Population pharmacokinetics and dosing regimen optimization of intravenous ceftazidime in critically ill children

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Introduction

Ceftazidimeis a third-generationcephalosporin and first-line agent against Gram-negative pathogens in critically ill children. Its time-dependent efficacy depends on free drug concentrations exceeding the MIC (%fT>MIC), but critical illness, augmented renal clearance, and cystic fibrosis produce substantial pharmacokinetic variability. This study developed a population pharmacokinetic model to optimize ceftazidime dosing in this population.

Methodology

Children aged 0–18 years receiving intravenous ceftazidime in seven specialty units at Necker–Enfants Malades University Hospital were included

ceftazidime plasma concentrations were measured using a HPLC–MS/MS
Data were modeled using nonlinear, mixed-effects modeling software.

Characteristics (ceftazidime):
Plasma protein binding: ~10%
Elimination: glomerular filtration
Half-life: ~1.5–2 h

GRAPHICAL DIAGNOSTIC CRITERIA:
1) Observed concentrations (DV) versus predicted concentrations.
2) NPDE
3) PC-VPC

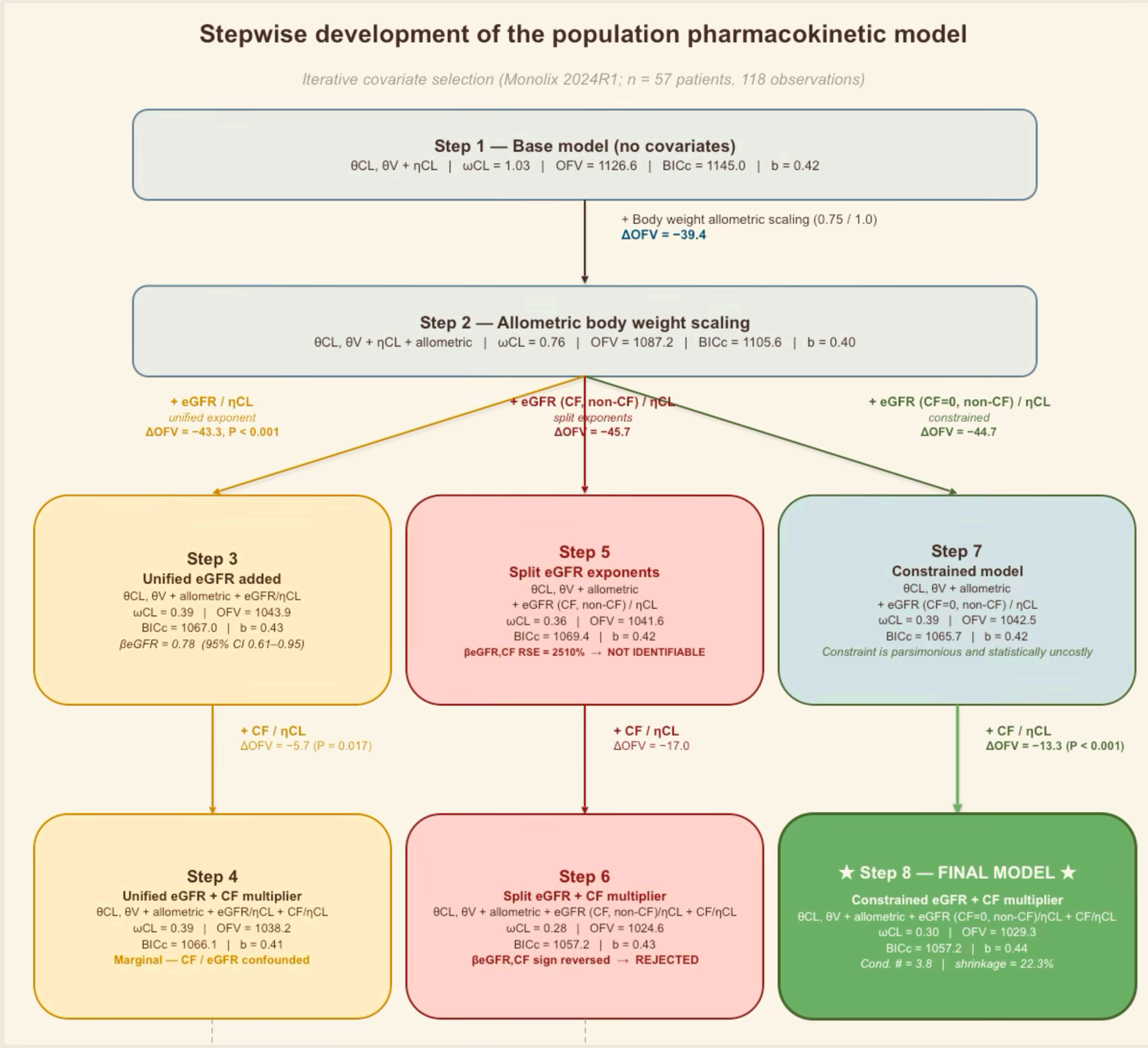
Results

Fifty-seven patients (median age 5.7 years; range 0.09–18.3) contributed 118 plasma ceftazidime concentrations. Fourteen patients (~25%) had cystic fibrosis.

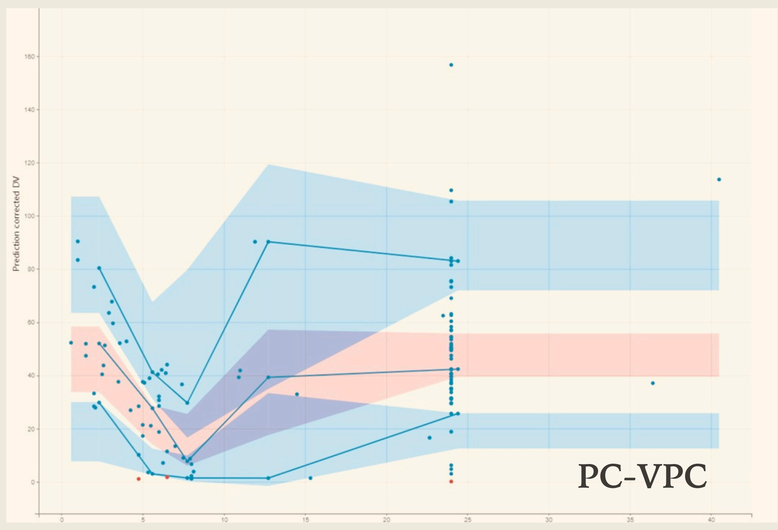
- one-compartment model
- proportional error model
- Retaining only the variabilityon clearance
- Allometric model

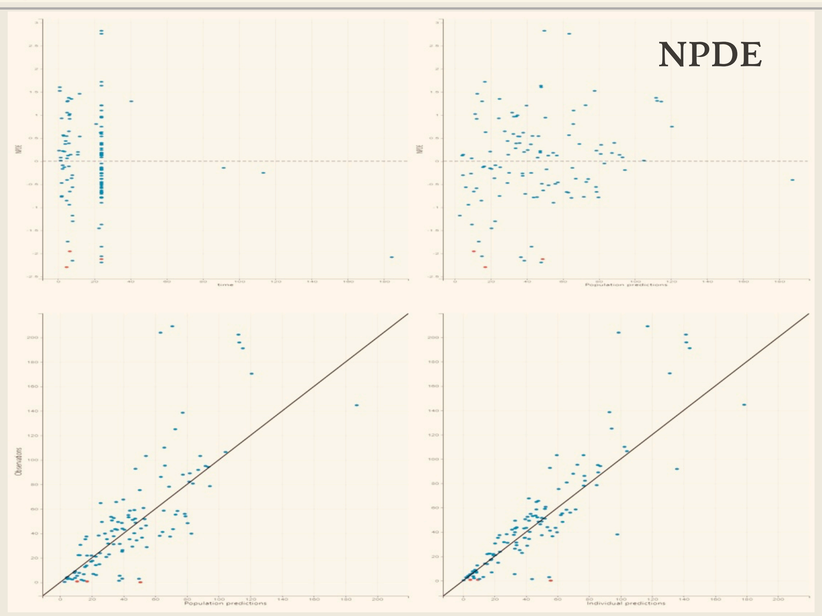
Covariates Evaluated:

BODY WEIGHT | AGE | HEIGHT | eGFR (Schwartz) | BMI | FAT-FREE MASS | SERUM CREATININE | Cystic Fibrosis Status | Organ Dysfunction Categories

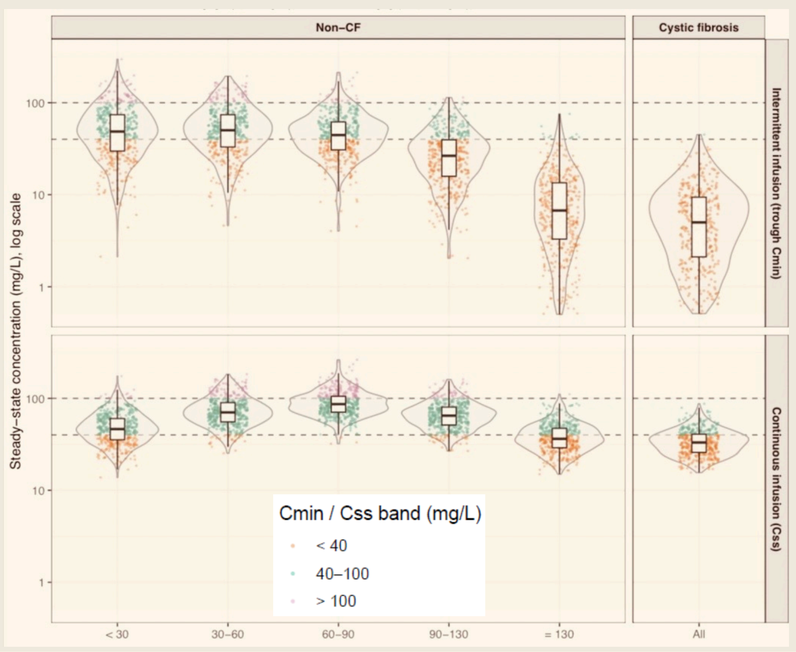


Model validation





Simulation



Simulated steady−state ceftazidime concentrations under renal−adjusted dosing, by eGFR stratum and infusion mode

-Renal−adjusted dosing — n = 500 per group
-All groups capped at 6 g/day
-eGFR < 30: continuous 25 mg/kg/day
-Intermittent 50 mg/kg q24h
-eGFR 30–60: continuous 75 mg/kg/day
-Intermittent 50 mg/kg q8h
-eGFR > 60 & CF: continuous 150 mg/kg/day
-Intermittent 50 mg/kg q8h

Conclusion

Incritically illchildren,ceftazidime concentrations varied widely, leaving many simulated patients outside the target window—under-exposed with augmented renal clearance or cystic fibrosis, over-exposed at low eGFR. Fixed regimens cannot reliably maintain target concentrations. The population pharmacokinetic model supports individualised, renal-function–guided, weight-based dosing, with higher doses and monitoring in cystic fibrosis.