Population pharmacokinetics of continuous-infusion ceftazidime in febrile neutropenic children undergoing HSCT: implications for target attainment for empirical treatment against *Pseudomonas aeruginosa*

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Objectives: To conduct a population pharmacokinetic analysis of continuous-infusion ceftazidime in a retrospective cohort of paediatric HSCT patients who were empirically treated for febrile neutropenia (FN) and who underwent therapeutic drug monitoring of ceftazidime steady-state plasma concentrations (C_{ss}) for optimization of drug exposure.

Methods: A non-parametric approach with Pmetrics was used for pharmacokinetic analysis and covariate evaluation. Monte Carlo simulations were performed to calculate the PTA of the pharmacodynamic determinant of efficacy ($C_{ss}/MIC \geq 4$) against *Pseudomonas aeruginosa* with continuous-infusion ceftazidime dosages of 1–6 g daily. The C_{ss} safety threshold was arbitrarily placed at 100 mg/L and advisable dosages were used.

Results: A total of 46 patients with 70 ceftazidime C_{ss} values were included. Estimated glomerular filtration rate (eGFR) and body surface area were the covariates associated with drug clearance. At the EUCAST clinical break-point of 8 mg/L, simulations showed that continuous-infusion ceftazidime dosages of 4–6 g daily attained optimal PTAs (>90%) across most of 16 different clinical scenarios based on four classes of eGFR (50–145, 145.1–200, 200.1–286 and 286.1–422 mL/min/1.73 m²) and body surface area (0.30–0.64, 0.65–0.88, 0.89–1.34 and 1.35–1.84 m²). In patients with body surface area 0.30–0.64 m² and eGFR ≤ 200 mL/min/1.73 m² the advisable dose of 3 g daily allowed only suboptimal PTAs (<75%). The cumulative fraction of response against MIC distribution of *P. aeruginosa* was >87%.

Conclusions: Continuous-infusion ceftazidime dosages ranging from 3 to 6 g daily according to different classes of eGFR and body surface area may allow optimized empirical treatment of *P. aeruginosa* infections in paediatric HSCT patients with FN.

Introduction

Febrile neutropenia (FN) is one of the most common complications in children who receive induction chemotherapy and undergo HSCT.¹ Bacteraemia accounts for around 30% of bacterial infections in children with high-risk FN,² and Gram-negative bacteria cause 53.9–65% of all reported episodes.^{3,4} *Pseudomonas aeruginosa* is one of the most common aetiological agents, together with *Klebsiella pneumoniae* and *Escherichia coli*.^{3,5}

P. aeruginosa bacteraemia is associated with high fatality rates in children,⁶ and in high-risk FN patients the rate may be as high as

52%.⁷ MDR strains are common.⁸ Current guidelines of the American Society of Clinical Oncology recommend monotherapy with an antipseudomonal β -lactam as empirical therapy in paediatric patients with high-risk FN.⁹ A second Gram-negative agent, such as an aminoglycoside, is reserved for patients who are clinically unstable, when resistant infection is suspected or for patients in centres with a high prevalence of resistant pathogens.⁹

Ceftazidime is an antipseudomonal third-generation cephalosporin that is widely used in patients with FN.¹⁰ Ceftazidime has a low potential for drug–drug interactions, is almost completely renally eliminated (80%–90%) and has low plasma protein binding

(~10%).^{11,12} It may have a more favourable safety profile compared with other antipseudomonal cephalosporins, with a lower risk of neurotoxicity.¹³

β -Lactams are often administered intermittently. However, administration by extended or continuous infusion may optimize the time free plasma drug concentrations are above the MIC ($fT_{>MIC}$) and therefore maximizing time-dependent antibacterial activity.¹⁴ This approach may be helpful especially in critically ill patients and/or in presence of pathogens with borderline susceptibility. There is growing evidence that administering β -lactams by prolonged or continuous infusion may improve clinical efficacy in patients with sepsis.^{15,16} A recent meta-analysis showed that prolonged infusion of antipseudomonal β -lactams for the treatment of patients with sepsis was associated with significantly lower mortality than intermittent infusion.¹⁶

The use of prolonged or continuous infusion of β -lactams is increasing even among the paediatric population,¹⁷ and this includes ceftazidime.^{18–21} The aim of this study was to conduct a population pharmacokinetic analysis in a cohort of paediatric HSCT children with FN who were empirically treated with continuous-infusion ceftazidime and to identify dosing regimens for optimizing empirical treatment of *P. aeruginosa* infections.

Methods

Study design

This retrospective study included a cohort of paediatric patients who underwent HSCT at the Institute for Maternal and Child Health IRCSS Burlo Garofolo (Trieste, Italy) and who received continuous-infusion ceftazidime for the empirical treatment of high-risk FN in the period between June 2012 and December 2017.

Ceftazidime treatment was started with a loading dose (LD) of 60–100 mg/kg infused in 1 h, which was immediately followed by a maintenance dose (MD) of 100–200 mg/kg daily administered by continuous infusion. Dosage adjustments were guided by real-time therapeutic drug monitoring (TDM) of ceftazidime steady-state plasma concentrations (C_{ss}), which were assessed after at least 2 days from starting therapy. Drug dosages were adjusted using linear scaling with a minimum dose modification of 500 mg. The desired range of ceftazidime plasma C_{ss} was set between 32 and 64 mg/L. The rationale was that of optimizing empirical treatment against *P. aeruginosa* by achieving a C_{ss} between 4-fold and 8-fold the EUCAST clinical breakpoint of ceftazidime versus *P. aeruginosa* which is 8 mg/L.²² This strategy may be especially helpful in the presence of severe infections.^{23,24}

TDM of ceftazidime was provided by the Institute of Clinical Pharmacology, Santa Maria della Misericordia University Hospital, Udine, Italy. TDM-guided clinical pharmacological advice for personalized ceftazidime dosages was usually provided to the attending clinicians on the day of the analysis. Ceftazidime concentrations were analysed by means of a validated HPLC with UV detection as described elsewhere.²⁵ Precision and accuracy were assessed by performing replicate analysis of quality control samples against calibration standards. Intra- and inter-assay coefficients of variation were <10%. The lower limit of detection was 0.1 mg/L.

The following demographic and clinical data were retrieved from patient clinical records: age, gender, weight, height, body surface area, duration of therapy, date of HSCT, type of underlying oncological or haematological disease and co-treatment with other antimicrobials. Baseline and end-of-treatment data on serum concentrations of ALT, aspartate aminotransferase (AST) and total bilirubin as well as signs and symptoms of neurotoxicity potentially related to ceftazidime therapy were also collected. Serum creatinine was measured at each TDM instance and

estimated glomerular filtration rate (eGFR) was calculated by means of the Schwartz formula.²⁶ Body surface area was calculated by means of the Mosteller formula.²⁷

Population pharmacokinetic modelling

One- and two-compartment models with zero-order input and first-order elimination from the central compartment were constructed and fitted to the observed concentrations using the non-parametric grid (NPAG) approach contained in the Pmetrics package of R (Laboratory of Applied Pharmacokinetics, Los Angeles, CA, USA).²⁸ Estimates of the assay error were included in the modelling process as a four-term polynomial equation, which relates drug concentrations to the standard deviations of the observations. Both γ and λ were tested in the error model for accounting for process error. Individual pharmacokinetic parameters [total CL, central compartment V and inter-compartment transfer rate constant from the central to the peripheral compartment (k_{cp}) and vice versa (k_{pc})] were estimated by a maximum *a posteriori* (MAP) probability Bayesian technique.

Initially, a base model without covariates was developed and fitted to the data. Subsequently, the relationship between Bayesian estimates of CL and V for each patient and clinically relevant covariates (age, weight, height, sex, body surface area, eGFR, time from HSCT, presence of acute leukaemia) was assessed. A forward-backward selection process for covariate inclusion was adopted by using the Pmetrics PMstep function. A final multivariate model including all the significant covariates was then developed and refitted to the data. The performance of the pharmacokinetic models was assessed by means of visual inspection of the observed-predicted plot, the coefficient of determination of the linear regression of the observed-predicted values and of the likelihood ratio test. Differences in the objective function value (OFV) >3.84 between each pharmacokinetic model and the base model ($P < 0.05$), coupled with evaluation of the Akaike information criterion (AIC), were considered as statistically significant additions to the model. Model performance was evaluated by means of normalized prediction distribution errors (NPDEs), a metric design to allow evaluation of non-linear mixed-effect models.

Monte Carlo simulation analysis for determining the PTA for empirical treatment against *P. aeruginosa*

Monte Carlo simulations for 1000 subjects based on the final model were performed for each of six incremental dosing regimens of continuous-infusion ceftazidime (1, 2, 3, 4, 5 and 6 g q24h) to determine the PTA for optimal empirical treatment against *P. aeruginosa*. Variability of the continuous covariates included in the final model was assessed by splitting each covariate distribution, as observed in our population, into four categories corresponding to four quartiles (0–25th, 25th–50th, 50th–75th and 75th–100th percentile).

Ceftazidime C_{ss} values were simulated at 48 h by means of the Pmetrics simulation engine. The desired pharmacodynamic target was $C_{ss}/MIC \geq 4$ at the EUCAST clinical breakpoint of 8 mg/L. PTAs were considered optimal when $\geq 90\%$.²⁹

For safety purposes, an upper threshold for simulated ceftazidime C_{ss} was placed at 100 mg/L (potential toxicity threshold). The rationale was based on previous studies suggesting that this choice might be helpful in minimizing the risk of neurotoxicity with high-dose continuous-infusion β -lactams.^{18,30} Dosing regimens associated with <10% probability of exceeding this threshold were considered as advisable for empirical treatment against *P. aeruginosa*.

The cumulative fractions of response (CFRs) achievable with the different continuous-infusion ceftazidime dosing regimens were tested against the MIC distribution of *P. aeruginosa* as reported by EUCAST³¹ ($n=32276$ isolates) as well as against the MIC distribution of *P. aeruginosa* collected at our centre in the period January–June 2018 ($n=179$ isolates). The CFR was calculated from the PTA obtained from the Monte Carlo simulation analysis. Computation of the risk-to-benefit ratios, defined as the ratio of the

probability of potential toxicity to the CFR observed for the ceftazidime dosages against *P. aeruginosa*, was also performed.

Ethics

The study was approved by the Ethics Review Board of the Institute for Maternal and Child Health IRCSS Burlo Garofolo, Trieste, Italy. The approval reference number was RC 26/18, Linea 2. Informed written consent was waived due to the retrospective nature of the investigation.

Statistical analysis

The Kolmogorov–Smirnov test was used to assess normal or non-normal distribution of the patients’ data. Accordingly, data were summarized as mean ± SD or median (IQR) in the descriptive statistics. Differences between continuous variables were assessed using Student’s *t*-test or the Mann–Whitney test depending on whether or not the data were normally distributed. All statistical analyses and plotting were performed with R, version 3.4.4 (R foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 46 HSCT children with high-risk FN were included in this study. Table 1 summarizes patient clinical and demographic characteristics. The median (minimum–maximum range) age, body surface area and eGFR were 7.5 years (0.5–16), 0.88 m² (0.34–1.84) and 200.0 mL/min/1.73 m² (50.0–422.6), respectively.

Most of the patients (32/46, 69.6%) had haematological malignancies, with ALL being the most frequent (22/46, 47.8%). Median (IQR) neutrophil count at start of therapy was 0.0 (0.0–10) cells/mm³, with a median duration of neutropenia of 16 (13–19) days.

Ceftazidime treatment was started after a median (IQR) of 6.0 (1.0–11.75) days from HSCT and had median (IQR) duration of 10.5 (7.0–16.0) days. The median (IQR) loading and maintenance doses of ceftazidime were 80.0 (49.2–139.7) and 145.9 (128.3–171.3) mg/kg daily. Median (IQR) total maintenance dose was 3.5 (2.5–5.0) g/day by continuous infusion, with a minimum–maximum range of 1–10 g/day. First TDM assessment occurred after a median (IQR) of 3.0 (2.0–5.75) days from starting therapy, and on that occasion the observed *C*_{ss} values were ≤8 mg/L (*C*_{ss}/MIC ≤1) and ≤32 mg/L (*C*_{ss}/MIC ≤4) in one and in nine patients, respectively. Among those patients who had at least two TDM assessments over time (17/46, 37.0%), the ceftazidime dosage was adjusted in 12 cases. All patients received antibiotic combination therapy. Amikacin (38/46, 82.6%) was the most frequently used, followed by glycopeptides, either vancomycin or teicoplanin (33/46, 71.7%).

No patient had signs of hepatic toxicity. Median baseline versus end-of-treatment levels were 21.0 versus 27.0 IU for AST (*P*=0.261), 21.0 versus 21.5 IU for ALT (*P*=0.437) and 0.62 versus 0.64 mg/dL (*P*=0.791) for bilirubin. Similarly, no episodes of ceftazidime-related neurotoxicity were reported, despite three patients having *C*_{ss} >100 mg/L.

Population pharmacokinetic modelling

A total of 70 plasma ceftazidime *C*_{ss} samples were included in the population pharmacokinetic model. A two-compartment model performed better than a one-compartment model (OFV of 612.9 versus 620.2 and AIC of 622.7 versus 626.6, *R*² of 0.88 versus 0.82,

Table 1. Demographic and clinical characteristics of the population

Total number of patients	46
Age (years), median (IQR)	7.5 (4.0–12.0)
Male/female, <i>n</i> / <i>n</i>	29/17
Weight (kg), median (IQR)	25.0 (14.03–39.80)
Height (m), median (IQR)	1.20 (1.01–1.49)
Body surface area (m ²), median (IQR)	0.88 (0.64–1.34)
eGFR (mL/min/1.73 m ²), median (IQR)	200.0 (145.0–286.0)
Time from HSCT (days), median (IQR)	6.0 (1.0–11.75)
Type of haematological disease, <i>n</i> (%)	
ALL	22 (47.8)
AML	5 (10.9)
juvenile myelomonocytic leukaemia/CML	5 (10.9)
aplastic/Fanconi anaemia	4 (8.7)
neuroblastoma	3 (6.5)
congenital immunodeficiency disorders	3 (6.5)
sickle-cell anaemia	2 (4.35)
Ewing sarcoma	2 (4.35)
Ceftazidime treatment characteristics	
dose/kg/day (mg/kg), median (IQR)	145.98 (128.31–171.27)
<i>C</i> _{ss} (mg/L), median (IQR)	49.23 (36.81–62.88)
no. of TDM instances, median (IQR)	1.0 (1.0–2.0)
duration of treatment (days), median (IQR)	10.5 (7.0–16.0)
additional antibiotics, <i>n</i> (%)	
amikacin	38 (82.6)
teicoplanin	19 (41.3)
vancomycin	14 (30.4)
levofloxacin	13 (28.3)
tigecycline	5 (10.9)
metronidazole	3 (6.5)

for the two- and one-compartment models, respectively). An additive λ term of 4.87 was estimated and included in the error model. Covariates that improved the fit of the model to the data were the patient’s body surface area and eGFR (when applied to ceftazidime CL), and the patient’s height (when applied to ceftazidime V). After the inclusion of these covariates, the OFV and AIC further improved to 578.3 and 596.6, respectively. The final structural model was as follows:

$$CL \text{ (L/h)} = \theta_1 \cdot \left(\frac{\text{body surface area}}{0.88}\right)^{\theta_2} \cdot \left(\frac{\text{eGFR}}{200.5}\right)^{\theta_3}$$
$$V(L) = \theta_4 \cdot \left(\frac{\text{height}}{120}\right)^{\theta_5}$$

Each covariate was normalized by the median of its relative distribution as observed in the population. The performance of the different models built for covariate analysis is reported in Table S1 (available as [Supplementary data](#) at JAC Online).

There was a good fit of the final model to the observed data (Figure 1). A linear regression of the observed–predicted values before and after the Bayesian step had an *R*² value of 0.216 and 0.877, respectively, with minimal bias and imprecision. The parameter estimates of ceftazidime for the final population Bayesian pharmacokinetic model are summarized in Table 2. The median (IQR) estimates of the final multivariate model were 3.18 L/h

Figure 1. Diagnostic plot for the final covariate model. Observed versus population predicted concentrations (left panel) and individual predicted concentrations (right panel) are shown. Continuous lines refer to linear regression between observed and predicted concentrations.

(1.78–4.79 L/h) for CL and 26.45 L (24.41–33.61 L) for V. NPDEs followed a Gaussian distribution and no trends were evident in the scatterplot of NPDE versus time and versus predicted outcome (Figure S1).

Monte Carlo simulation

A total of 96 Monte Carlo simulations were conducted in order to test six incremental dosing regimens of continuous-infusion ceftazidime (ranging from 1 g q24 h to 6 g q24 h) across 16 different clinical scenarios. These clinical scenarios resulted from the combination of four classes of body surface area (0.30–0.64, 0.65–0.88, 0.89–1.34 and 1.35–1.88 m²) and four classes of eGFR (50–145, 145.1–200, 200.1–286 and 286.1–422 mL/min/1.73 m²).

Figure 2 shows the continuous-infusion ceftazidime dosages needed for attaining the desired C_{ss}/MIC ratio ≥ 4 at the EUCAST clinical breakpoint against *P. aeruginosa* (8 mg/L) in the different clinical scenarios. In patients with eGFR of 50–145 mL/min/1.73 m², ceftazidime dosages ranged between 4 g q24 h for body surface area ≤ 1.34 m² and 5 g q24 h for body surface area >1.34 m². Likewise, in patients with eGFR of 145.1–200 mL/min/1.73 m², ceftazidime dosages were 4 g q24 h for body surface area ≤ 0.88 and 5 g q24 h for body surface area >0.88 m². In patients with eGFR of 200.1–286 mL/min/1.73 m² and 286.1–422 mL/min/1.73 m², ceftazidime dosages were 4 g q24 h for body surface area ≤ 0.64 , 5 g q24 h for body surface area between 0.65 and 1.34 m², and 6 g q24 h for body surface area >1.34 m².

Table S2 summarizes the PTA associated with three different weight-based dosing regimens of ceftazidime (50 mg/kg LD over 1 h followed by an MD of 100 mg/kg/day by continuous infusion, 75 mg/kg LD over 1 h followed by an MD of 150 mg/kg/day by continuous infusion, 100 mg/kg LD over 1 h followed by an MD of 200 mg/kg/day by continuous infusion) in children weighing <40 kg and having eGFR of 50–422 mL/min/1.73 m². Optimal PTAs were attained at an MIC of 8 mg/L only with the highest dosing regimen tested.

The percentage probabilities of achieving ceftazidime C_{ss} above the safety threshold of 100 mg/L in the different clinical scenarios

Table 2. Parameter estimates of ceftazidime for the final covariate two-compartment population pharmacokinetic model

	Mean	Standard deviation	Coefficient of variation (%)	Median
$CL (L/h) = \theta_1 \cdot \left(\frac{\text{body surface area}}{0.88}\right)^{\theta_2} \cdot \left(\frac{eGFR}{200.5}\right)^{\theta_3}$				
θ_1	2.83	1.29	45.66	2.71
θ_2	0.68	0.37	54.31	0.84
θ_3	0.34	0.19	55.79	0.28
$V(L) = \theta_4 \cdot \left(\frac{\text{height}}{120}\right)^{\theta_5}$				
θ_4	33.95	32.09	94.52	25.89
θ_5	0.95	0.82	86.02	0.85
$k_{cp} (h^{-1})$	11.51	14.69	127.74	3.70
$k_{pc} (h^{-1})$	15.42	3.56	23.11	14.91

are reported in Table 3. For safety purposes, continuous-infusion ceftazidime dosages should not exceed 3 g q24 h in patients with body surface area 0.30–0.64 m² and eGFR 50–200 mL/min/1.73 m², 4 g q24 h in those with body surface area 0.30–0.64 m² and eGFR 200.1–422 mL/min/1.73 m² and in those with body surface area 0.65–0.88 m² and eGFR 50–145 mL/min/1.73 m², and 5 g q24 h in those with body surface area 0.30–0.64 m² and eGFR 145.1–200 mL/min/1.73 m².

Table 4 summarizes a nomogram for selecting the most appropriate dosages for optimal empirical treatment of *P. aeruginosa* infection and for minimizing the risk of overexposure with continuous-infusion ceftazidime in HSCT children with high-risk FN according to different classes of eGFR and body surface area. Advisable dosages should be 4 g q24 h by continuous infusion and 5 g q24 h by continuous infusion in six clinical scenarios each. The highest dose of 6 g q24 h by continuous infusion should be advisable only in those patients with the highest classes of body surface area and eGFR. In patients having the lowest body surface area

Figure 2. PTA of $C_{ss}/MIC \geq 4$ at the EUCAST clinical breakpoint of 8 mg/L against *P. aeruginosa* with incremental dosages of continuous-infusion ceftazidime in relation to different classes of eGFR and of body surface area. Horizontal broken lines identify the threshold for optimal PTA ($\geq 90\%$).

estimates (0.30–0.64 m²) and decreased renal function (eGFR 50–145 or 145.1–200 mL/min/1.73 m²), advisable ceftazidime dosages should not exceed 3 g q24h by continuous infusion, but this may allow only suboptimal PTAs (74 and 70%, respectively). However, a dose increase to 3.5 g q24h by continuous infusion may be considered in children with eGFR of 145.1–200 mL/min/1.73 m², as PTA increases to 85.6% with a probability of toxicity of only 2.1%. In both these scenarios, the dose of 3 g q24h by continuous infusion enabled the attainment of the less aggressive targets of $C_{ss}/MIC \geq 1$ and $C_{ss}/MIC \geq 2$, with PTA >97.8%.

The CFRs against *P. aeruginosa* achievable in HSCT children with the advisable continuous-infusion ceftazidime dosages are summarized in Table 5. Overall, all regimens were associated with CFRs >87.1% when considering the EUCAST MIC distribution and >79.4% when considering our local MIC distribution. CFRs associated with a less aggressive target of $C_{ss}/MIC \geq 1$ are reported in Table S3. CFRs were >96.2% when considering the EUCAST MIC distribution and >88.1% when considering our local MIC distribution. The risk-to-benefit ratios for the CFRs that were associated with the target of a $C_{ss}/MIC \geq 4$ are provided in Table S4.

Table 3. Percentage probability of causing ceftazidime overexposure (defined as $C_{ss} > 100$ mg/L) with incremental dosages administered by continuous infusion in HSCT children with high-risk FN according to different classes of eGFR and body surface area

eGFR (mL/min/1.73 m ²)	Body surface area (m ²)	Ceftazidime dosage (g q24h)					
		1	2	3	4	5	6
50.0–145.0	0.30–0.64	0	0.1	3.0	29.4	45.5	48.7
	0.65–0.88	0	0	0	2.6	14.6	39.1
	0.89–1.34	0	0	0	0.1	3.6	8.8
	1.35–1.84	0	0	0	0	0.7	4.9
145.1–200.0	0.30–0.64	0	0	0.5	11.3	36.2	46.6
	0.65–0.88	0	0	0	0.2	2.1	18.0
	0.89–1.34	0	0	0	0	0	1.7
	1.35–1.84	0	0	0	0	0	0.1
200.1–286.0	0.30–0.64	0	0	0	5.0	22.0	38.3
	0.65–0.88	0	0	0	0.1	0.5	6.4
	0.89–1.34	0	0	0	0	0	0.3
	1.35–1.84	0	0	0	0	0	0
286.1–422.0	0.30–0.64	0	0	0	2.2	16	28.1
	0.65–0.88	0	0	0	0	0.4	2.5
	0.89–1.34	0	0	0	0	0	0
	1.35–1.84	0	0	0	0	0	0

Table 4. Advisable continuous-infusion ceftazidime dosages (g q24h) for optimizing empirical treatment against *P. aeruginosa* (PTA $\geq 90\%$ of achieving $C_{ss}/MIC \geq 4$ against the EUCAST clinical breakpoint of 8 mg/L) in HSCT children with high-risk FN in relation to classes of eGFR and body surface area

eGFR (mL/min/1.73 m ²)	Body surface area (m ²)			
	0.30–0.64	0.65–0.88	0.89–1.34	1.35–1.84
50.0–145.0	3 ^a	4	4	5
145.1–200.0	3 ^b	4	5	5
200.1–286.0	4	4	5	6
286.1–422.0	4	5	5	6

Superscript letters identify suboptimal PTAs: ^aPTA <75% and ^bPTA <70%.

Discussion

In this study we developed a population pharmacokinetic model for determining the most advisable dosages of continuous-infusion ceftazidime for treatment of *P. aeruginosa* in HSCT children with neutropenia.

The median estimated CL (3.18 L/h or 0.14 L/h/kg) in our population was comparable to the values previously observed among hospitalized paediatric patients aged between 6 and 18 years (0.17–0.23 L/h/kg)³² and/or infants aged <2 years (0.17 L/h/kg).³³ V was also consistent with values reported for patients of similar ages (13.0–22.2 L).³²

The finding that eGFR was a significant covariate affecting ceftazidime CL is consistent with a population pharmacokinetic study previously conducted in infants.³³ Ceftazidime is predominantly eliminated via the renal route. Dosages should be adjusted

according to the degree of renal function. Body surface area was also a significant covariate of ceftazidime CL in our study population. This finding was not described previously and seems biologically plausible, as in children renal weight was found to be significantly correlated with body surface area.³⁴ Interestingly, guidelines on paediatric dosing of hydrophilic drugs that are renally excreted recommend dose normalization to body surface area when children are aged >2 years.³⁵

To the best of our knowledge, the pharmacokinetics of continuous-infusion ceftazidime were previously assessed only once in FN children with cancer.¹⁹ This was an early prospective study carried out among 20 onco-haematological paediatric patients with FN, with a median age of 5.4 years and mean eGFR of 108 ± 18 mL/min/1.73 m², who were empirically treated with a dose of 200 mg/kg daily. In that study continuous-infusion ceftazidime was well tolerated and the only pharmacokinetic parameter reported was C_{ss} , so we had no chance to compare our estimates for the pharmacokinetic parameters.

Mortality from *P. aeruginosa* bacteraemia remains unacceptably high in children and adolescents with FN.⁸ A recent retrospective study conducted among 31 children with FN showed that appropriate antimicrobial treatment and combination therapy of an antipseudomonal β -lactam with an aminoglycoside was associated with higher survival rates.³⁶ This suggests that optimized antimicrobial treatment may increase the percentage of favourable clinical outcomes.

Preclinical and clinical studies showed that targeting continuous-infusion ceftazidime C_{ss} at $4 \times MIC$ was effective against *P. aeruginosa* infections.^{18,37} Our findings suggest that continuous-infusion ceftazidime dosages of 4–6 g daily may achieve this pharmacodynamic target in most cases.

It is worth noting that theoretically, when considering a more conservative pharmacodynamic target of $C_{ss}/MIC \geq 1$,

Table 5. CFR with the advisable continuous-infusion ceftazidime dosages targeting $C_{ss}/MIC \geq 4$ against *P. aeruginosa* in relation to the MIC distribution of EUCAST and that observed at our centre in HSCT children with high-risk FN in relation to classes of eGFR and body surface area

eGFR (mL/min/1.73 m ²)	Body surface area (m ²)	Ceftazidime dosage (g q24h)	CFR (%)	
			according to EUCAST distribution	according to our local distribution
50.0–145.0	0.30–0.64	3	88.3	80.3
	0.65–0.88	4	90.2	81.8
	0.89–1.34	4	88.3	80.2
	1.35–1.84	5	88.9	80.7
145.1–200.0	0.30–0.64	3	87.1	79.4
	0.65–0.88	4	89.1	80.9
	0.89–1.34	5	89.2	80.9
	1.35–1.84	5	88.5	80.4
200.1–286.0	0.30–0.64	4	90.1	81.7
	0.65–0.88	4	88.2	80.2
	0.89–1.34	5	88.7	80.5
	1.35–1.84	6	88.8	80.6
286.1–422.0	0.30–0.64	4	89.4	81.2
	0.65–0.88	5	89.9	81.4
	0.89–1.34	5	88.3	80.2
	1.35–1.84	6	88.0	79.9

these dosages could be helpful even in the presence of resistant strains of *P. aeruginosa* with an MIC up to 32 mg/L. Interestingly, a similar approach was chosen in the treatment of an 18-year-old female with a bacteraemia caused by a resistant strain of *P. aeruginosa* with an MIC of 64 mg/L. It was shown that high-dose continuous-infusion ceftazidime (9.6 g daily) for 6 consecutive days with a targeted C_{ss} of 80–100 mg/L was successful.¹⁸

Our study has some limitations. Its retrospective design with sparse TDM sampling is probably the most important. The high λ value used in the error model that implies the presence of relevant process noise is another limitation to report. Finally, we were unable to assess the specific role of ceftazidime in clinical outcome as most of the patients received an antipseudomonal combination therapy.

In conclusion, our findings suggest that eGFR and body surface area are important clinical covariates affecting the population pharmacokinetics of continuous-infusion ceftazidime in HSCT children with high-risk FN. Dosages ranging between 4 and 6 g daily, by achieving C_{ss} 4-fold higher than the EUCAST clinical breakpoint of ceftazidime versus *P. aeruginosa*, may maximize the empirical treatment of *P. aeruginosa* infections in most clinical scenarios. TDM may be helpful in appropriately targeting ceftazidime C_{ss} in this patient population.

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Transparency declarations

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awards from the National Institutes of Health, the Medical Research Council, the National Institute of Health Research, the FDA and the European Commission (FP7 and IMI), has received personal fees in his capacity as a consultant for F2G, Amplyx, Ausperix, Spero Therapeutics and BLC/TAZ, and is an Ordinary Council Member for BSAC. F. P. has participated in speaker bureaus for Basilea Pharmaceutica, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Pfizer and Sanofi Aventis, and in advisory boards for Basilea Pharmaceutica, Gilead, Merck Sharp & Dohme, Nordic Pharma and Pfizer. All other authors: none to declare.

Supplementary data

Tables S1 to S4 and Figure S1 are available as [Supplementary data](#) at JAC Online.

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