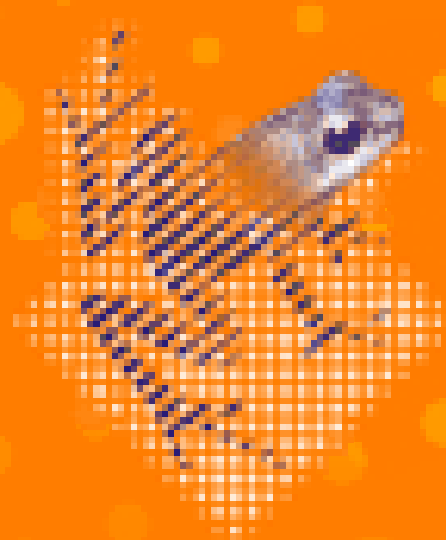




A pooled pharmacokinetic analysis of piperacillin-tazobactam in different patient populations



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Background and Objectives

- Piperacillin-tazobactam is a β -lactam/ β -lactamase inhibitor combination product used against severe infections in the intensive care unit setting¹. However, pharmacokinetics (PK) of piperacillin typically depends on the type of patient population and

disease progression^{2, 3}.

- This study aimed to describe the PK of piperacillin (PIP) in different patient populations by a single model instead of multiple subgroup-specific ones.

Methods

- PK studies of piperacillin-tazobactam were identified through a PubMed search. Individual patient data was provided by the corresponding authors for 13 out of 58 identified studies⁴⁻¹⁶. The characteristics of the patients are summarized in Table 1.
- A pooled population PK model was developed based on these data. Different patient characteristics were tested in the model as covariates to explain the observed variability in PK parameters across patients and studies.

Table 1. Summary of patient characteristics.

	Min	Median	Max
Post-menstrual age (yr)	0.485	39.77	94.77
Body weight (kg)	0.473	63	200
Height (cm)	29	167	198
Serum creatinine (mg/dL)	0.17	0.653	6.1
Number of females/males		177/258	

Parameter estimates

Table 2. Parameter estimates of the final model.

Parameters	Estimates	RSE (%)	IIV (%)	RSE (%)
V1 (L (70 kg) ⁻¹)	9.02	4	36.6	28
CL (L (h 70 kg) ⁻¹)	10.8	2	45.7	11
V2 (L (70 kg) ⁻¹)	12.7	2	64.6	26
Q (L (h 70 kg) ⁻¹)	18.7	5	28.1	66
γ_1	3.10	9		
ME ₅₀ (yr)	1.18	47		
DE ₅₀ (yr)	83.1	3		
E _{CR} (dL mg ⁻¹)	0.336	10		
θ_{DBS} (%)	64.6	7		
σ_{prop}	0.0959	8		
σ_{add}	0.0314	60		

- CL at first increases with PMA, reaching 50% of the maximum value at 1.18 years. Later in life, CL decreases with PMA, to 50% of maximum values at 83.1 years.
- For every 1 mg dL⁻¹ rise in serum creatinine, CL decreases 28.5%.
- PIP concentrations in dried blood spot (DBS) samples were also fitted. The estimate of θ_{DBS} suggested that PIP concentrations in DBS samples were 64.6% lower than total plasma concentrations, which might result from red blood cells that serve as a diluent of whole blood concentrations⁶.
- Given that the nonlinear PK of PIP was reported in previous studies¹⁷, single saturable elimination and parallel linear + saturable elimination were both tested by in this work. The single saturable elimination increase objective function value (OFV) by 11.1. The parallel elimination decrease OFV by 8.2 with 4 more parameters, which was not a significant improvement. Therefore, no improvement was showed in fitting the data after using the nonlinear elimination.

Final PK model

- A 2-compartment model with covariates including body weight (WT), postmenstrual age (PMA) and serum creatinine (SCR) was found to best describe the data:

$$V1 = \theta_{V1} \times F_{SIZE} \times e^{\eta_1} \quad (1)$$

$$CL = \theta_{CL} \times (F_{SIZE})^{0.75} \times F_{MAT} \times F_{DEC} \times F_{SCR} \times e^{\eta_2} \quad (2)$$

$$V2 = \theta_{V2} \times F_{SIZE} \times e^{\eta_3} \quad (3)$$

$$Q = \theta_Q \times (F_{SIZE})^{0.75} \times e^{\eta_4} \quad (4)$$

- Allometric scaling, PMA-based maturation and decline and SCR-related PK changes were characterized by F_{SIZE} , F_{MAT} , F_{DEC} and F_{SCR} respectively. SCR were standardized ($STCR$) based the previous work of our group¹⁸:

$$F_{SIZE} = WT/70 \quad (5)$$

$$F_{MAT} = PMA^{\gamma_1} / (PMA^{\gamma_1} + ME_{50}^{\gamma_1}) \quad (6)$$

$$F_{DEC} = EXP[-\ln(2) \times (PMA/DE_{50})] \quad (7)$$

$$STCR = EXP \left[1.45 - 1.19 \times \left(\frac{PMA}{100} \right)^{-0.5} - 0.206 \times \left(\frac{PMA}{100} \right)^{-0.5} \times \ln \left(\frac{PMA}{100} \right) \right] \quad (8)$$

$$F_{CR} = EXP[-E_{CR} \times (SCR - STCR)] \quad (9)$$

- The parameter θ_{DBS} was used to describe the difference between PIP concentrations in DBS and those in plasma:

$$C_{Plasma} = IPRED \times (1 + \sigma_{prop}) + \sigma_{add} \quad (10)$$

$$C_{DBS} = IPRED \times (1 - \theta_{DBS}) \times (1 + \sigma_{prop}) + \sigma_{add} \quad (11)$$

Goodness-of-fit plot

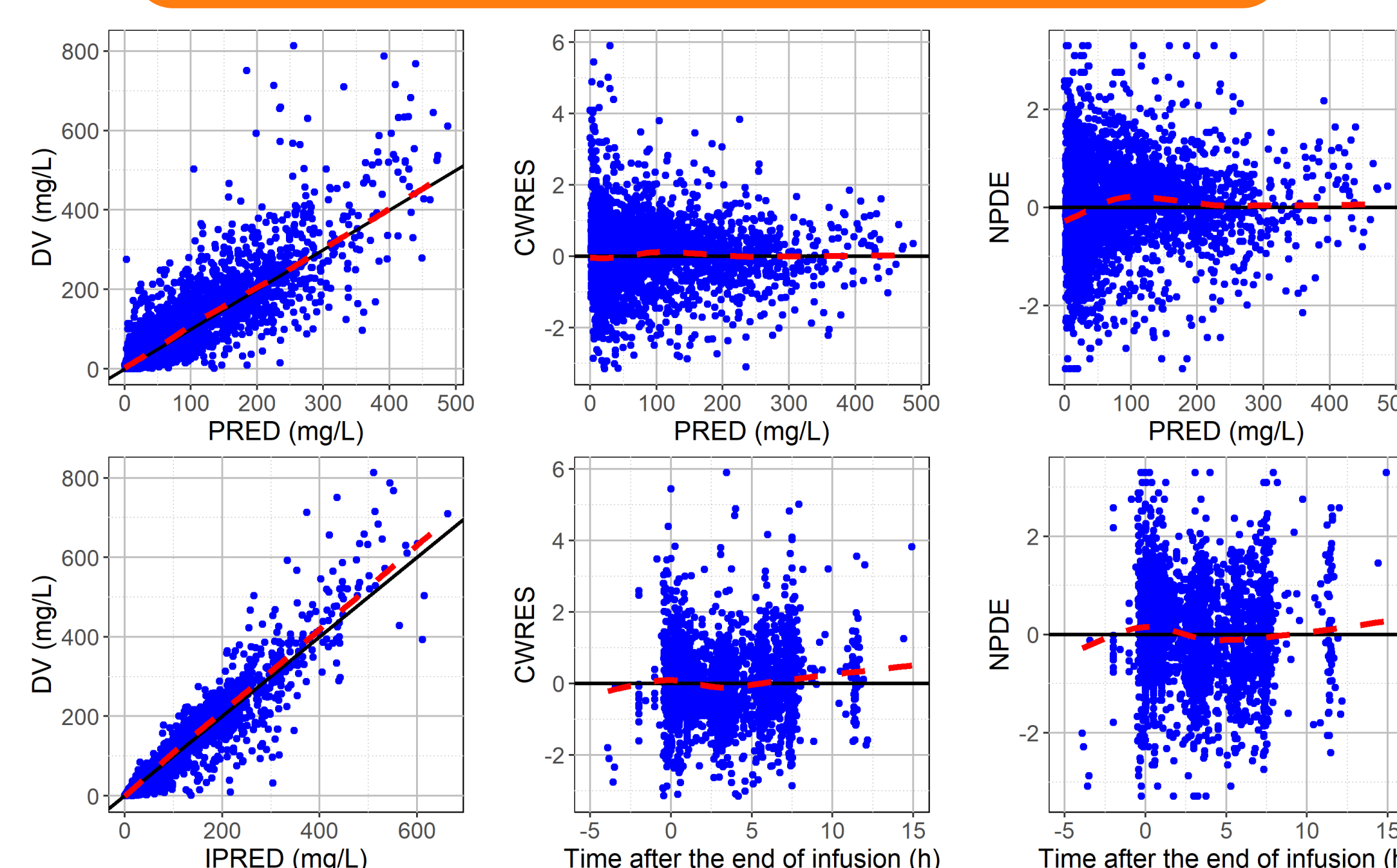


Figure 1. Goodness-of-fit plots shows no trend of model misspecification. Identity and local regression lines are presented in black and red, respectively.

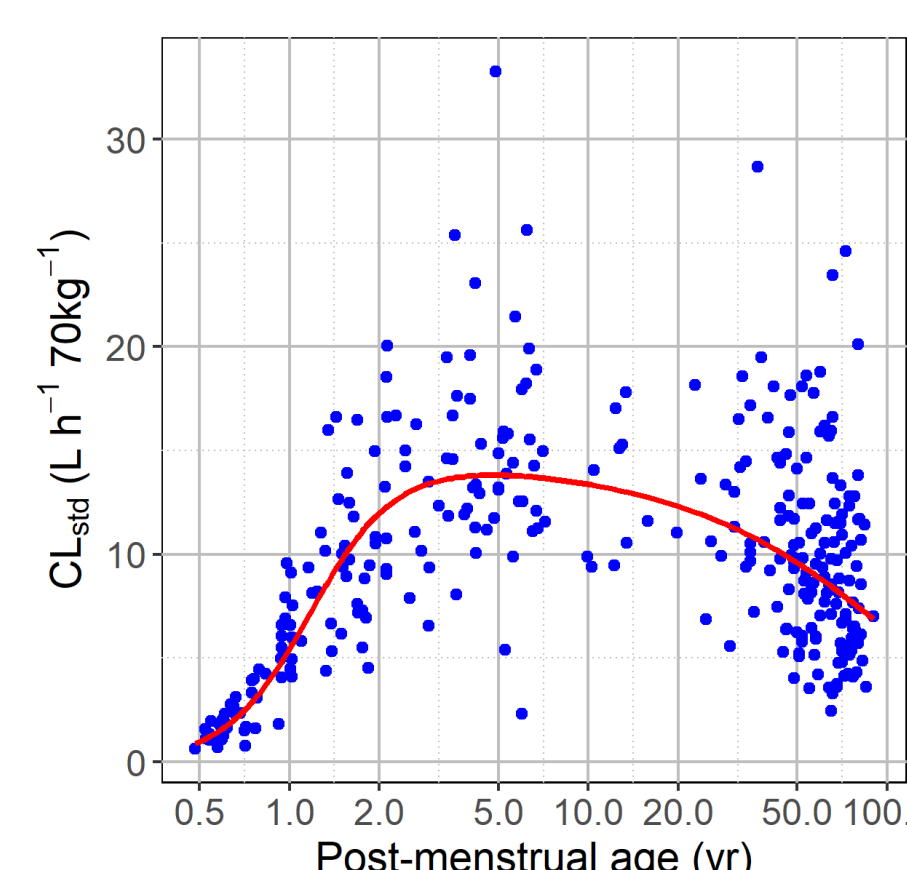


Figure 2. Standardized CL [CL_{std}] (L h⁻¹ 70kg⁻¹) for PIP throughout life. Typical CL according to our model is shown with a solid red line. Post-hoc CLstd values for all the patients in our dataset are shown with solid blue circles.

Conclusions

A pooled population PK model was established, which can be used to predict PK exposure of PIP in a variety of patients. This work are going to be expanded with PIP unbound plasma concentrations and PK data of tazobactam, which will help to further individualize PIP regimens¹⁸.

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