

**Authors:** Seef ABDALLA<sup>1,2\*</sup>, William ROYER<sup>1</sup>, Agathe BÉRANGER<sup>1,3</sup>, Claire HEILBRONNER<sup>1,3</sup>, Vanessa LOPEZ-LOPEZ<sup>1,4</sup>, Pierre-Louis LÉGER<sup>1,5</sup>, Romain BERTHAUD<sup>1,6</sup>, David DRUMMOND<sup>1,7</sup>, Martin CASTELLE<sup>1,8</sup>, Elsa KERMORVANT<sup>1,9</sup>, Jean-Marc TRÉLUYER<sup>1,2</sup>, Mehdi OUALHA<sup>1,3</sup>, Déborah HIRT<sup>1,2</sup>

**Affiliations:** <sup>1</sup> Université Paris Cité, Inserm, Pharmacologie et évaluations des thérapeutiques chez l'enfant et la femme enceinte, F-75006 Paris, France, <sup>2</sup> Service de pharmacologie périnatale, pédiatrique et adulte, AP-HP, Hôpital Cochin, rue du Faubourg-Saint-Jacques, F-75014 Paris, Hôpital Européen Georges Pompidou, rue Leblanc, F-75015 Paris, France, <sup>3</sup> Service de réanimation et surveillance continue médicochirurgicales pédiatriques, AP-HP, Hôpital Necker Enfants malades, rue de Sèvres, F-75015 Paris, France, <sup>4</sup> Service d'Anesthésie réanimation pédiatrique et obstétricale, AP-HP, Hôpital Necker Enfants malades, rue de Sèvres, F-75015 Paris, France, <sup>5</sup> Service de Réanimation néonatale pédiatrique, AP-HP, Hôpital Armand-Trousseau, avenue du Docteur Arnold-Netter, F-75012 Paris, France, <sup>6</sup> Service de Néphrologie pédiatrique, AP-HP, Hôpital Necker Enfants malades, rue de Sèvres, F-75015 Paris, France, <sup>7</sup> Service de Pneumologie et allergologie pédiatriques, AP-HP, Hôpital Necker Enfants malades, rue de Sèvres, F-75015 Paris, France, <sup>8</sup> Service d'Immuno-Hématologie et Rhumatologie pédiatriques, AP-HP, Hôpital Necker Enfants malades, rue de Sèvres, F-75015 Paris, France, <sup>9</sup> Service de Néonatalogie et réanimation néonatale, AP-HP, Hôpital Necker Enfants malades, rue de Sèvres, F-75015 Paris, France

## Introduction

- Critically ill patients are subject to important pharmacokinetic alteration that can lead to under- or over-exposure.
- Children and neonates undergo physical growth and organ maturation that alter drug exposure.
- Children with sickle cell disease (SCD) frequently experience organ dysfunctions. [1]
- Cefotaxime is one of the most prescribed antibiotics in pediatric intensive care units. [2, 3]



**Objectives:** The aim of this study is to describe the pharmacokinetics of cefotaxime and its main metabolite desacetyl-cefotaxime in critically ill children and children living with sickle cell disease, assess current dose recommendations and suggest alternative doses for this population if necessary.

## Materials and Methods



**Population studied:** Children were hospitalized in intensive care unit (ICU) at Necker-Enfants Malades Hospital between 2015 and 2021. Main inclusion criteria was children from pediatric ICU, aged less than 18 years old and receiving intravenous cefotaxime doses.

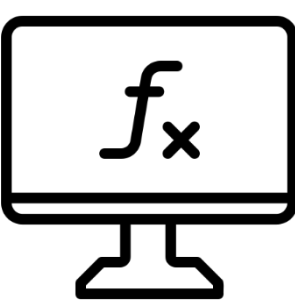


**Samples:** Blood samples were collected as part of their therapeutic drug monitoring.



**Assay:** Both cefotaxime and its main metabolite the desacetyl-cefotaxime plasma concentrations were measured using high-performance liquid chromatography (HPLC) with UV wavelength or HPLC-tandem mass spectrometry (LC-MS/MS).

**Modeling:** A pharmacokinetic analysis has been performed to characterize cefotaxime and desacetyl-cefotaxime time-concentration profiles via a population approach using Monolix. [4]



**Simulations:** 500 Monte-Carlo simulations of trough and steady-state concentrations were computed according to various administration settings for each patient. Tested doses were 100, 150, 200, 300 and 400 mg/kg/J every 4 hours or 6 hours, through a 30-minutes infusion or through a continuous infusion. Simulations were used to calculate probability of target attainments (PTA).

**Pharmacokinetic target:** Cefotaxime free concentrations should be 100% of the time above four times the minimum inhibitory concentration ( $fT > 4 \times MIC$ ), and trough concentrations ( $C_{tr}$ ) or steady-state concentrations (CSS) below 60 mg/L. Cefotaxime free fraction is assumed to be 70%.

## Results

### 242 Children from ICU

- Age: from 0.01 to 18 years old
- Sex: 122 M / 120 F
- Weight: from 2.4 to 98 kg
- eGFR (Schwarz formula): from 6 to 566 L/min/1.73 m<sup>2</sup>
- 50 patients living with Sickle Cell disease



- ✓ 497 cefotaxime concentrations measured
- ✓ 300 desacetyl-cefotaxime concentrations measured

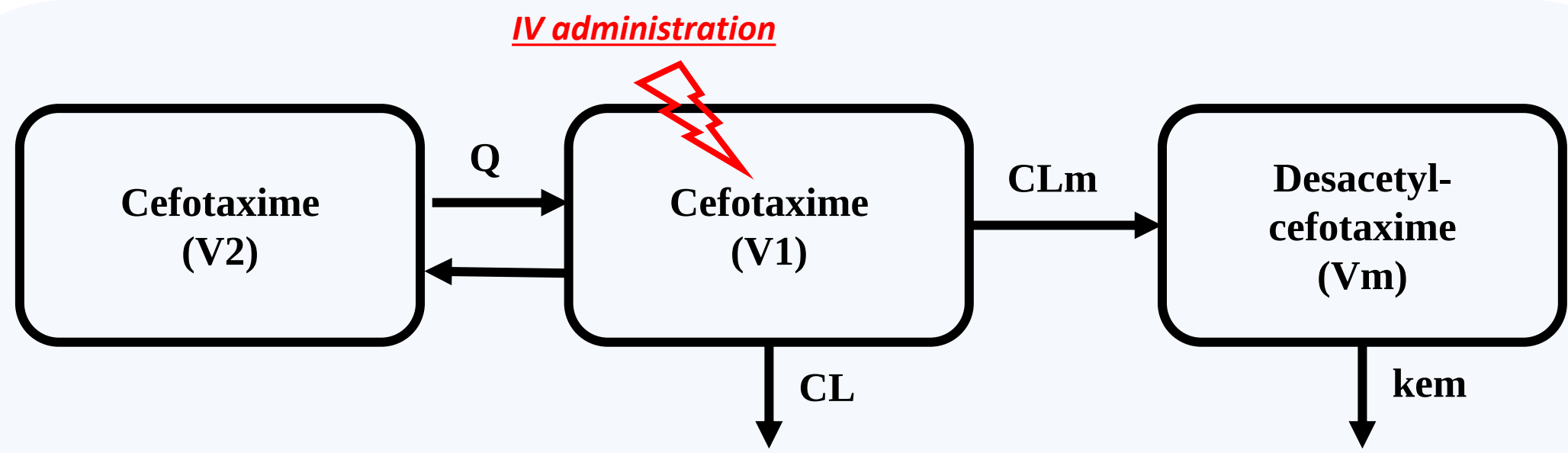


Figure 1. Schematic representation of the final cefotaxime/desacetyl-cefotaxime pharmacokinetic model.



### Pharmacokinetic model:

Data was best described by:

- A **two-compartment model** for cefotaxime with first-order absorption and elimination
- An **additional compartment for desacetyl-cefotaxime** to represent the metabolization process
- Allometrically scaling** with bodyweight
- An **effect of eGFR** on non-metabolic cefotaxime elimination (CL) and desacetyl-cefotaxime elimination ( $k_{em}$ )
- An **effect of sickle cell status** on non-metabolic cefotaxime elimination (CL)
- A hill equation using post-menstrual age to represent maturation of elimination function (CL and CL<sub>m</sub>) for neonates:

$$f_{mat}(\%) = \frac{PMA^\gamma}{PMA^\gamma + MAT_{50}^\gamma}$$

- On average, 26% of cefotaxime total dose is metabolised to its desacetyl-derivative form
- CL and  $k_{em}$  were on average 60% higher for patients with augmented renal clearance (i.e. eGFR > 200 mL/min/1.73 m<sup>2</sup>) compared to other patients
- Patients with SCD had CL increased by 35% compared to other patients
- In term newborns, 50% of adult elimination capacities were acquired within the first week of life

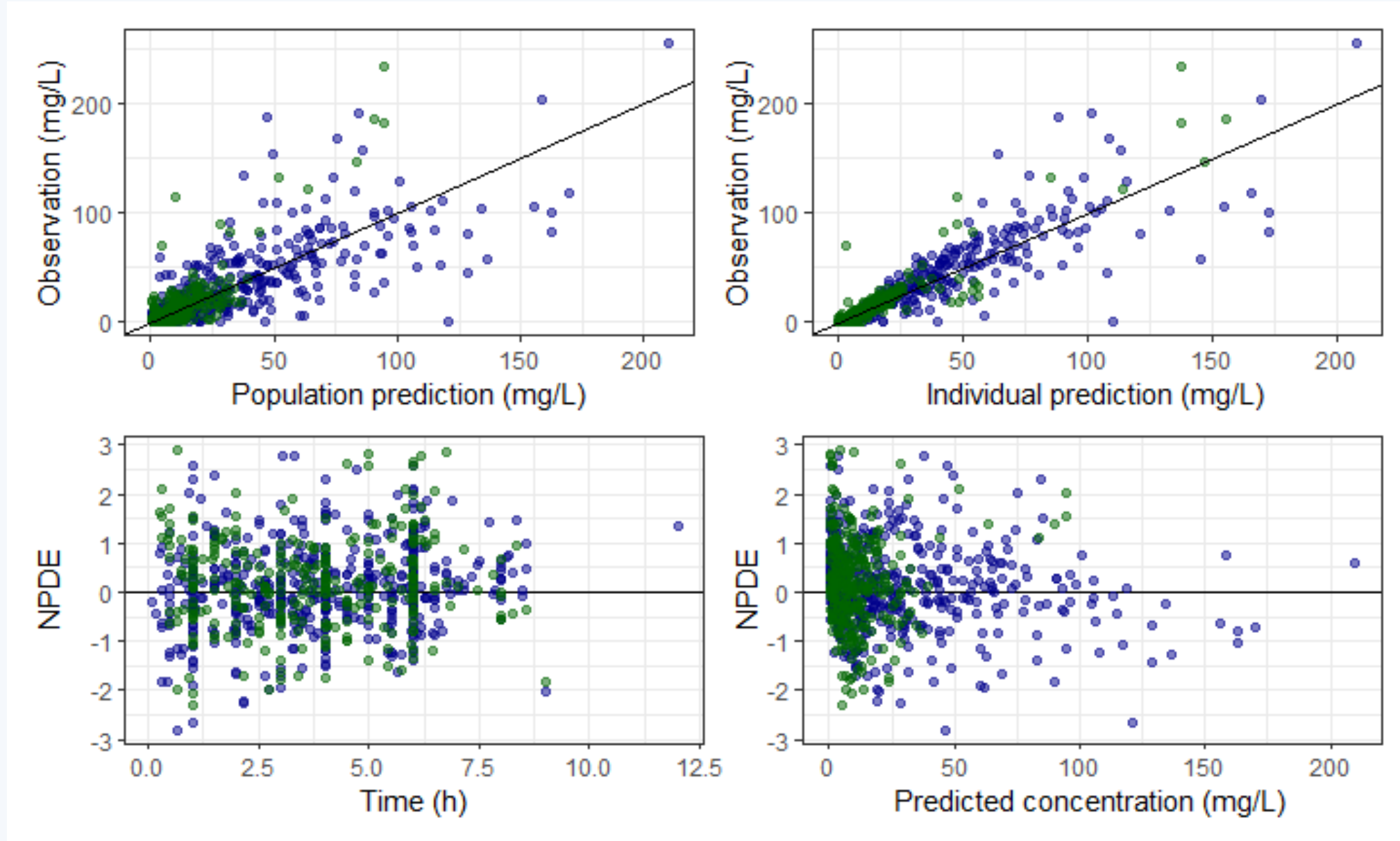


Figure 2. Diagnostic plots of the final cefotaxime/desacetyl-cefotaxime pharmacokinetic model. Blue dots represent cefotaxime observations, red dots represent desacetyl-cefotaxime observations. Dashed orange curve represents the spline.

### Simulations:

- Poor pharmacokinetic target attainments are observed with a « standard » dose of 30-minutes cefotaxime infusion of 100 mg/kg/day every 6 hours within this population

- According to simulations, continuous infusion was the most performant way to optimize the pharmacological target attainment in most scenarios.

- Doses with the highest PTA were displayed in Table 1.

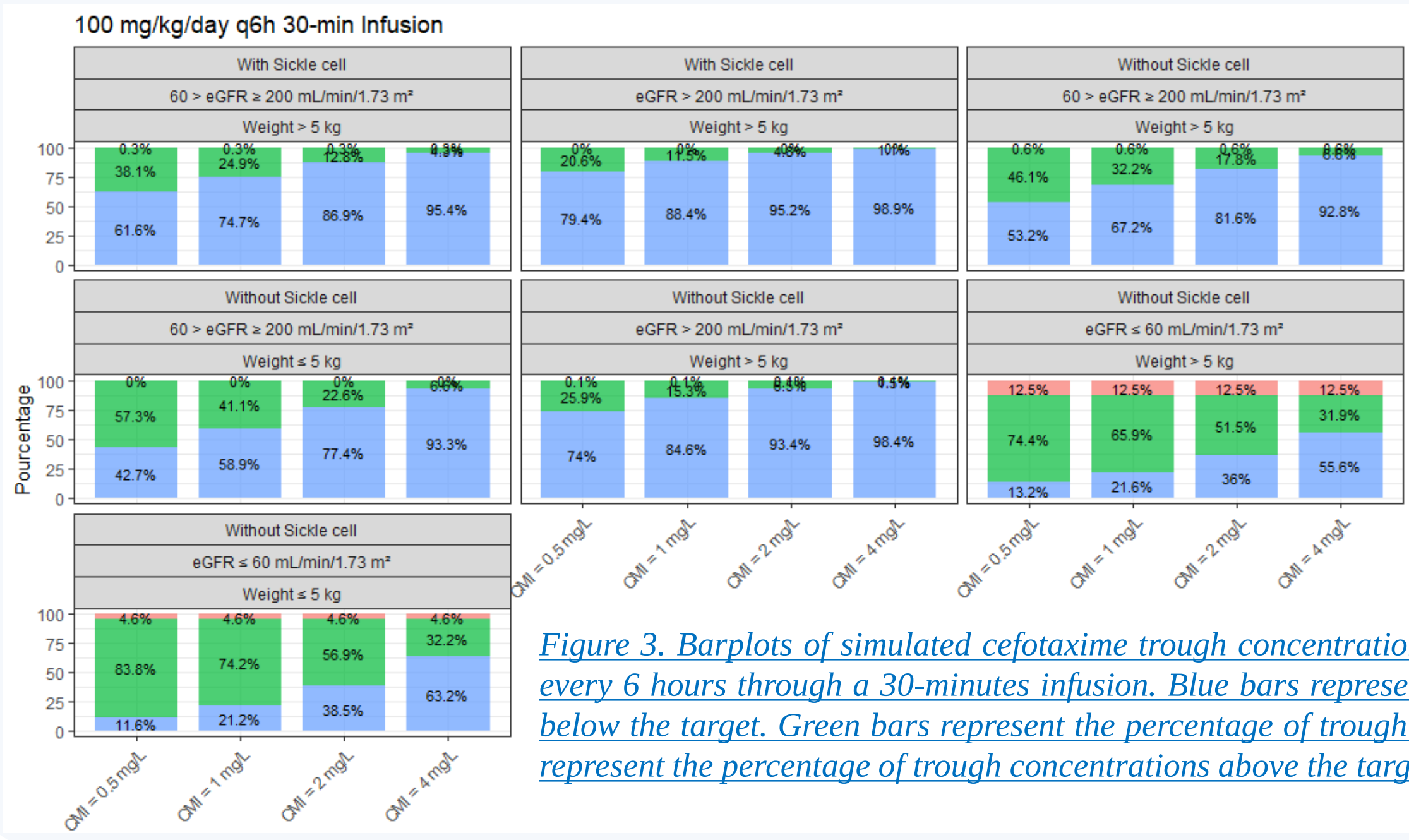


Figure 3. Barplots of simulated cefotaxime trough concentrations for an administration of 100 mg/kg/day every 6 hours through a 30-minutes infusion. Blue bars represent the percentage of trough concentrations below the target. Green bars represent the percentage of trough concentrations within the target. Red bars represent the percentage of trough concentrations above the target.

| Weight | Sickle cell disease | eGFR (mL/min/1.73m²) | CMI                                |                          |                           |                          |
|--------|---------------------|----------------------|------------------------------------|--------------------------|---------------------------|--------------------------|
|        |                     |                      | 0.5 mg/L                           | 1 mg/L                   | 2 mg/L                    | 4 mg/L                   |
| ≤ 5 kg | No                  | ≤ 60                 | 100 mg/kg/day 30-min inf q4h (86%) |                          | 100 mg/kg/day CI (74.21%) |                          |
|        |                     | 60 < eGFR ≤ 200      | 100 mg/kg/day CI (98.6%)           |                          | 150 mg/kg/day CI (76%)    |                          |
| > 5 kg | No                  | ≤ 60                 | 100 mg/kg/day 30-min inf q4h (76%) |                          | 100 mg/kg/day CI (59.6%)  |                          |
|        |                     | 60 < eGFR ≤ 200      | 100 mg/kg/day CI (95.5%)           |                          | 150 mg/kg/day CI (80.7%)  | 200 mg/kg/day CI (55.7%) |
|        | Yes                 | > 200                | 100 mg/kg/day CI (98.3%)           | 150 mg/kg/day CI (93.8%) | 200 mg/kg/day CI (81.2%)  | 300 mg/kg/day CI (55.3%) |
|        |                     | 60 < eGFR ≤ 200      | 100 mg/kg/day CI (95%)             |                          | 150 mg/kg/day CI (79.3%)  | 200 mg/kg/day CI (53.2%) |

Table 1. Cefotaxime dosing recommendations (and their respective PTA expressed in percentage) administered through continuous perfusion (CI) or 30-minutes infusion every 4 hours (q4h), according to patient characteristics and based on 500 simulations for each patient of our population

## Conclusion

While creating this cefotaxime/desacetyl-cefotaxime population PK model, we identified bodyweight, SCD status and eGFR as significant covariate that influence cefotaxime PK. Continuous infusion was the most performant way to achieve the pharmacological target in critically ill children and neonates, making a first necessary step toward individualized prescription in this fragile population.