Assessment of Piperacillin-Tazobactam Variability in Obesity Through Population Pharmacokinetic Modeling

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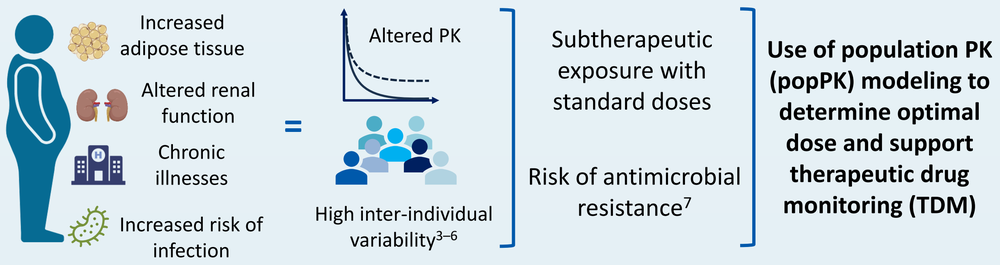
Introduction

- Obesity, a global epidemic affecting 890 million adults worldwide is diagnosed by a body mass index (BMI) ≥ 30 kg/m², anthropometric measures above thresholds (e.g. waist circumference) and signs and symptoms of organ dysfunction[1,2]
- Piperacillin-tazobactam is a widely used broad-spectrum beta-lactam antibiotic[3,4]
- It exhibits time-dependent activity and relies on precise dosing regimens to maintain therapeutic efficacy[3,4]



Objectives

1. Describe piperacillin's PK in obese adults with popPK modeling
2. Evaluate PK/pharmacodynamics (PD) target attainment throughout different doses in obese adults

Methods

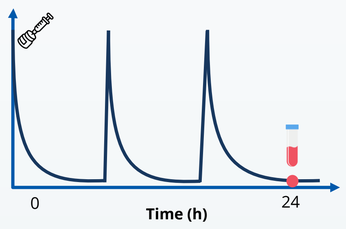
Validation dataset

Prospective pilot study

Hôpital Charles LeMoyne – Centre affilié universitaire et régional de la Montérégie – Université de Sherbrooke

- ✓ Obese adults
- ✓ Piperacillin-tazobactam administration in the last 24h

Standard infusion (30-min) or Prolonged infusion (3- or 4-h)



External evaluation

Evaluation of models developed on obese and critically ill adults[3,8,9]

NONMEM® – The program for Nonlinear Mixed Effects Modeling; RStudio®

Prediction error (PE)	$\frac{C_{pred} - C_{obs}}{C_{obs}} \times 100\%$
Bias (MDPE)	Median(PE) **±20%**
Imprecision (MDAPE)	Median(|PE|) **≤30%**

If models fail to accurately predict concentrations, a new model can be built

New model

Development of a popPK model

- $PRIOR subroutine for sparse datasets
  - Stabilizes parameter estimation
  - From studies found in external evaluation
- Internal validation
  - Goodness-of-fit plots
  - Bootstrap resampling
  - Simulation-based diagnoses (pcVPC, NPDE histogram, QQ plots, etc.)

Monte Carlo simulations

Probability of target attainment (PTA) for multiple dosing regimens

- 2 g
- 3 g
- 4 g

- Intermittent
- Prolonged
- Continuous

Minimum inhibitory concentration (MIC) range
0.5 to 64 mg/L

100% $fT_{>MIC}$

Results

Table 1. Patient characteristics of validation dataset and the best-performing studies included in the evaluation

	HCLM	Chung et al.[10]	Kong et al.[11]	Andersen et al.[12]
***N* (F/M)**	45 (22/23)	27 (10/17)	435 (179/256)	22 (10/12)
Blood samples (*n*)	34	198	3798	176
Age (years)	63.78 (18.02)	51 (12)	46 [0.003–94]	57 (33–76)
Weight (kg)	100.6 (15.93)	122 (47)	73.1 [0.5–200]	76 (64–82)
Body mass index (kg/m²)	37.1 (7.24)	39.9 (15.7)	–	–
Creatinine clearance (mL/min)	81.73 (45.91)[a]	109 (58)[b]	–	83.9 (46–152)[a]
Creatinine (µmol/L)	104.73 (62.95)	–	73.7 [17.7–512.8]	97 (66–132)
Infusion type	I/P	P	I/P	I
Estimated CL (L/h)	9.98	11.3	10.6	8.58
Estimated V_c (L)	24.8	31.3	10.4	12.4
Estimated Q (L/h)	–	–	15.2	3.54
Estimated V_p (L)	–	–	11.58	3.48

Data presented as mean (standard deviation) or median [range]
HCLM Hôpital Charles-Le Moyne, *I* intermittent, *P* prolonged, *CL* clearance, V_c central volume of distribution, *Q* intercompartmental clearance, V_p peripheral volume of distribution
[a] Estimated with Cockroft-Gault equation
[b] Measured in urine

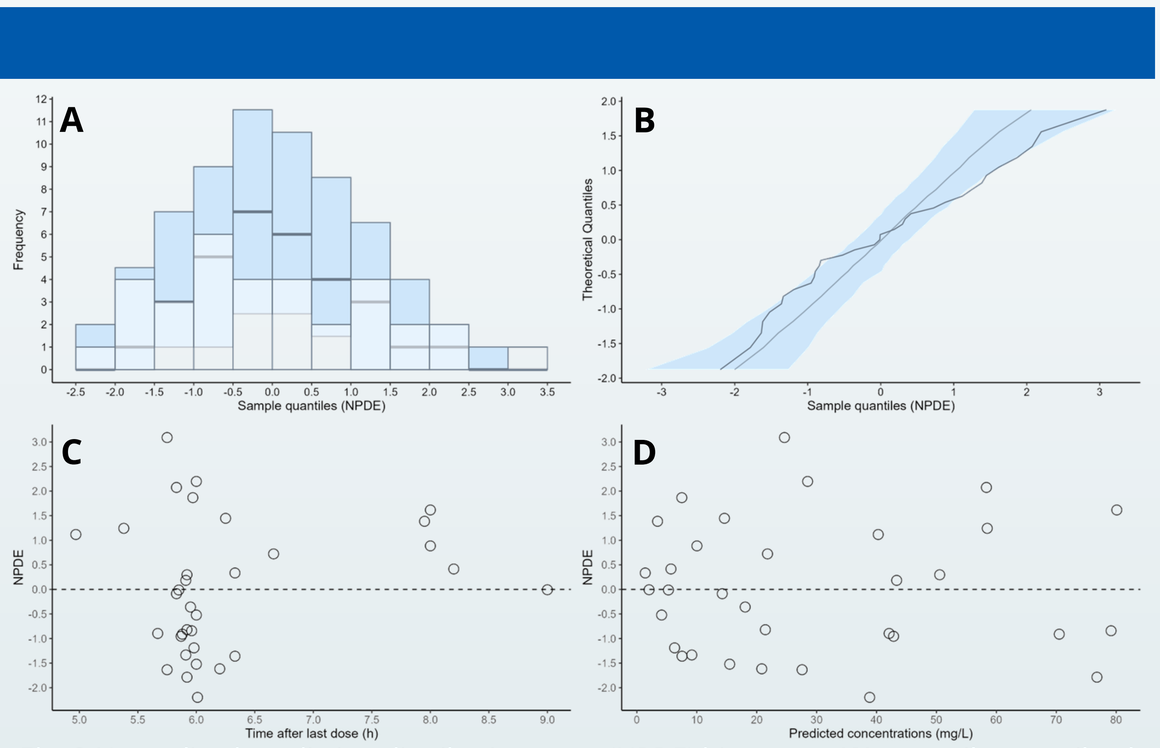


Fig. 3 Normalized prediction distribution error (NPDE) histogram **(A),** quantile-quantile plot **(B)**, NPDE vs. time after last dose **(C)**, NPDE vs. population predicted concentrations **(D)**

Table 2. Bias and imprecision of the 3 best-performing models

	Population predictions		Individual predictions	
	MDPE (%)	MDAPE (%)	MDPE (%)	MDAPE (%)
Obese adults				
Chung et al.[10]	-18	57.7	-6.6	22.6
Kong et al.[11]	7.8	58.9	-6.7	6.7
Critically ill adults				
Andersen et al.[12]	8.3	54.6	-1.1	1.5

MDPE median predicted error, *MDAPE* median absolute predicted error

*Model development using the **$PRIOR** subroutine from the model Chung et al.[10]*

Table 3. Final popPK model estimates of Piperacillin

Parameter	Estimate (%RSE) [%Shr]	Bootstrap estimate (95% CI)
$V = \theta_1$		
θ_1 (L)	24.8 (17.5)	25.2 (21.8–28.5)
$CL = \theta_2 \times (CL_{CR}/68.7)^{\theta 3}$		
θ_2 (L/h)	9.98 (11.7)	10.0 (8.32–11.9)
θ_3	0.756 (11.5)	0.756 (0.516–0.941)
Interindividual variability		
ω_V (%)	33.9 (15.9) [25.0]	34.8 (31.4–42.4)
ω_{CL} (%)	21.1 (22.5) [8.00]	20.0 (16.3–26.1)
Residual variability		
$\sigma_{proportional}$ (%)	20.1 (48.0) [48.0]	19.0 (14.9–34.9)

RSE relative standard error, *Shr* shrinkage, *CI* confidence interval, *V* volume of distribution (L), *CL* clearance (L/h), CL_{CR} creatinine clearance

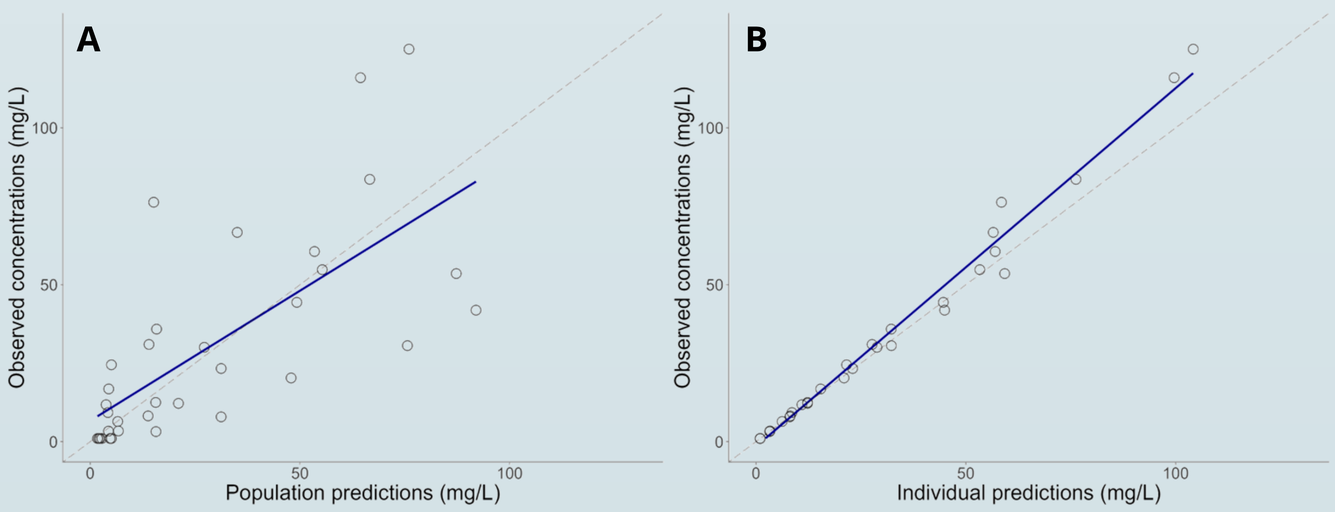


Fig. 1 Observed concentrations vs. population predicted concentrations **(A)** and individual predicted concentrations **(B)** of the final model

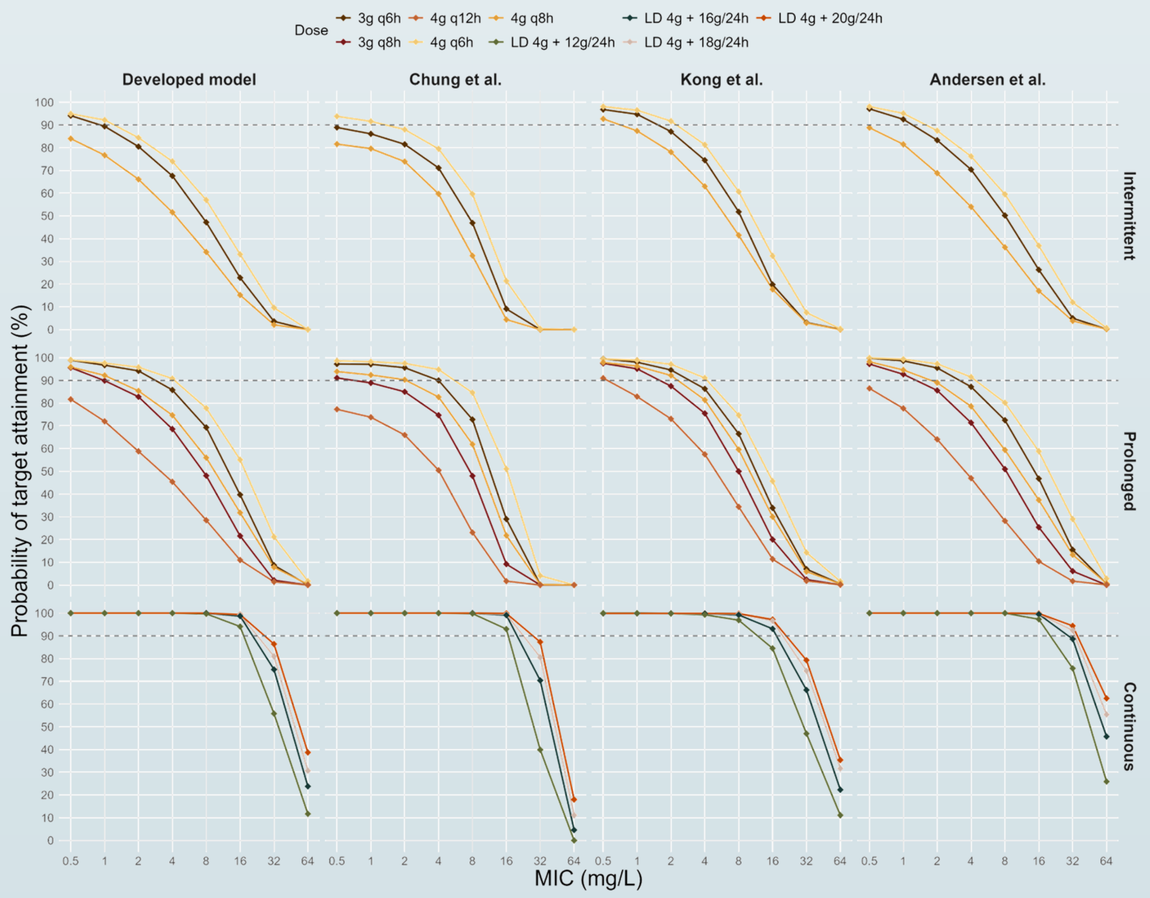


Fig. 4 Probability of target attainment of piperacillin at 100% $fT_{>MIC}$ using the developed model and models from the external evaluation[10–12] with intermittent (30 min), prolonged (half of dosing interval), and continuous infusion strategies (24h)
qxh every x hours, *LD* loading dose, *MIC* minimum inhibitory concentration

Conclusion

- Models evaluated in the external evaluation had acceptable biases (MDPE) but imprecisions (MDAPE) remained above thresholds
- Despite sparsity of data, a popPK model of piperacillin was built by using prior knowledge from a previously built model[10]
- CL_{CR} was a significant covariate on CL and no covariate screening was done on V (trough concentrations)
- Higher doses and prolonged or continuous infusions may help attain higher PK/PD targets in obese adults
- Future work should rely on larger cohorts and richer sampling designs to investigate safety and clinical outcomes

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