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

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Abstract

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

METHODS: 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 CI ceftazidime dosages of 1 to 6 g daily. 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} were included. Estimated glomerular filtration rate (eGFR) and body surface area (BSA) were the covariates associated with drug clearance. At the EUCAST clinical breakpoint of 8 mg/L, simulations showed that CI 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, 286.1-422 mL/min/1.73 m^2) and BSA (0.30-0.64, 0.65-0.88, 0.89-1.34, 1.35-1.84 m^2). In patients with BSA 0.30-0.64 m^2 and eGFR $\leq$ 200 mL/min/1.73 m^2 the advisable dose of 3 g daily allowed only suboptimal PTAs (<75%). The cumulative fraction of response against MIC distribution of *Pseudomonas aeruginosa* was > 87%.

CONCLUSIONS: CI ceftazidime dosages ranging from 3 and 6 g daily according to different classes of eGFR and BSA may allow optimized empirical treatment of *Pseudomonas aeruginosa* infections in pediatric 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] Bacteremia 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 etiological agents, together with *Klebsiella pneumoniae* and *Escherichia coli*.[3, 5]

Pseudomonas aeruginosa bacteremia is associated with high fatality rates in children,[6] and in high-risk FN patients may be as high as 52%.[7] Multidrug-resistant strains are common.[8] Current guidelines of the American Society of Clinical Oncology recommend monotherapy with an anti-pseudomonal beta-lactam as empirical therapy in pediatric 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 centers with 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 to 90%) and has low plasma protein binding (approximately 10%).[11, 12] It may have a more favorable safety profile compared to other anti-pseudomonal cephalosporins, with a lower risk for neurotoxicity.[13]

Beta-lactams are often administered intermittently. However, administration by extended or continuous infusion (CI) may optimize the time free plasma drug concentrations are above the MIC (*f*T>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 beta-lactams by prolonged or CI may improve clinical efficacy in patients with sepsis.[15, 16] A recent meta-analysis showed that prolonged infusion of antipseudomonal beta-lactams for the treatment of patients with sepsis was associated with significantly lower mortality than intermittent infusion.[16]

The use of prolonged or CI of beta-lactams is increasing even among the pediatric population,[17] including for ceftazidime.[18-21] The aim of this study was to conduct a population pharmacokinetic analysis in a cohort of pediatric HSCT children with FN who were empirically treated with CI ceftazidime and to identify dosing regimens for maximizing empirical treatment of *Pseudomonas aeruginosa* infections.

Methods

Study design

This retrospective study included a cohort of pediatric patients who underwent HSCT at the Institute for Maternal and Child Health IRCSS Burlo Garofolo, Trieste, Italy, and who received CI 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 hour, which was immediately followed by a maintenance dose (MD) of 100-200 mg/kg daily administered by CI. 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 a 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 maximizing 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 when in 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 advices for personalized ceftazidime dosages were usually provided to the attending clinicians within the same day of the analysis. Ceftazidime concentrations were analyzed 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 coefficient 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 (BSA), duration of therapy, date of HSCT and type of underlying oncological or hematological disease and co-treatment with other antimicrobials. Baseline

and end-of-treatment data on serum concentrations of ALT, AST and total bilirubin as well as sign and symptoms of neurotoxicity potentially related with ceftazidime therapy were also collected. Serum creatinine was measured at each TDM instances and estimated glomerular filtration rate (eGFR) was calculated by means of the Schwartz formula.[26] BSA was calculated by means of the Mosteller formula.[27]

~~Clinical outcome to ceftazidime treatment was classified as cured, unchanged or failed according the response assessed by the attending physician. A patient was classified as cured in the presence of a decrease of C-RP and body temperature and of an improvement of clinical conditions. A patient was classified as unchanged or failed after three days of ceftazidime treatment whenever CRP, body temperature or clinical conditions did not improve or deteriorate, respectively. In these cases, antimicrobial therapy was escalated to meropenem.~~

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 gamma and lambda were tested in the error model for accounting for process error. Individual pharmacokinetic parameters (total CL, volume of distribution of the central compartment [V], 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, BSA, eGFR, time from HSCT, presence of acute leukemia) 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) greater than 3.84 between each pharmacokinetic model and the base model ($p < 0.05$), coupled with evaluation of the Akaike information criteria (AIC), were considered as statistically significant additions to the model. Model performance was evaluated by means of normalized prediction distribution errors (NPDEs), which is a metric design to allow evaluation of non-linear mixed-effect models.

Monte Carlo simulation analysis for determining the probability of target attainment for empirical treatment against *Pseudomonas aeruginosa*

1000-subject Monte Carlo simulations based on the final model were performed for each of six incremental dosing regimens of CI ceftazidime (1g q24h, 2g q24h, 3g q24h, 4g q24h, 5g q24h and 6g q24h) for determining the PTA for maximized empirical treatment against *Pseudomonas 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 percentile, 25th-50th percentile, 50th-75th percentile, 75th-100th percentile).

Ceftazidime C_{ss} 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 ~~acceptable when $\geq$ 80%, and~~ 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 CI beta-lactams.[18, 30] Dosing

158 regimens associated with less than 10% of probability of exceeding this threshold were considered as
159 advisable for the empirical treatment against *Pseudomonas aeruginosa*.

160 The cumulative fractions of response (CFR) achievable with the different CI ceftazidime
161 dosing regimens were tested against the MIC distribution of *Pseudomonas aeruginosa* as reported by
162 EUCAST[31] (n=32276 isolates) as well as against the MIC distribution of *Pseudomonas aeruginosa*
163 collected at our center in the period January - June 2018 (n=179 isolates). The CFR was calculated
164 from the PTA obtained from the Monte Carlo simulation analysis. Computation of the risk-to-benefit
165 ratios defined as the ratio of the probability of potential toxicity over the CFR observed for the
166 ceftazidime dosages against *Pseudomonas aeruginosa* was also provided.

167

168 **Etichs**

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

172

173 **Statistical analysis**

174 The Kolmogorov-Smirnov test was used to assess normal or non-normal distribution of
175 patient's data. Accordingly, data were summarized as mean ± standard deviation or median with
176 25^{th}-75^{th} percentiles, in the descriptive statistics. Differences between continuous variables were
177 assessed using the Student *t* test or Mann-Whitney test depending on whether the data were normally
178 distributed. All statistical analysis and plotting were performed with R, version 3.4.4 (R foundation
179 for Statistical Computing, Vienna, Austria).

180

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 (min-max range) age, BSA and eGFR were 7.5 years (0.5-16), 0.88 m^2 (0.34-1.84) and 200.0 mL/min/1.73 m^2 (50.0-422.6), respectively.

Most of the patients (32/46, 69.6%) had hematological malignancies, with acute lymphatic leukemia being the most frequent (22/46, 47.8%). Median (IQR) neutrophil count at start of therapy was 0.0 (0.0 – 10) cells/mm^3 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 of 80.0 (49.2-139.7) mg/kg and of 145.9 (128.3 – 171.3) mg/kg daily. Median (IQR) total maintenance dose was of 3.5 (2.5 – 5.0) g/day by CI, with a min-max 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 in that occasion the observed C_{ss} were ≤ 8 mg/L (C_{ss}/MIC≤1) and ≤ 32 mg/L (C_{ss}/MIC≤4) in 1 and in 9 patients, respectively. Among those patients who had ≥ 2 TDM assessments over time (17/46, 36.9%), 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. ~~Cure was observed in 39% of patients (18/46), whereas clinical conditions did not improve in 54.3% (25/46) of cases and an escalation to meropenem was deemed necessary. Three patients died from complications directly related to their hematological malignancies.~~

Population pharmacokinetic modeling

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, for the two- and the one-compartment model, respectively). An additive lambda 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 BSA 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 furtherly improved to 578.3 and 596.6, respectively. The final structural model was as follows:

$$\text{CL (L/h)} = \theta_1 \bullet \left(\frac{BSA}{0.88}\right)^{\theta_2} \bullet \left(\frac{eGFR}{200.5}\right)^{\theta_3}$$

$$\text{V (L)} = \theta_4 \bullet \left(\frac{height}{120}\right)^{\theta_5}$$

where, BSA, eGFR and height represent the values of body surface area, estimated glomerular filtration rate and patients' height, respectively. 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 of the Supplementary Material.

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 of 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 estimates of the final multivariate model were 3.18 L/h (1.78 – 4.79 L/h) for CL and 26.45 L (24.41 – 33.61 L) for V. Distribution of NPDEs followed a gaussian distribution and no trends were evident in the scatterplot of NPDE versus time and versus predicted outcome (Supplementary Figure S1).

Monte Carlo simulation

A total of ninety-six Monte Carlo simulations were conducted in order to test six incremental dosing regimens of CI ceftazidime (ranging from 1 g q 24h to 6 g q 24h) across sixteen different clinical scenarios. These clinical scenarios resulted from the combination of four classes of BSA (0.30-0.64, 0.65-0.88, 0.89-1.34 and 1.35-1.88 m^2) and of four classes of eGFR (50-145, 145.1-200, 200.1-286 and 286.1-422 mL/min/1.73 m^2).

Figure 2 shows the CI ceftazidime dosages needed for attaining the desired C_{ss}/MIC ratio ≥ 4 at the EUCAST clinical breakpoint against *Pseudomonas aeruginosa* (8 mg/L) in the different clinical scenarios. In patients with eGFR of 50-145 mL/min/1.73 m^2, ceftazidime dosages ranged between 4 g q24h CI for BSA ≤ 1.34 m^2 and 5 g q24h CI for BSA > 1.34 m^2. Likewise, in patients with eGFR of 145.1-200 mL/min/1.73 m^2, ceftazidime dosages were 4 g q24h CI for BSA ≤ 0.88, and 5 g q24h CI for BSA > 0.88 m^2. In patients with eGFR of 200.1-286 mL/min/1.73 m^2 and 286.1-422 mL/min/1.73 m^2, ceftazidime dosages were 4 g q24h CI for BSA ≤ 0.64, 5 g q24h CI for BSA between 0.65 and 1.34 m^2, and 6 g q24h CI for BSA > 1.34 m^2.

Table S2 summarizes the PTA associated with three different weight-based dosing regimens of ceftazidime (50 mg/kg LD over 1h followed by an MD of 100 mg/kg/day by CI, 75 mg/kg LD over 1 h followed by an MD of 150 mg/kg/day by CI, 100 mg/kg LD ovder 1h followed by an MD of 200 mg/kg/day by CI) in children weighting < 40 kg and having eGFR of 50-422 mL/min/1.73 m^2. Optimal PTAs were attained at an MIC of 8 mg/L only with the highest dosing regimen tested.

The percentages of probability of achieving ceftazidime C_{ss} above the safety threshold of 100 mg/L in the different clinical scenarios are reported in Table 3. For safety purposes, CI ceftazidime dosages should not exceed 3g q24h CI in patients with BSA 0.30-0.64 m^2 and eGFR 50-200 mL/min/1.73 m^2, 4g q24h CI in those with BSA 0.30-0.64 m^2 and eGFR 200.1-422 mL/min/1.73 m^2 and in those with BSA 0.65-0.88 m^2 and eGFR 50-145 mL/min/1.73 m^2, and 5g q24h CI in those with BSA 0.30-0.64 m^2 and eGFR 145.1-200 mL/min/1.73 m^2.

Table 4 summarizes a nomogram for selecting the most appropriate dosages for maximizing empirical treatment of *Pseudomonas aeruginosa* infection and minimizing the risk of overexposure

with CI ceftazidime in HSCT children with high risk FN according to different classes of eGFR and BSA. Advisable dosages should be of 4g q24h CI and of 5g q24h CI in six clinical scenarios each. The highest dose of 6g q24h CI should be advisable only in those patients with the highest classes of BSA and eGFR. In patients having the lowest BSA estimates (0.30-0.64 m^2) and decreased renal function (eGFR of 50-145 or 145.1-200 mL/min/1.73 m^2), advisable ceftazidime dosages should not exceed 3g q24h CI, but this may allow only suboptimal PTAs (74 and 70%, respectively). However, a dose increase to 3.5 g q24h by CI may be considered in children with eGFR of 145.1-200 mL/min/1.73 m^2, as PTA increases to 85.6% with a probability of toxicity of only 2.1%. In both these scenario, the dose of 3g q24h by CI 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 *Pseudomonas aeruginosa* achievable in HSCT children with the advisable CI 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.

Discussion

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

The mean estimated CL (3.18 L/h or 0.14 L/h/kg) in our population was comparable to the values previously observed among hospitalized pediatric 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. BSA 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 BSA.[34] Interestingly, guidelines on pediatric dosing of hydrophilic drugs that are renally excreted recommend dose normalization to BSA when children are aged more than 2 years.[35]

To the best of our knowledge, the pharmacokinetics of CI ceftazidime was previously assessed only once in FN children with cancer.[19] This was an early prospective study carried out among 20 onco-hematologic pediatric patients with FN, with a median age of 5.4 years and mean eGFR of 108 ± 18 mL/min/1.73 m^2, who were empirically treated with a dose of 200 mg/kg daily. In that study CI ceftazidime was well tolerated, and the only pharmacokinetic parameter reported was C_{ss}, so that we had no chance to compare our estimates for the pharmacokinetic parameters.

Mortality from *Pseudomonas aeruginosa* bacteremia 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

beta-lactam with an aminoglycoside was associated with higher survival rates.[36] This suggests that optimized antimicrobial treatment may increase the percentage of favorable clinical outcomes.

Preclinical and clinical studies showed that targeting CI ceftazidime C_{ss} at 4 times the MIC was effective against *Pseudomonas aeruginosa* infections.[18, 37] Our findings suggest that CI 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, these dosages could be helpful even when in presence of resistant strains of *Pseudomonas 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 bacteremia caused by a resistant strain of *Pseudomonas aeruginosa* with an MIC of 64 mg/L. It was shown that high-dose CI 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 lambda value used in the error model that implies the presence of relevant process noise is a 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 BSA are important clinical covariates affecting the population pharmacokinetics of CI 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.

Transparency Declaration Section

Federico Pea participated in speaker bureau for Basilea Pharmaceutica, Gilead, Hikma, Merck Sharp & Dohme, Nordic Pharma, Pfizer, and Sanofi Aventis, and in advisory board for Basilea Pharmaceutica, Gilead, Merck Sharp & Dohme, Nordic Pharma, and Pfizer. William Hope holds or has recently held research grants with F2G, AiCuris, Astellas Pharma, Spero Therapeutics, Matinas Biosciences, Antabio, Amplyx, Allecra, Bugworks, NAEJA-RGM, AMR Centre, and Pfizer. He holds awards from the National Institutes of Health, Medical Research Council, National Institute of Health Research, FDA and the European Commission (FP7 and IMI). He has received personal fees in his capacity as a consultant for F2G, Amplyx, Ausperix, Spero Therapeutics and BLC/TAZ. He is an Ordinary Council Member for the British Society of Antimicrobial Chemotherapy. All other authors have no conflicts to declare.

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This study was conducted as part of our routine work

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Table 1. Demographic and clinical characteristics of the population.

Total number of patients	46
Age (years)	7.5 (4.0 – 12.0)
Gender (male/female)	29/17
Weight (kg)	25.0 (14.03 – 39.80)
Height (m)	1.20 (1.01 – 1.49)
Body surface area (m^2)	0.88 (0.64 – 1.34)
eGFR (mL/min/1.73 m^2)	200.0 (145.0 – 286.0)
Time from HSCT (days)	6.0 (1.0 – 11.75)
Type of hematological disease	
ALL	22 (47.8)
AML	5 (10.9)
JMML/CML	5 (10.9)
Aplastic/Fanconi anemia	4 (8.8)
Neuroblastoma	3 (6.5)
Congenital immunodeficiency disorders	3 (6.5)
Sickle cell anemia	2 (4.3)
Ewing sarcoma	2 (4.3)
Ceftazidime treatment characteristics	
Dose/kg/day (mg/kg)	145.98 (128.31 – 171.27)
C_{ss} (mg/L)	49.23 (36.81 – 62.88)
No. of TDM instances	1.0 (1.0 – 2.0)
Duration of treatment (days)	10.5 (7.0 – 16.0)
Additional antibiotics	
Amikacin	38 (82.6)
Teicoplanin	19 (41.3)
Vancomycin	14 (30.4)
Levofloxacin	13 (28.3)
Tigecycline	5 (10.9)
Metronidazole	3 (6.5)

Data for continuous variable are presented as median (IQR) and data for dichotomous variables are presented as number (%). ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BSI, blood stream infections; CML, chronic myeloid leukemia; C_{ss}, ceftazidime steady-state plasma concentration; FN, febrile neutropenia; JMML, juvenile myelomonocytic leukemia; HSCT, hematopoietic stem cell transplantation.

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) = $\theta_1 \bullet (\frac{BSA}{0.88})^{\theta_2} \bullet (\frac{eGFR}{200.5})^{\theta_3}$				
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) = $\theta_4 \bullet (\frac{height}{120})^{\theta_5}$				
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

BSA, body surface area; CL, total clearance of fluconazole; eGFR, estimated glomerular filtration rate; *k*cp and *k*pc, first-order inter-compartmental transfer rate constant connecting the central and peripheral compartments; V, volume of distribution of the central compartment.

Table 3. Percentages of probability of causing ceftazidime overexposure (defined as steady-state concentrations [C_{ss}] > 100 mg/L) with incremental dosages administered by continuous infusion (CI) in HSCT children with high risk febrile neutropenia according to different classes of estimated glomerular filtration rate (eGFR) and body surface area (BSA).

Class of eGFR (mL/min/1.73 m^2)	Class of BSA (m^2)	Ceftazidime dosages (g q24h CI)					
		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 (CI) ceftazidime dosages for maximizing empirical treatment against *Pseudomonas aeruginosa* (PTA ≥ 90% of achieving C_{ss}/MIC ≥ 4 against the EUCAST clinical breakpoint of 8 mg/L) in HSCT children with high risk FN in relation to different classes of estimated glomerular filtration rate (eGFR) and of body surface area (BSA).

Class of eGFR (mL/min/1.73 m^2)	Class of BSA (m^2)			
	0.30-0.64	0.65-0.88	0.89-1.34	1.35-1.84
50.0-145.0	3 g q24h CI *	4 g q24h CI	4 g q24h CI	5 g q24h CI
145.1-200.0	3 g q24h CI °	4 g q24h CI	5 g q24h CI	5 g q24h CI
200.1-286.0	4 g q24h CI	4 g q24h CI	5 g q24h CI	6 g q24h CI
286.1-422.0	4 g q24h CI	5 g q24h CI	5 g q24h CI	6 g q24h CI

Symbols identify suboptimal PTAs: * PTA <75%; ° PTA <70%

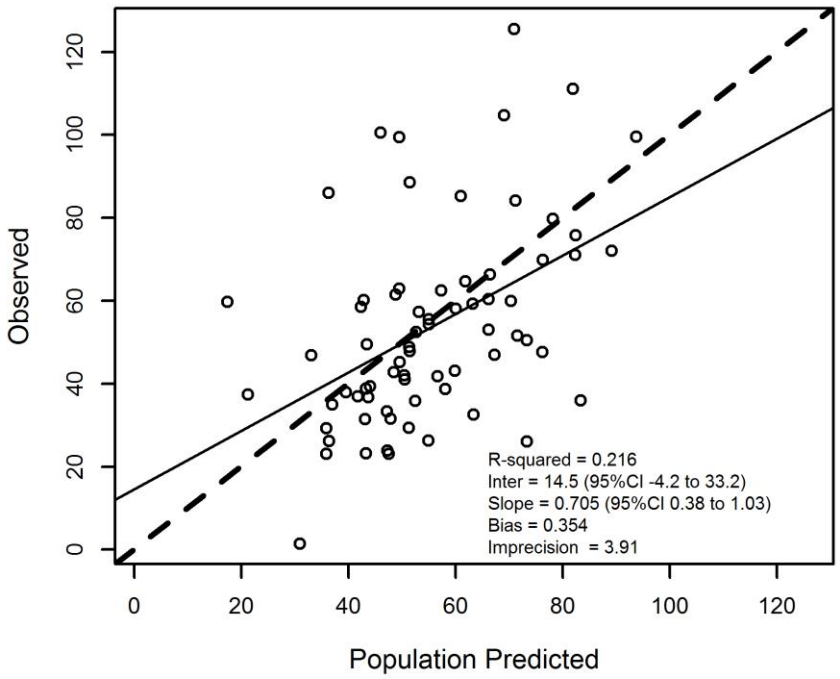
Table 5. Cumulative fraction of response with the advisable continuous infusion (CI) ceftazidime dosages targeting C_{ss}/MIC ≥ 4 against *Pseudomonas aeruginosa* in relation to the MIC distribution of EUCAST and that observed at our center in HSCT children with high risk FN in relation to different classes of estimated glomerular filtration rate (eGFR) and of body surface area (BSA)

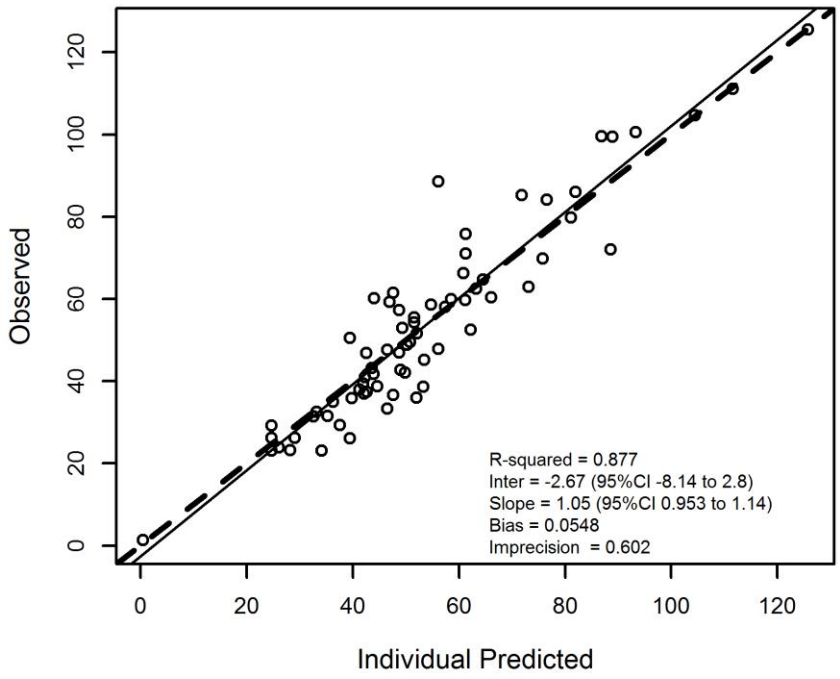
Class of eGFR (mL/min/1.73 m^2)	Class of BSA (m^2)	Ceftazidime dosages	CFR (%)	
			According to EUCAST distribution	According to our local distribution
50.0-145.0	0.30-0.64	3 g q24h CI	88.3	80.3
	0.65-0.88	4 g q24h CI	90.2	81.8
	0.89-1.34	4 g q24h CI	88.3	80.2
	1.35-1.84	5 g q24h CI	88.9	80.7
145.1-200.0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

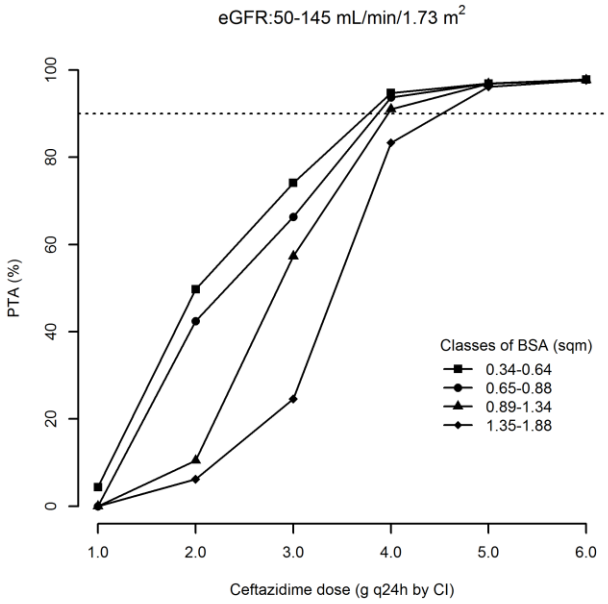
Figure Legend

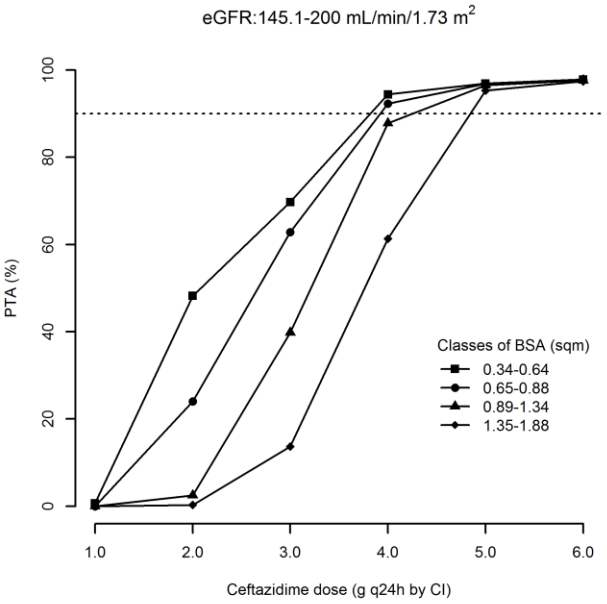
Figure 1. Diagnostic plot for the final covariate model. Observed versus population predicted concentrations (left panel) and individual predicted concentrations (right panel) are shown. Solid lines refer to linear regression between observed and predicted concentrations.

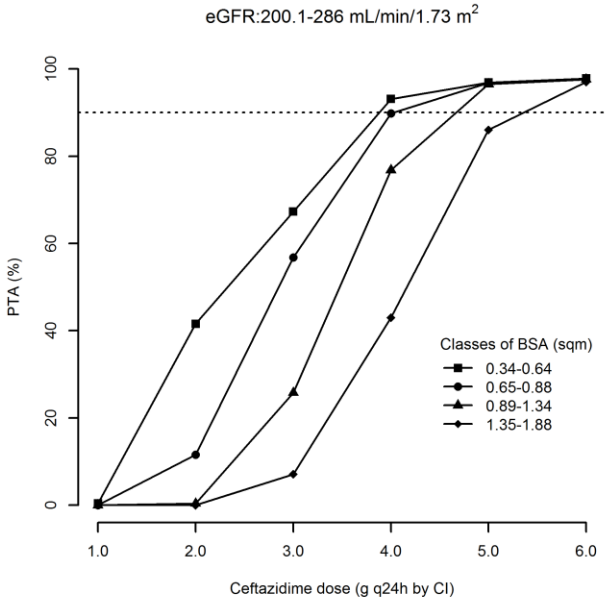
Figure 2. Probability of target attainment (PTA) of C_{ss}/MIC $\geq$ 4 at the EUCAST clinical breakpoint of 8 mg/L versus *Pseudomonas aeruginosa* with incremental dosages of continuous infusion (CI) ceftazidime in relation to different classes of estimated glomerular filtration rate (eGFR) and of body surface area (BSA). Horizontal dotted lines identify the threshold for optimal PTA ($\geq$ 90%).

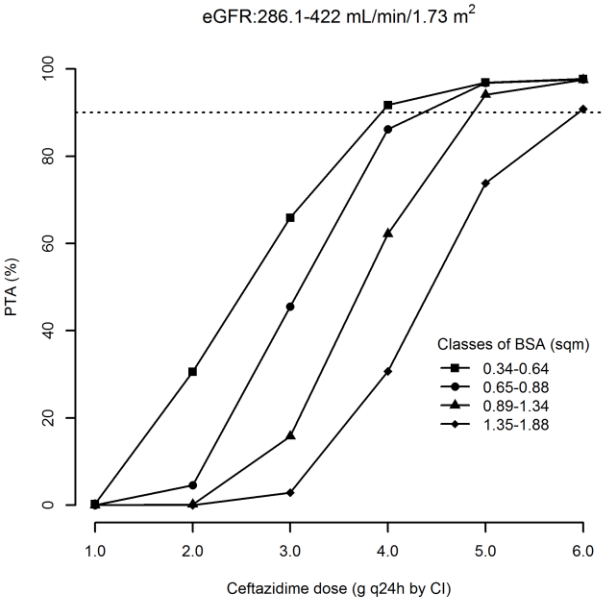

Observed
Population Predicted
0
20
40
60
80
100
120
R-squared = 0.216
Inter = 14.5 (95%CI -4.2 to 33.2)
Slope = 0.705 (95%CI 0.38 to 1.03)
Bias = 0.354
Imprecision = 3.91


Observed
Individual Predicted
0
20
40
60
80
100
120
R-squared = 0.877
Inter = -2.67 (95%CI -8.14 to 2.8)
Slope = 1.05 (95%CI 0.953 to 1.14)
Bias = 0.0548
Imprecision = 0.602


eGFR:50-145 mL/min/1.73 m2
PTA (%)
0
20
40
60
80
100
1.0
2.0
3.0
4.0
5.0
6.0
Ceftazidime dose (g q24h by CI)
Classes of BSA (sqm)
0.34-0.64
0.65-0.88
0.89-1.34
1.35-1.88


eGFR:145.1-200 mL/min/1.73 m2
PTA (%)
0
20
40
60
80
100
1.0
2.0
3.0
4.0
5.0
6.0
Ceftazidime dose (g q24h by CI)
Classes of BSA (sqm)
0.34-0.64
0.65-0.88
0.89-1.34
1.35-1.88


eGFR:200.1-286 mL/min/1.73 m2
PTA (%)
0
20
40
60
80
100
1.0
2.0
3.0
4.0
5.0
6.0
Ceftazidime dose (g q24h by CI)
Classes of BSA (sqm)
0.34-0.64
0.65-0.88
0.89-1.34
1.35-1.88


eGFR:286.1-422 mL/min/1.73 m2
PTA (%)
0
20
40
60
80
100
1.0
2.0
3.0
4.0
5.0
6.0
Ceftazidime dose (g q24h by CI)
Classes of BSA (sqm)
0.34-0.64
0.65-0.88
0.89-1.34
1.35-1.88