

Piperacillin population pharmacokinetics and dosing regimen optimization in critically ill children with different renal clearances

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INTRODUCTION

Piperacillin +/- Tazobactam :

- β -lactam antibiotic agent
- Time-dependent drug : attainment of the maximum kill rate when the concentration is 1 to 4 times the minimum inhibitory concentration (MIC), from 50% to 100% $fT_{>(1-4) \times MIC}$ [1-3].

In Pediatric Intensive Care Unit (PICU) :

- Alterations in PK parameters : $\uparrow Vd + \uparrow CL$
- Maturation during childhood

→ Reduction in the beta-lactam concentrations

Aims :

- To develop a PK population model for piperacillin
- To propose an individualized dosing regimen

PATIENTS & METHODS

Prospective study in Necker Enfants-Malades Hospital (Paris, France)

- Inclusion criteria : > 2.5 kg, < 18 years old
- Exclusion criteria : recent kidney or liver transplant < 2 weeks, extracorporeal membrane oxygenation, plasmapheresis and renal replacement therapy.

Blood samples were collected during routine laboratory tests. Piperacillin concentrations were quantified by high performance liquid chromatography (Pharmacology, Cochin Hospital, Paris, France).

Pharmacokinetics model : Monolix.
Monte Carlo simulations :

- 50% $fT_{>MIC}$, 50% $fT_{>4 \times MIC}$, 100% $fT_{>MIC}$, and 100% $fT_{>4 \times MIC}$
- MICs from 0.25 to 128 mg.L⁻¹

RESULTATS

50 patients, 132 prélèvements

- sex ratio : 24/26
- Age : 2.3 (0.1-18) years old
- Weight : 11.9 (2.7-50) kg
- Dosing regimen : 300 (150-470) mg.kg⁻¹.j⁻¹
- Comorbidities : 46 (92%)
- PELOD-2 : 10 (0-16)
- eGFR : 142 (29-675) mL.min⁻¹.1.73m⁻²
- 23 infections in 22 patients (18 pathogens with measured MIC)
- Death : 14 (28%)

Pharmacokinetics parameters (Figure 1, 2 et 3, Table 1)

- One-compartment model
- First order elimination

Equations :

- $CL_i = 12.6 \times (BW_i/70)^{0.75} \times (eGFR_i/142)^{0.42}$
- $V_i = 24.6 \times (BW_i/70)^1 \times 1.5^{PEL2}$

Table 1. Estimates of the final population pharmacokinetics parameters of Piperacillin standardized for a body weight of 70 kg

	Estimations	RSE (%)
Structural model		
CL _{pop} (L.h ⁻¹)	12.6	10
V _{pop} (L)	24.6	17
PWR(eGFR)	0.42	6
Sev	1.5	25
Statistical model		
ωCL	0.54	14
ωV	0.41	29
Residual proportional error	0.18	23
Residual additive error	4	26

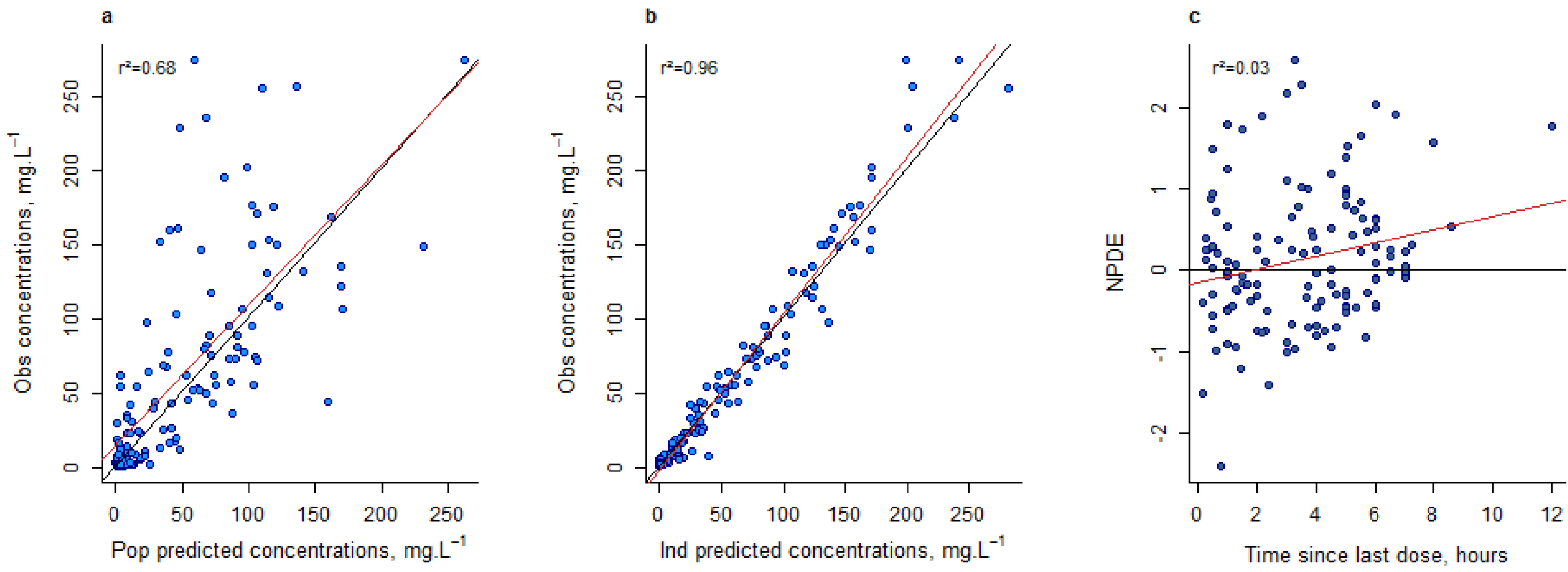


Fig. 1 Goodness-of-fit plots. *a*, Observed (Obs) concentrations versus population (Pop) predicted concentrations. *b*, Observed (Obs) concentrations versus individual (Ind) predicted concentrations. *c* Normalized prediction distribution error (NPDE) versus time. The red lines depict the regression line.

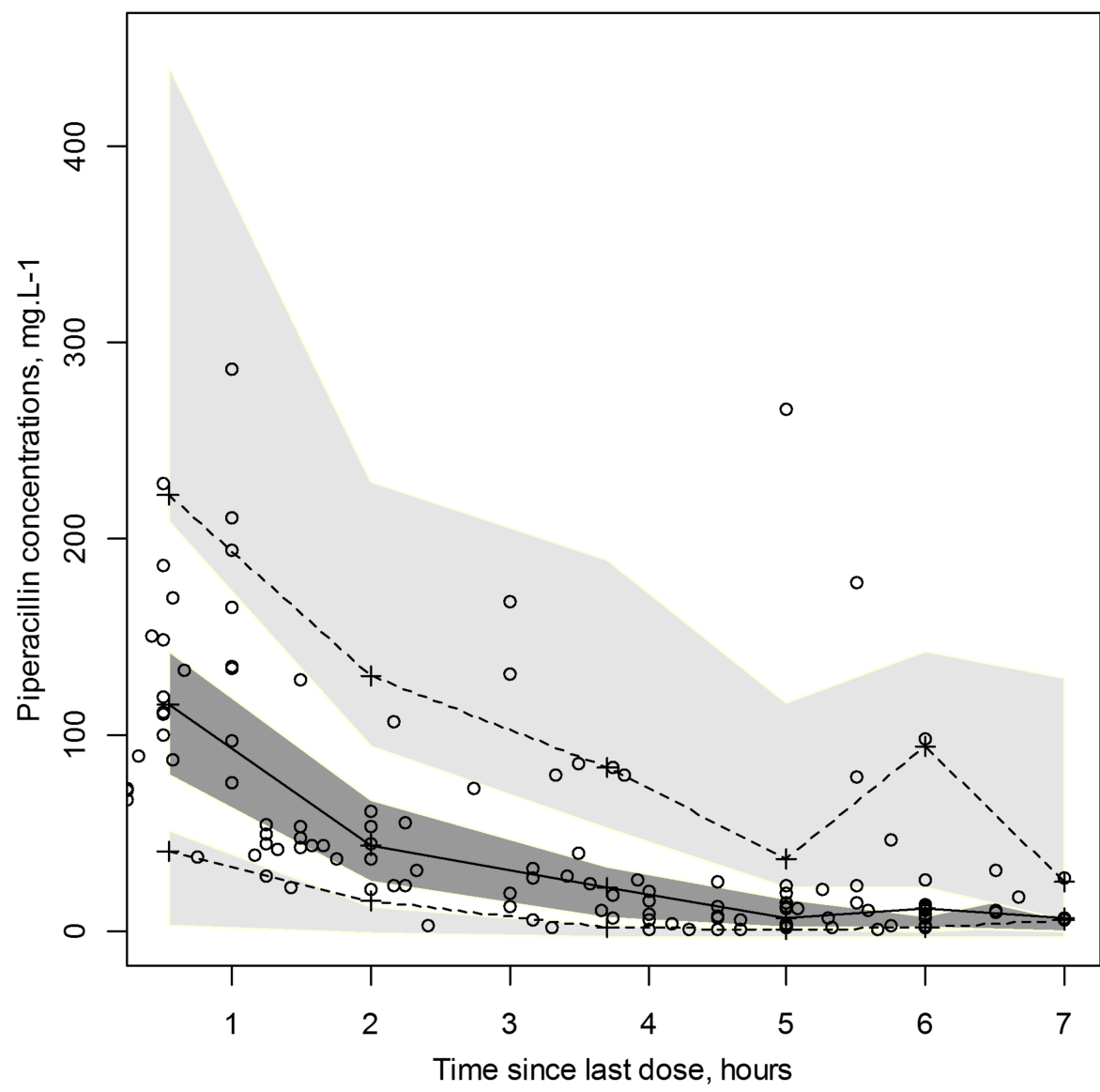


Fig. 2 Prediction-corrected visual predictive check. The thick and dashed lines depict the 10th, 50th, and 90th percentiles of observed data. The grey areas represent the 95th confidence interval of the 10th, 50th, and 90th percentiles.

Table 2. Attainment of the pharmacokinetic target

	50% $fT_{>MIC}$	50% $fT_{>4 \times MIC}$	100% $fT_{>MIC}$	100% $fT_{>4 \times MIC}$
Cohort (n=50)	29 (58%)	15 (30%)	17 (34%)	5 (10%)
Patients with an identified pathogens and MIC (n=18)	15 (83.3%)	13 (72.2%)	12 (66.7%)	5 (27.8%)

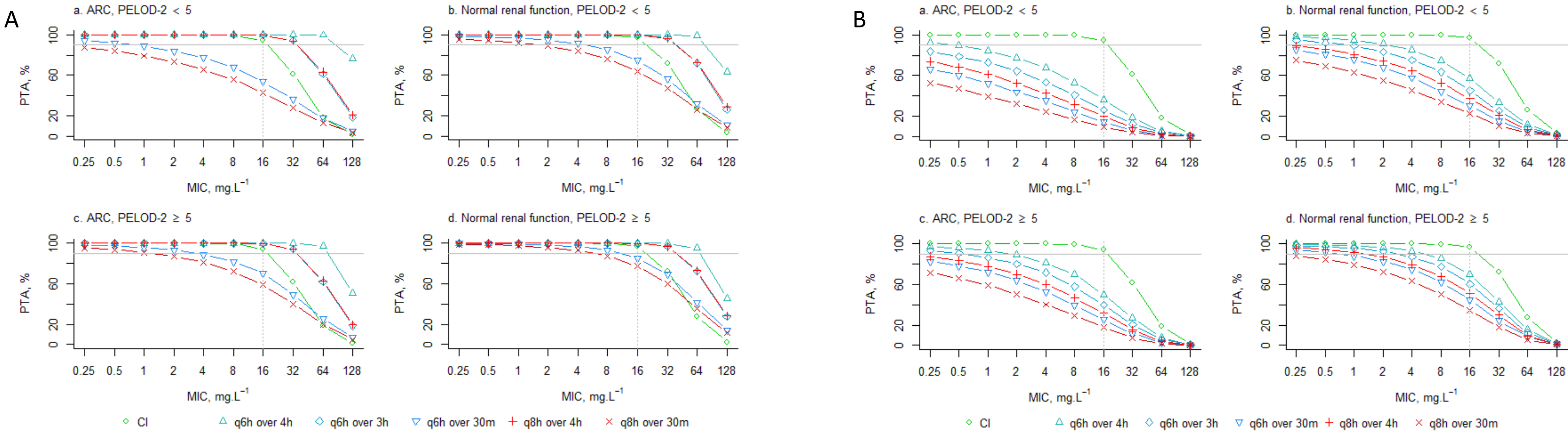


Fig. 3 Probability of target attainment obtained from 6000 simulations for a target defined as 50% $fT_{>MIC}$ (A) and 100% $fT_{>MIC}$ (B) . Four groups were defined according to renal function (a and c for augmented, and b and d for normal) and PELOD-2 severity score (a and b if < 5 , and c and d if ≥ 5). Daily dosing regimens were defined according to renal function: 400 mg.kg⁻¹.day⁻¹ for augmented, 300 mg.kg⁻¹.day⁻¹ for normal. Various infusion modalities were tested: every x hours (qxh), continuous infusion (CI), administered over various periods (30 minutes, 3 hours, and 4 hours).

DISCUSSION & CONCLUSION

- Piperacillin standard dosing regimens in critically ill children are insufficient to reach the PK target of 50% $fT_{>MIC}$ or 100% $fT_{>MIC}$.
- Between-subject variability is explained by eGFR and PELOD-2 severity score.
- Continuous or extended infusion should be used for patients, especially those with augmented renal clearance [4-6].
- Accurate estimation of the glomerular filtration is a major issue in the PICU that must not be overlooked, and thus necessitating additional exploration.

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