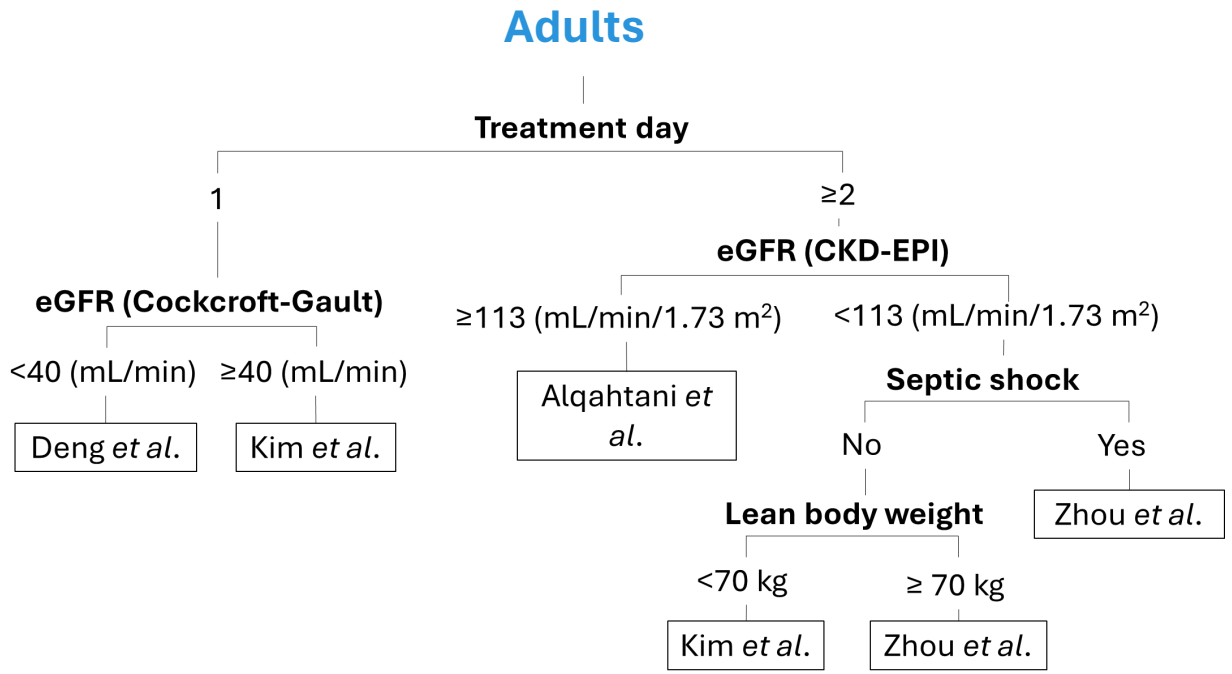
PK – pharmacokinetic
RRT – renal replacement therapy

Greppmair *et al*. 2023

Subgroup-identification for model selection

- Genetic algorithm: subset of **vancomycin pharmacokinetic models** → determined the best fitting model for each patient → built a classification tree to predict the model





Percentage of predictions within 20%

One model for all: 42.6%

Model selection approach: **45.5%** Soeorg *et al.* at ECCMID 2023

Median absolute percentage error

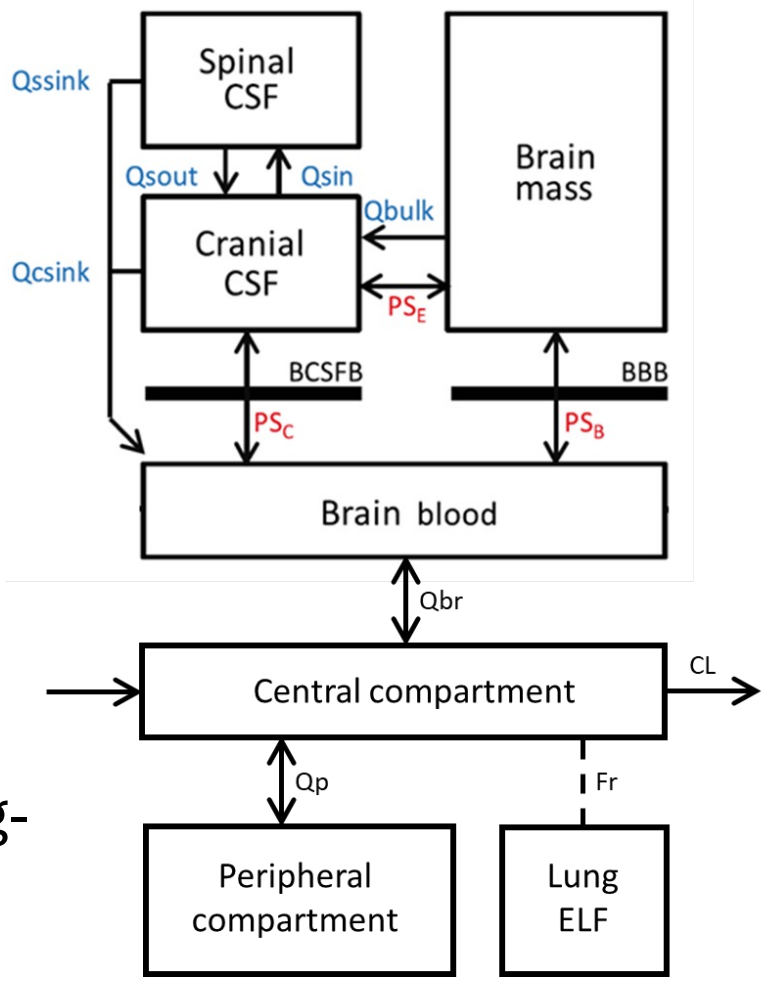
One model for all: 30.1%

Model selection approach: **28.3%** Unpublished data

Improving models for MIPD

- **Machine learning** methods
  - Outperform PK models (7 studies), but not in all scenarios
  - May be **unreliable when extrapolating** to unseen time points (Janssen *et al*. 2022)
  - ML models **not interpretable** (Li et al. 2023)
- **Physiologically based PK models**
  - Anatomical and physiological parameters and drug-specific data (e.g., physicochemical properties)
  - Require **detailed data**

Ampicillin concentration in cerebrospinal fluid in neonates

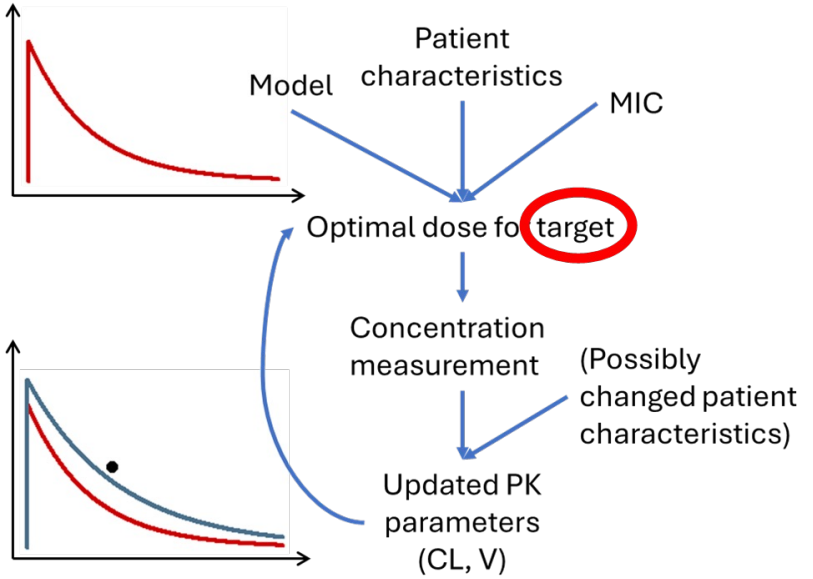


Schematic outline modified from Verscheijden *et al*. 2019

Padari *et al*. 2021

MIPD – model-informed precision dosing
ML – machine learning
PK – pharmacokinetic

Target in MIPD

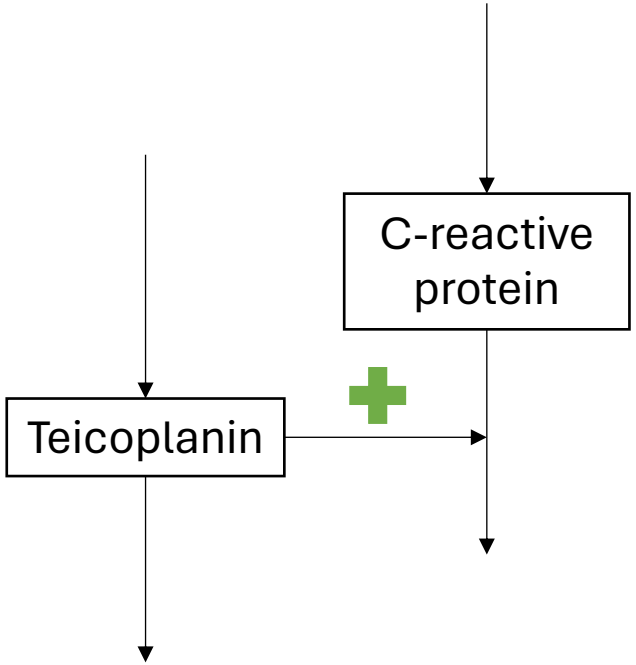


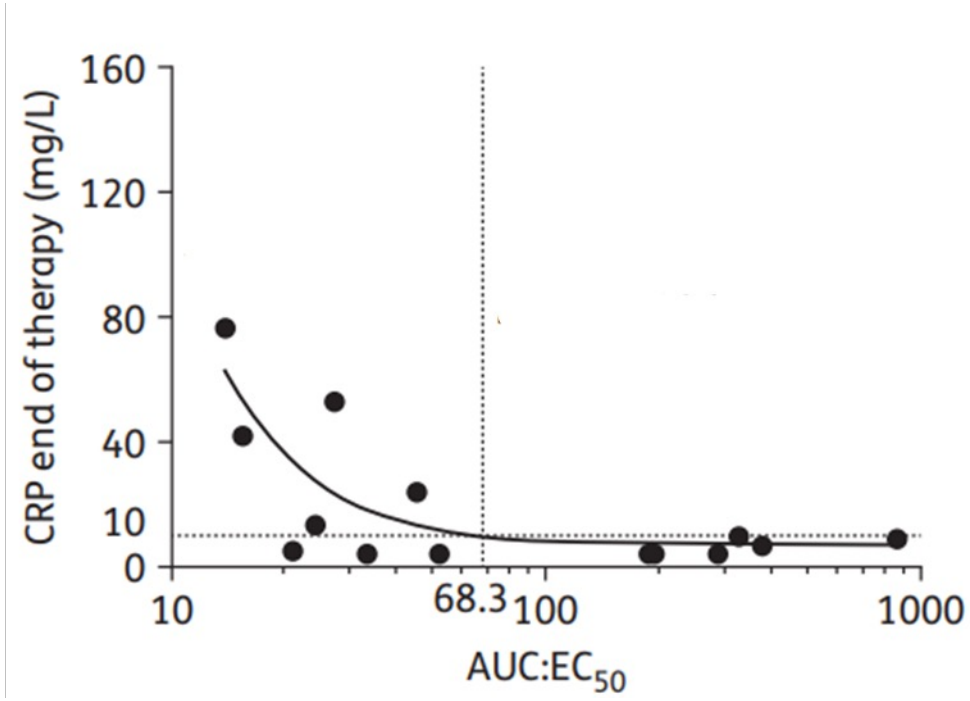
- MIC-based PKPD targets
  - **MIC not known:** negative blood cultures (52-80% in neonates/infants) (Fleischmann *et al*. 2021, Wagstaff *et al*. 2019, Lutsar *et al*. 2020)
  - **Variability of an MIC** measurement
    - Acceptable deviation of **one dilution from the mode** (Mouton *et al*. 2018)
    - A single measurement indicates whether the strain is wild-type (without acquired resistance) (Mouton *et al*. 2018)
  - PKPD target **varies depending on PK** – in case of meropenem (Kristoffersson *et al*. 2016)
    - Augmented renal clearances: T>MIC
    - Renal dysfunction: AUC/MIC
- **Tissue penetration of antibiotics varies**
  - Penetration rate of ampicillin into lung epithelial lining fluid in neonates is 8%–80% (Padari *et al*. 2021)

AUC – area under the curve
MIC – miinimum inhibitory concentration
PKPD – pharmacokinetic-pharmacodynamic
T – time

Biomarker-based PKPD targets

- PKPD model of teicoplanin in neonates





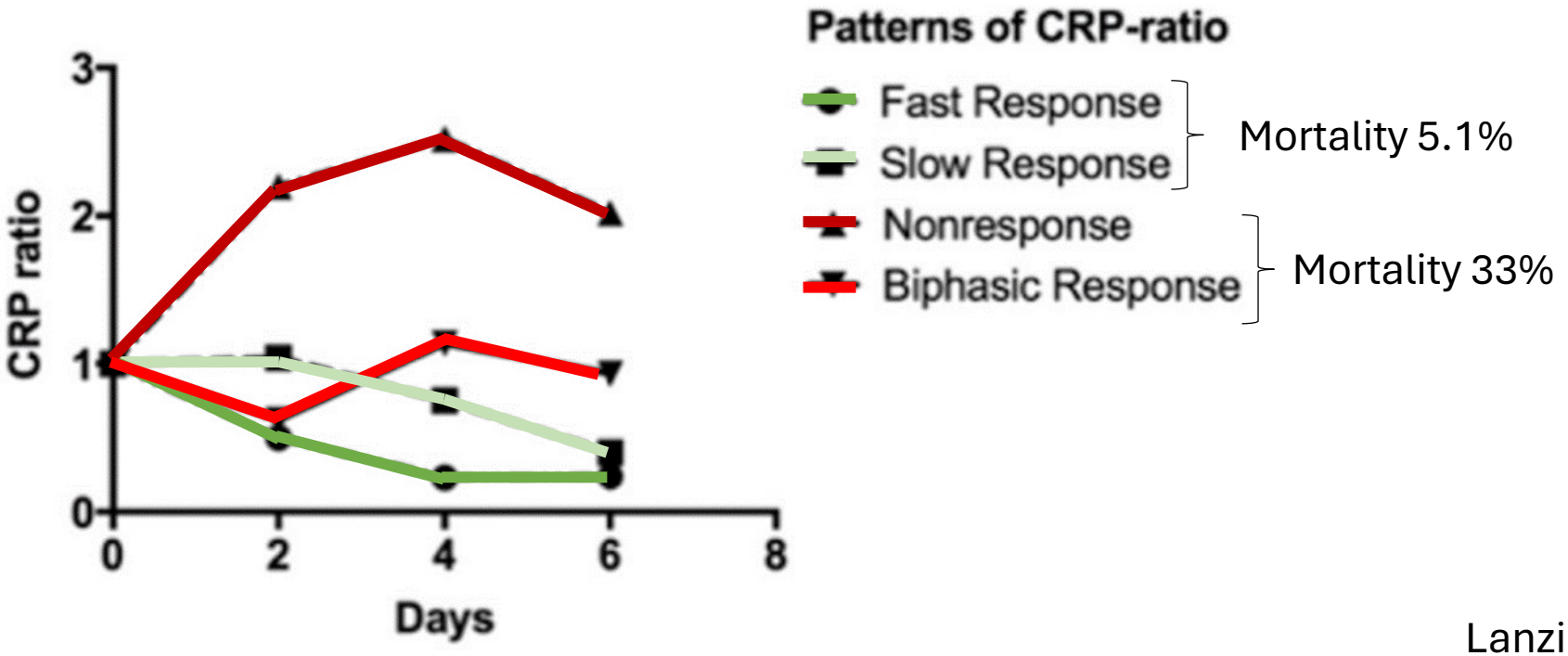
EC_{50} is the concentration of teicoplanin (mg/L) that produces the half-maximal effect (CRP inhibition)

AUC – area under the curve
CRP – C-reactive proteiin
PKPD – pharmacokinetic-pharmacodynamic

Ramos-Martin *et al*. 2016

Biomarker dynamics

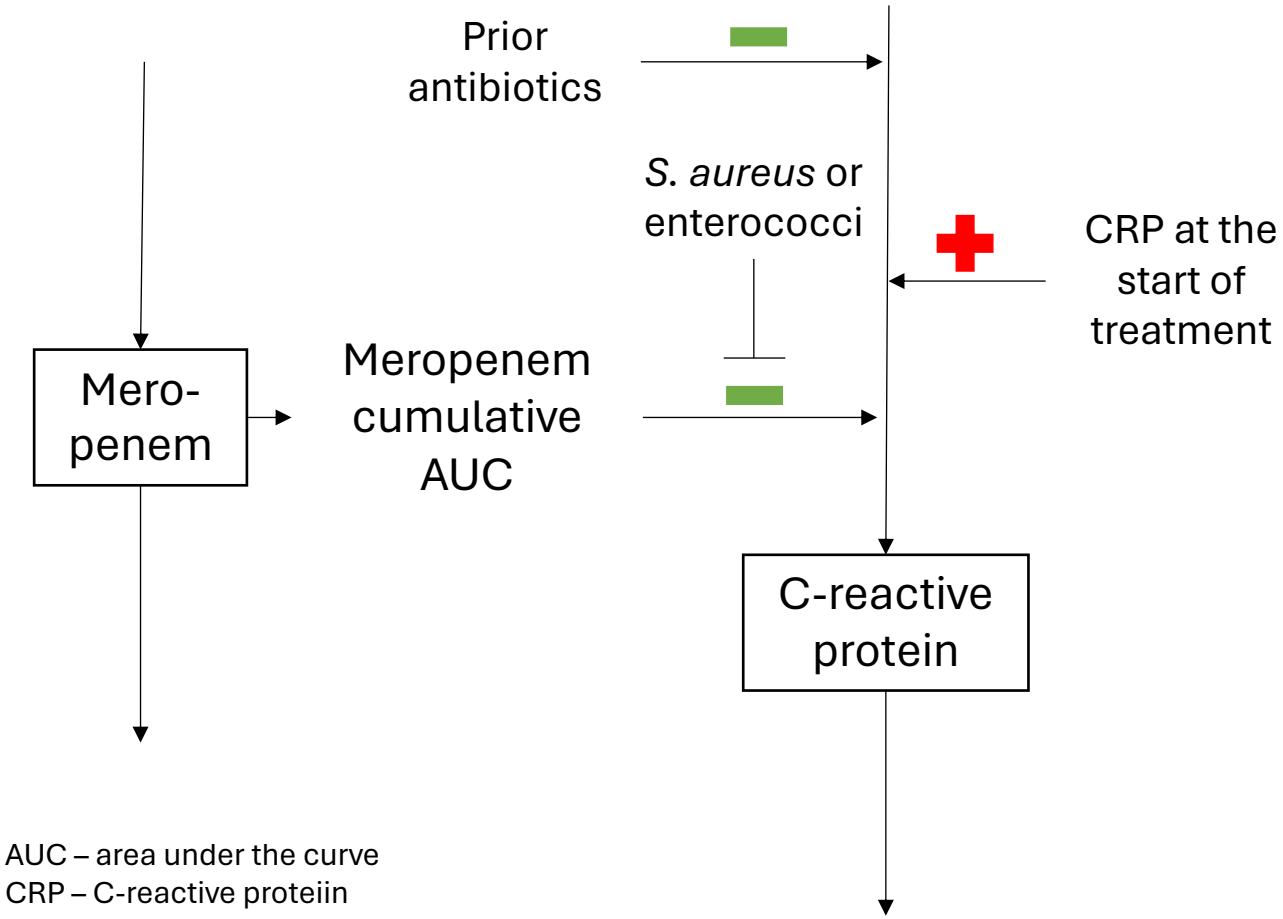
- C-reactive protein (CRP) ratio (in relation to CRP at the start of treatment) response to antibiotics in children with sepsis



Lanziotti *et al*. 2018

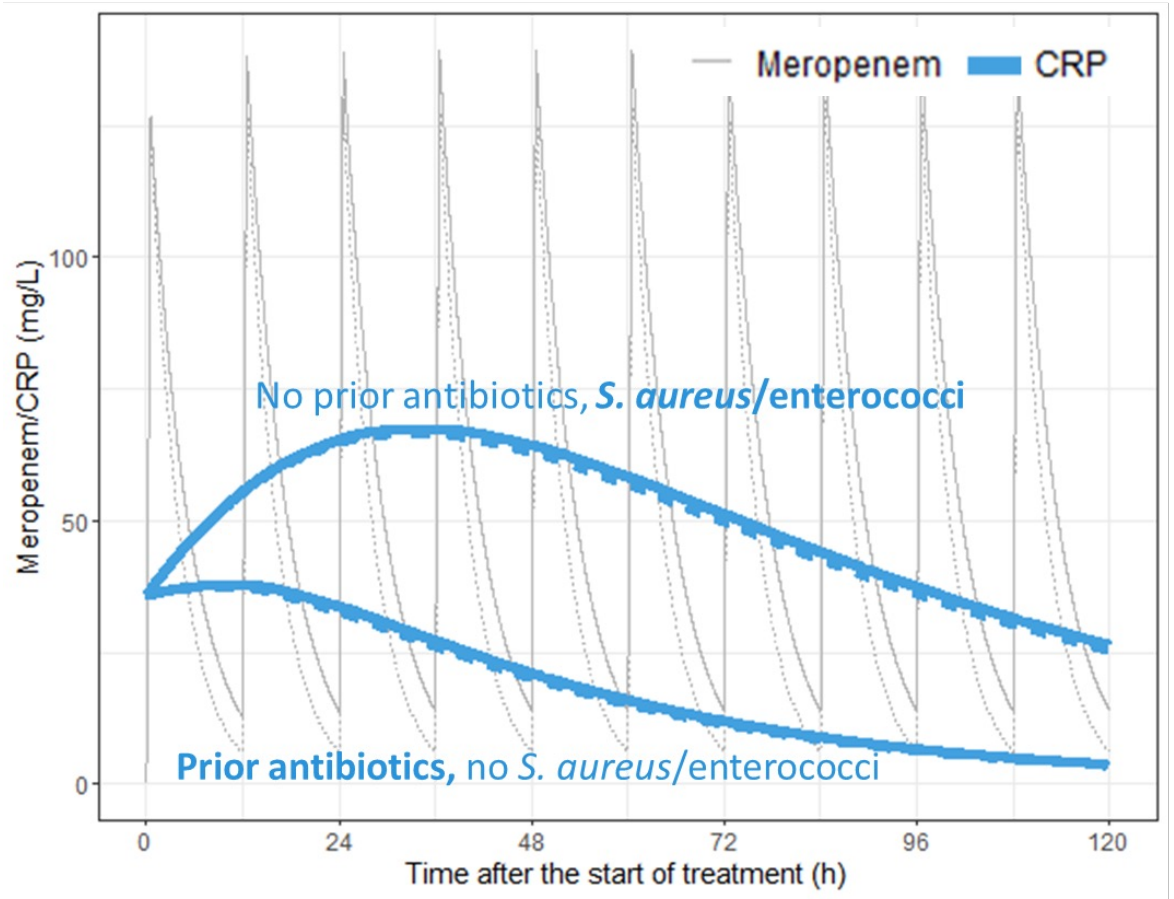
Meropenem and CRP PKPD model

- Neonates/infants with late-onset sepsis or meningitis (n=60)



AUC – area under the curve
CRP – C-reactive proteiin
PKPD – pharmacokinetic-pharmacodynamic

Gestational age 27 weeks initial CRP 35.8 mg/L, meropenem 20 mg/kg q12 h:

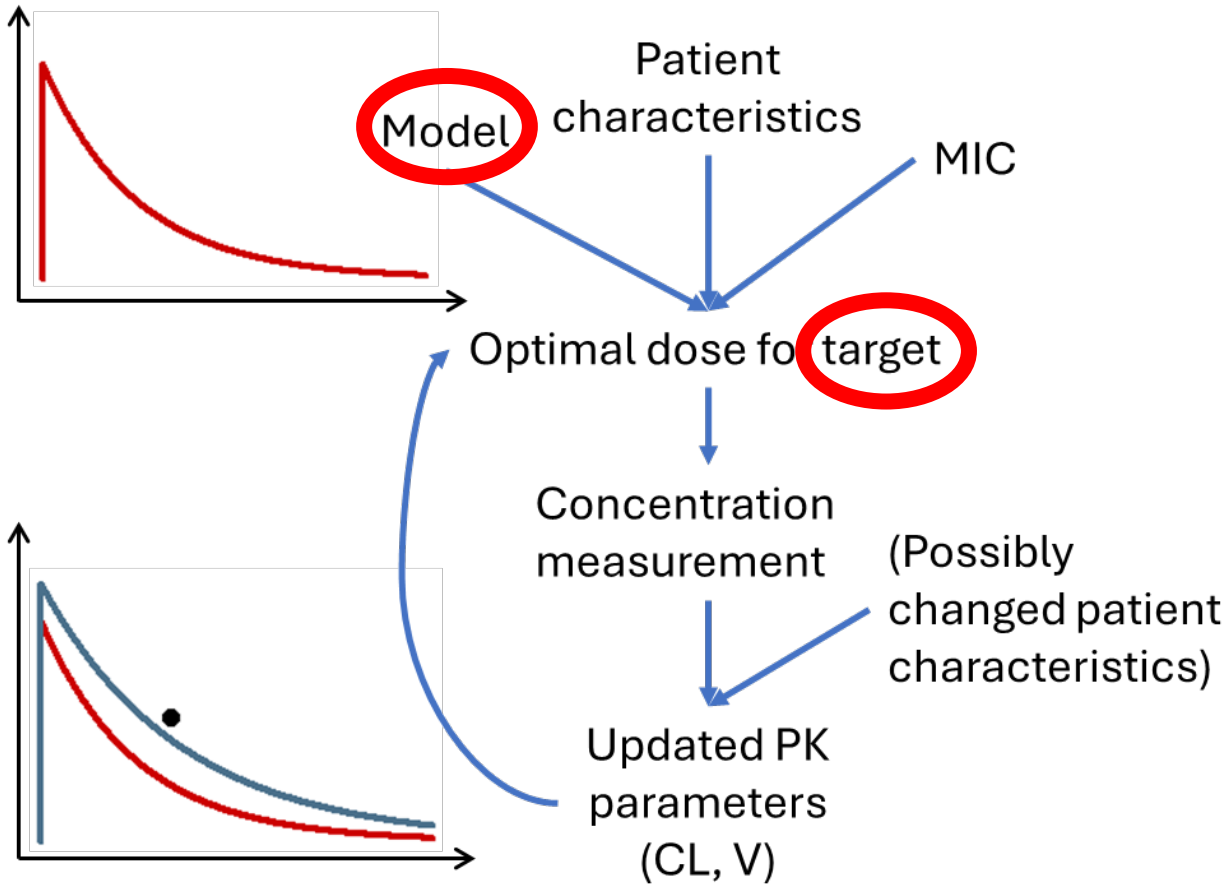


The ratio of the **5th treatment day CRP** to **peak value within 72 hours** after the start of treatment was predicted with error of **<0.2** in **70-79%** of neonates and infants, even when no data during treatment was known.

Soeorg *et al*. at ESPID 2023

Conclusion

- MIPD
  - Improves target attainment
  - Reduces toxicity
  - More evidence needed
- Model
  - One model for all → **model selection**
  - Machine learning, PBPK?
- Target
  - **Biomarker-based** PKPD targets?



CL – clearance
MIC – minimum inhibitory concentration
MIPD – model-informed precision dosing
PBPK – physiologically-based PK
PK – pharmacokinetic
PKPD – PK-pharmacodynamic
V – volume of distribution

Thank you!

- Tuuli Metsvaht
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  - Intensive Care 2
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  - Department of Anaesthesiology and Intensive Care
- East Tallinn Central Hospital
  - Neonatology department

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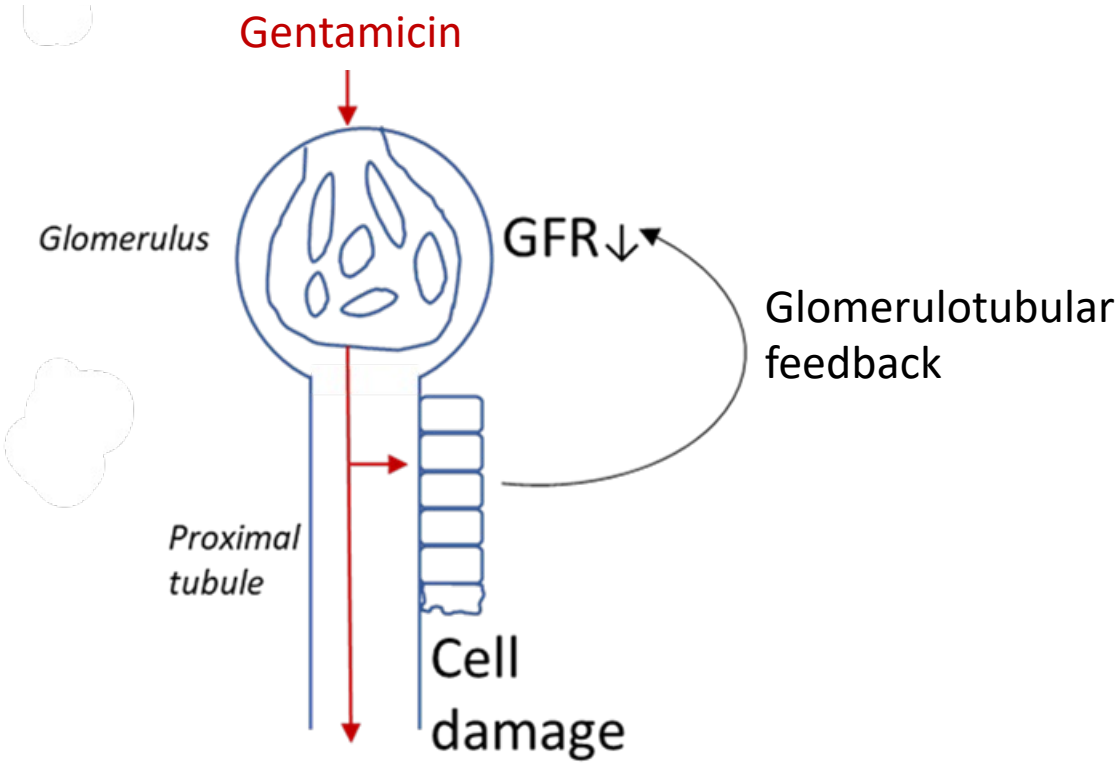
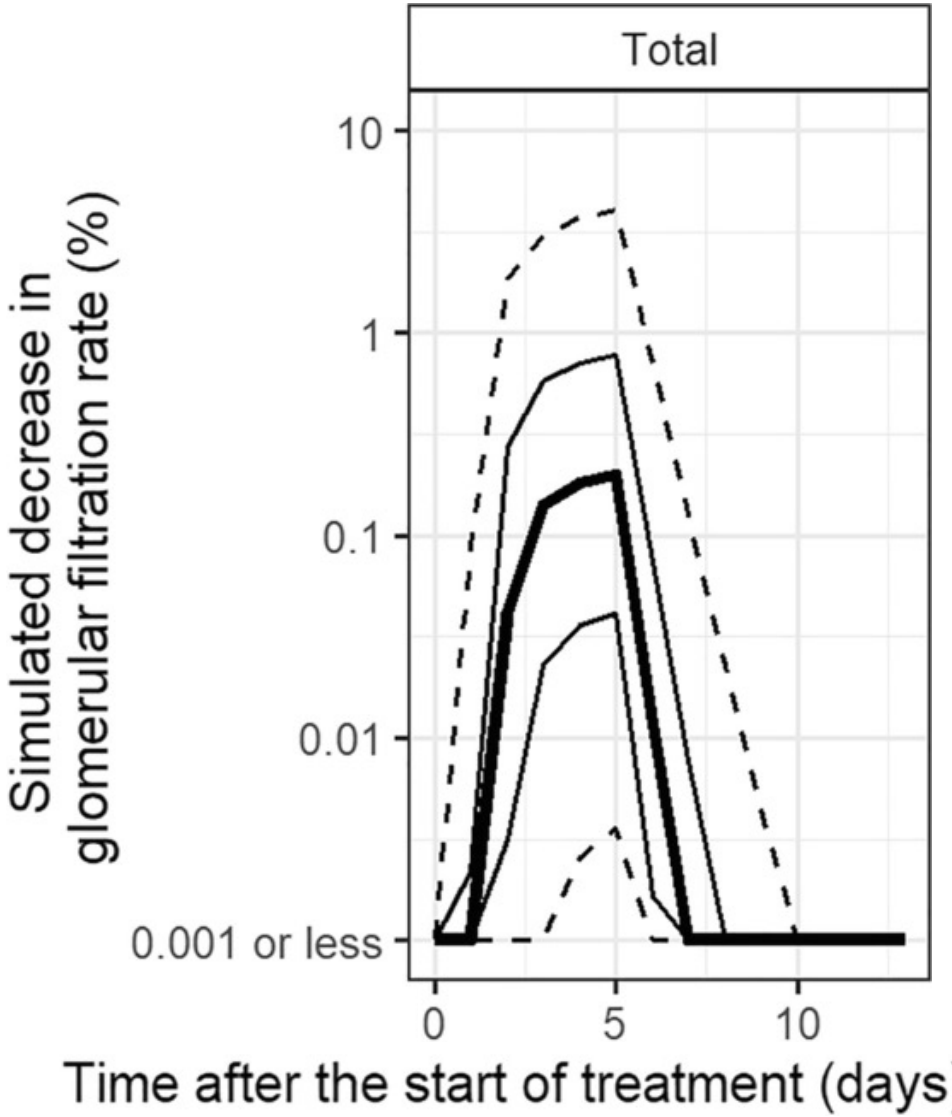
- European Regional Development Fund

PD models for toxicity

- Gentamicin nephrotoxicity in neonates





Soeorg *et al*. 2022