

Toward Precision Dosing of Ceftriaxone in Children with Sickle Cell Disease

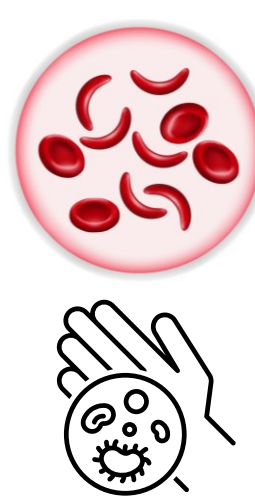
Aysenur Yaliniz^{1,2}, Laurence Clouâtre², Thomas Pincez^{3,4}, Niina Kleiber^{3,4}, Yves Pastore^{3,4}, Yves Théorêt^{4,5}, Julie Autmizguine^{3,4,5}, Amélie Marsot^{1,2,4}

¹STP2 Laboratory, Faculty of Pharmacy, Université de Montréal, Canada, ²Faculty of Pharmacy, Université de Montréal, Canada,

³Department of Pediatrics, Faculty of Medicine, Université de Montréal, Canada, ⁴Research center, CHU Sainte-Justine, Canada,

⁵Department of Pharmacology and Physiology, Faculty of Medicine, Université de Montréal, Canada

Introduction

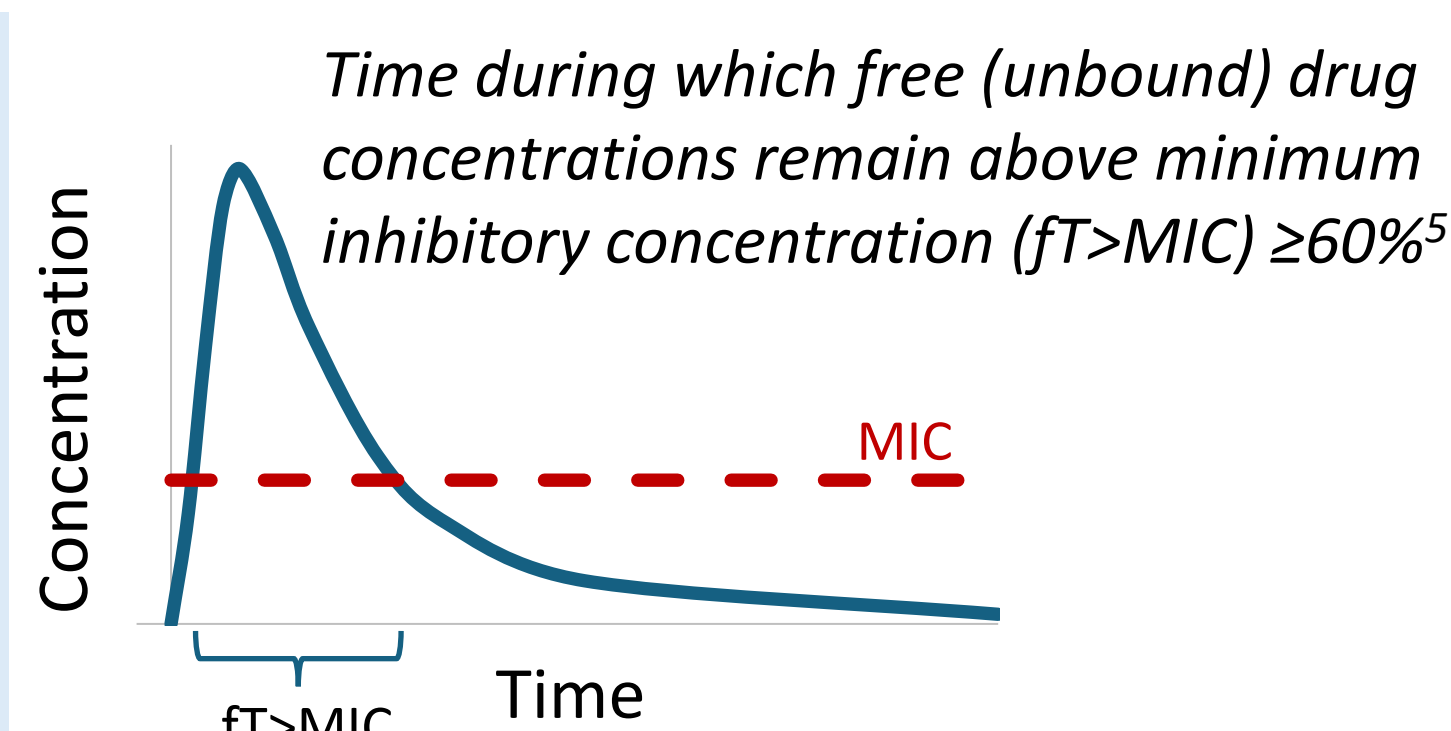


Sickle cell disease (SCD): One of the most common inherited hemoglobin disorders worldwide, leading to severe health complications¹⁻³

- Infections: leading cause of mortality in patients with SCD¹⁻³
- High risk of severe infections such as sepsis, meningitis and pneumonia¹⁻³

Ceftriaxone: One of the most commonly used antibiotics in SCD patients^{1,4}

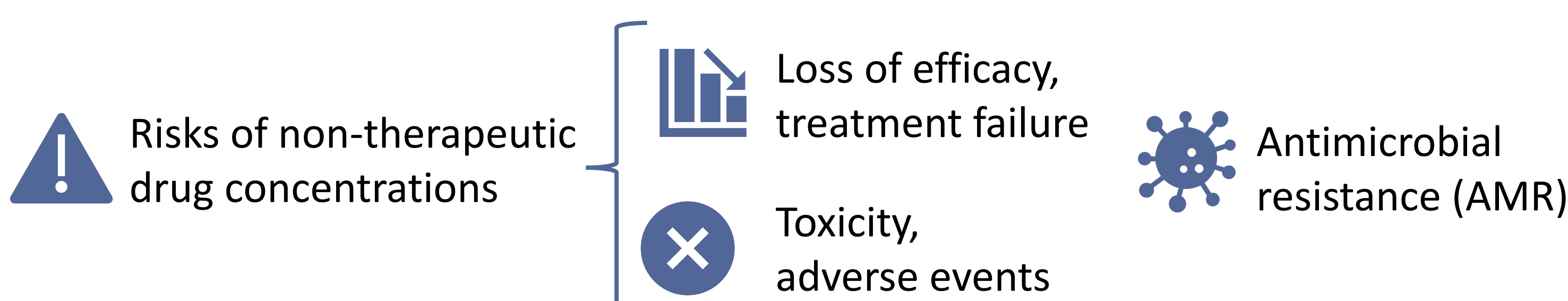
- ✓ β -lactam cephalosporin^{1,4}
- ✓ Broad-spectrum antimicrobial activity^{1,4}
- ✓ Long half-life $\rightarrow$ once-daily administration^{1,4}
- ✓ Extensive and saturable albumin binding^{1,4}
- ✓ Pharmacodynamic (PD) efficacy target $\rightarrow$



Pediatric patients with SCD: Age- and disease-related characteristics may affect ceftriaxone pharmacokinetics (PK) and target attainment

- Multisystem disease involving several organs, including the kidneys, primary elimination route of ceftriaxone^{2,4}
- Variations in the unbound fraction⁶

Are standard pediatric dosing regimens suited for this subpopulation?



Solution: Population pharmacokinetic (popPK) modeling

- ✓ Characterize ceftriaxone PK in pediatric SCD patients
- ✓ Inform the optimization of dosing regimens to improve target attainment

Objectives

- To evaluate published pediatric popPK models of ceftriaxone
- To identify the model with the best predictive performance in patients with SCD

Methods

1- Literature review through PubMed



- From inception to January 2026
- Ceftriaxone popPK models (nonlinear mixed-effects modeling)
- Pediatric SCD patients, < 18 years old

"ceftriaxone, pediatrics and pharmacokinetics"

2- Prospective data collection and blood sampling

- Centre Hospitalier Universitaire Sainte-Justine (CHUSJ) Montreal, 03/2022 – 07/2023
- Patients under 18 years old and diagnosed with SCD
- Patients receiving intravenous (IV) or intramuscular (IM) ceftriaxone
- Opportunistic blood sampling strategy
- Quantification of total plasma concentrations using HPLC-MS/MS (high-performance liquid chromatography-tandem mass spectrometry)



3- Statistical analyses

- Descriptive statistical analyses
- Two-tailed tests were done to compare the populations ($\alpha=0.05$) (Shapiro-Wilk, Wilcoxon signed-rank, Chi-squared)



4- Pharmacokinetic analysis – External evaluation

- Performed by calculating prediction error (PE), bias and imprecision

$$PE(\%) = \frac{(Concentration_{predicted} - Concentration_{observed})}{Concentration_{observed}} \times 100\%$$

$$Bias = Median(PE\%)$$
$$Imprecision = Median|PE\%|$$



- Pre-established ranges for satisfactory model predictive performance
 - $\pm 20\%$ for bias and $\leq 30\%$ for imprecision^{7,8}

Results

Records identified
n=147

Full-text articles
assessed
n=25

Studies retained⁹⁻¹⁶
n=8

Figure 1. Literature review results based on PRISMA principles

Table 1. Characteristics of pediatric SCD patients

Characteristics (units)	Median [range]
Number of patients (M/F)	17 (6/11)
Age (years)	4.92 [0.25-9.83]
Body weight (kg)	19.9 [6.02-28.3]
Height (cm)	109 [45-137]
Serum creatinine (mg/dL)	42 [33-58]
Administered dose (mg/kg)	68.2 [46.1-84.6]
Number of occasions	19
Number of blood samples [range per patient]	21 [1-3]

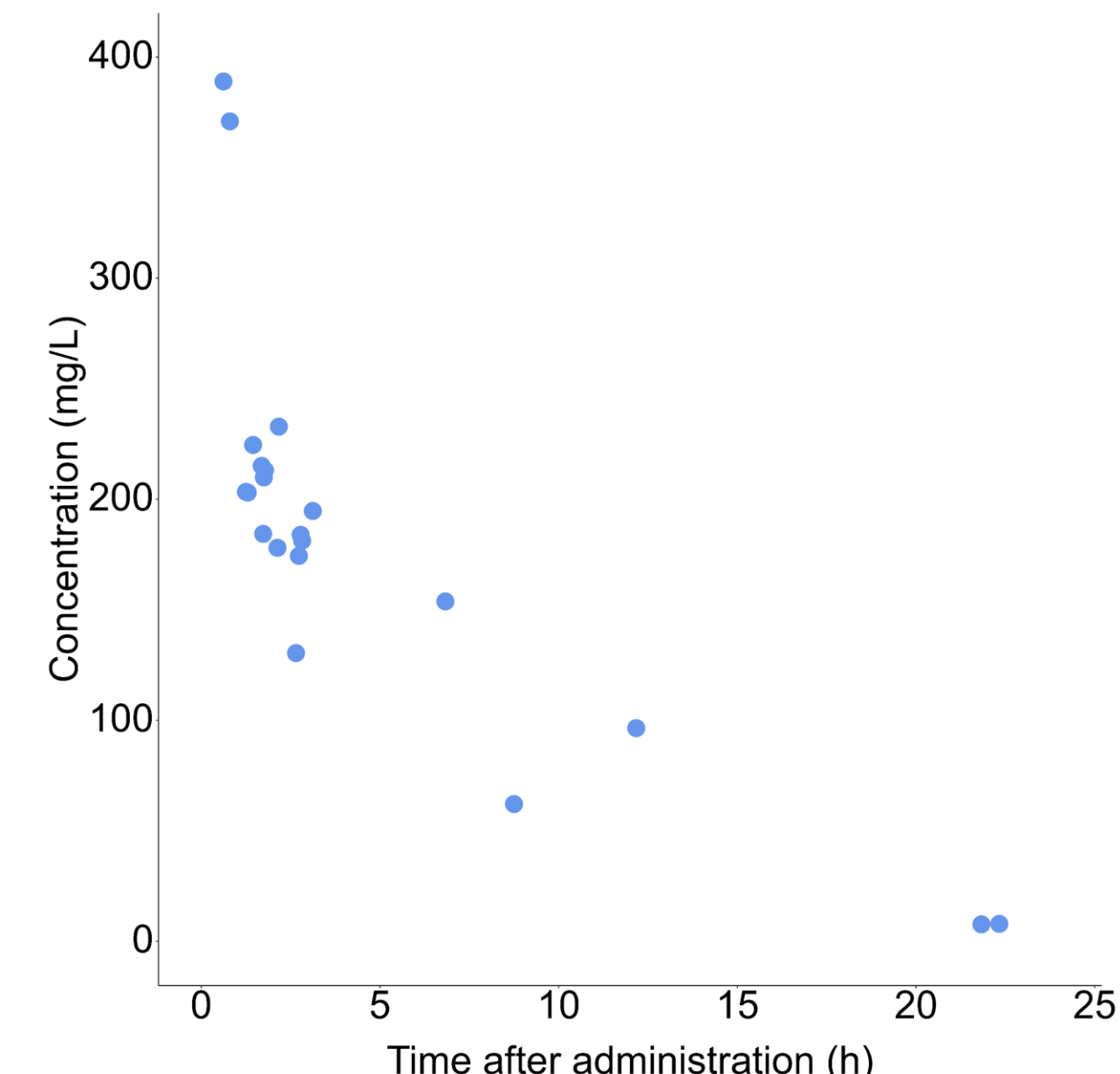


Figure 2. Concentration-time profile

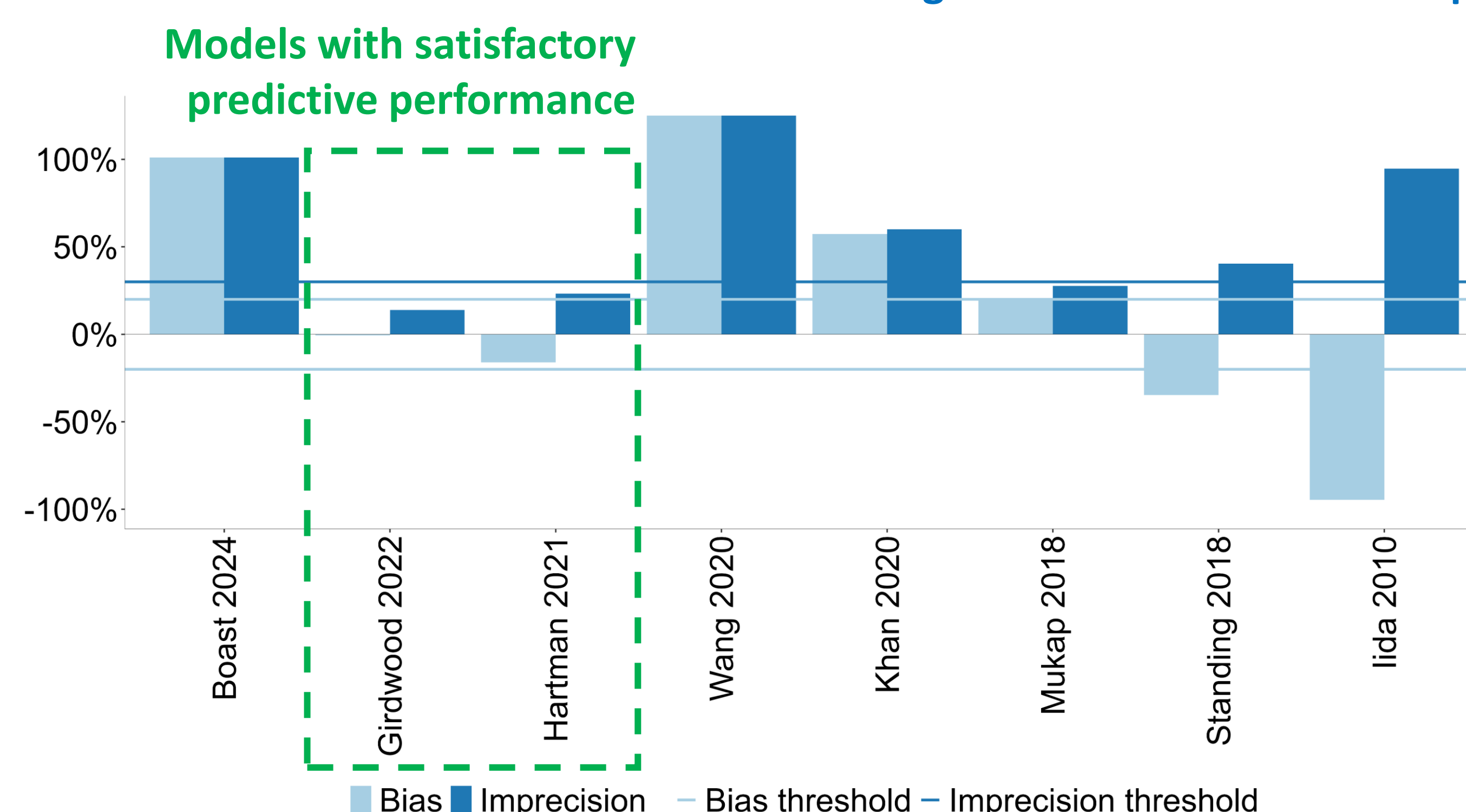


Figure 3. Predictive performance of retained popPK models

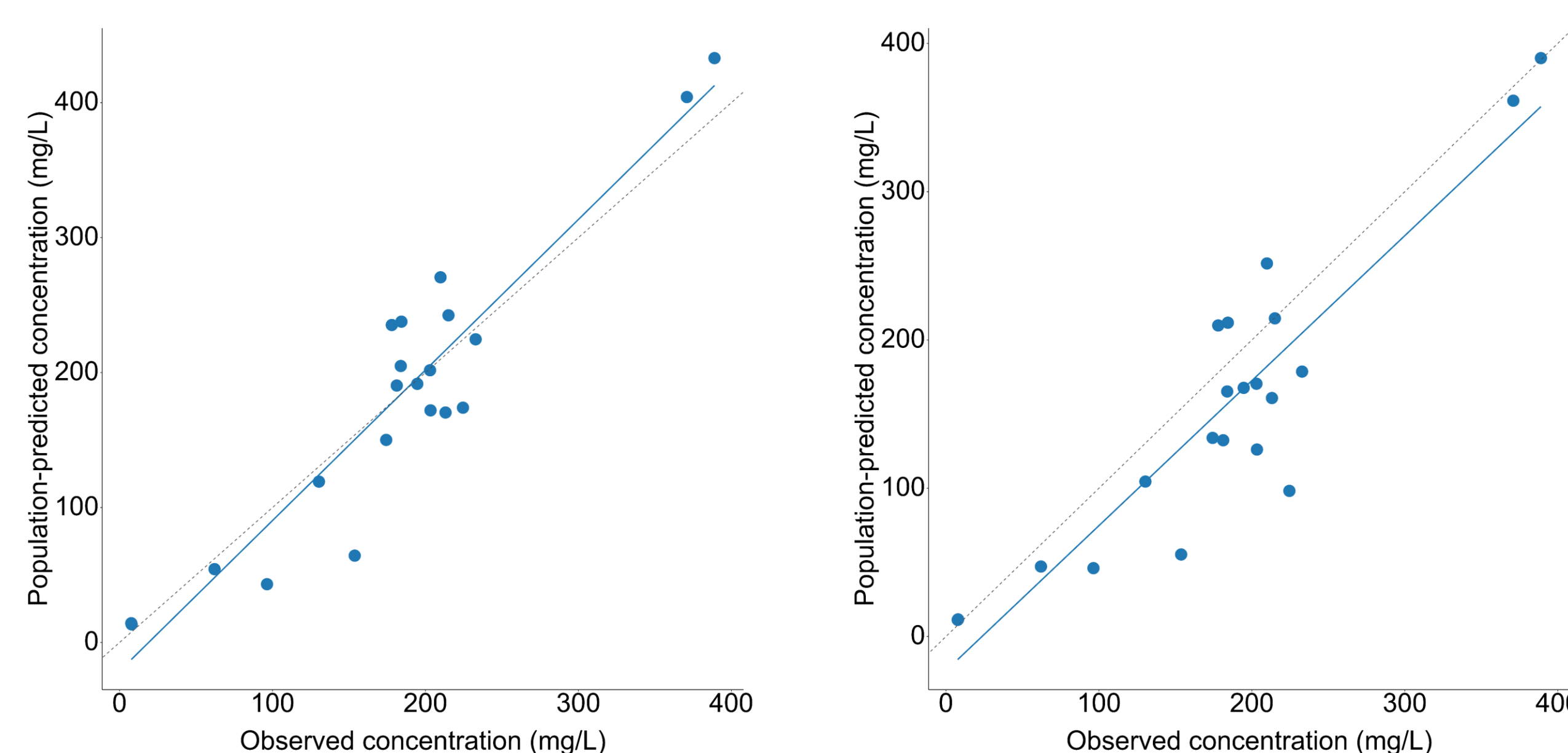


Figure 4. Goodness-of-fit plots of the two satisfactory popPK models

Girdwood¹⁰ (left) and Hartman¹¹ (right). Dashed and solid lines represent identity and regression lines, respectively.

Key findings

- ✓ Two ceftriaxone popPK models^{10,11} were identified as suitable for pediatric patients with SCD in Quebec
- ✓ Key covariates: body weight and renal function^{10,11}
- ✓ Findings were consistent with the central role of body size in pediatrics and the drug's predominant renal elimination
- ✓ Pediatric popPK models may therefore be applicable to patients with SCD

Perspective

Model-based simulations will be performed to define an optimized dosing regimen that ensures therapeutic target attainment in children with SCD.



- References:**
- ¹Canadian Haemoglobinopathy Association. Consensus Statement on the Care of Patients with Sickle Cell Disease in Canada (2015).
 - ²Ware RE et al. Lancet (2017).
 - ³World Health Organization. Sickle-cell disease (2025).
 - ⁴Seddon M et al. Antimicrob Agents Chemother (1980).
 - ⁵Craig WA. Clin Infect Dis (1998).
 - ⁶Pfizer Canada Inc. Ceftriaxone Sodium for Injection BP [PRODUCT MONOGRAPH] (2022).
 - ⁷Miyabe-Nishiwaki T et al. J Vet Pharmacol Ther (2013).
 - ⁸Hara M et al. Br J Anaesth (2017).
 - ⁹Boast A et al. Antimicrob Agents Chemother (2024).
 - ¹⁰Girdwood S et al. Antimicrob Agents Chemother (2022).
 - ¹¹Hartman SJF et al. Clin Pharmacokinet (2021).
 - ¹²Wang YK et al. Antimicrob Agents Chemother (2020).
 - ¹³Khan MW et al. Eur J Clin Pharmacol (2020).
 - ¹⁴Mukap M et al. Antimicrob Agents Chemother (2018).
 - ¹⁵Standing JF et al. Clin Pharmacol Ther (2018).
 - ¹⁶Iida S et al. J Pharm Pharmacol (2011).