

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

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23 **Abstract**

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

28 **METHODS:** Non-parametric approach with Pmetrics was used for pharmacokinetic analysis and
29 covariate evaluation. Monte Carlo simulations were performed to calculate the PTA of the
30 pharmacodynamic determinant of efficacy ($C_{ss}/MIC \geq 4$) against *Pseudomonas aeruginosa* with CI
31 ceftazidime dosages of 1 to 6 g daily. C_{ss} safety threshold was arbitrarily placed at 100 mg/L and
32 advisable dosages were used.

33 **RESULTS:** A total of 46 patients with 70 ceftazidime C_{ss} were included. Estimated glomerular
34 filtration rate (eGFR) and body surface area (BSA) were the covariates associated with drug
35 clearance. At the EUCAST clinical breakpoint of 8 mg/L, simulations showed that CI ceftazidime
36 dosages of 4-6 g daily attained optimal PTAs (>90%) across most of 16 different clinical scenarios
37 based on four classes of eGFR (50-145, 145.1-200, 200.1-286, 286.1-422 mL/min/1.73 m²) and BSA
38 (0.30-0.64, 0.65-0.88, 0.89-1.34, 1.35-1.84 m²). In patients with BSA 0.30-0.64 m² and eGFR \leq 200
39 mL/min/1.73 m² the advisable dose of 3 g daily allowed only suboptimal PTAs (<75%). The
40 cumulative fraction of response against MIC distribution of *Pseudomonas aeruginosa* was > 87%.

41 **CONCLUSIONS:** CI ceftazidime dosages ranging from 3 and 6 g daily according to different classes
42 of eGFR and BSA may allow optimized empirical treatment of *Pseudomonas aeruginosa* infections
43 in pediatric HSCT patients with FN.

44

45 **Introduction**

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

51 *Pseudomonas aeruginosa* bacteremia is associated with high fatality rates in children,⁶ and in
52 high-risk FN patients may be as high as 52%.⁷ Multidrug-resistant strains are common.⁸ Current
53 guidelines of the American Society of Clinical Oncology recommend monotherapy with an anti-
54 pseudomonal beta-lactam as empirical therapy in pediatric patients with high-risk FN.⁹ A second
55 Gram-negative agent, such as an aminoglycoside, is reserved for patients who are clinically unstable,
56 when resistant infection is suspected or for patients in centers with high prevalence of resistant
57 pathogens.⁹

58 Ceftazidime is an antipseudomonal third-generation cephalosporin that is widely used in
59 patients with FN.¹⁰ Ceftazidime has a low potential for drug-drug interactions, is almost completely
60 renally eliminated (80 to 90%) and has low plasma protein binding (approximately 10%).^{11,12} It may
61 have a more favorable safety profile compared to other anti-pseudomonal cephalosporins, with a
62 lower risk for neurotoxicity.¹³

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

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

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81 **Methods**

82 **Study design**

83 This retrospective study included a cohort of pediatric patients who underwent HSCT at the
84 Institute for Maternal and Child Health IRCSS Burlo Garofolo, Trieste, Italy, and who received CI
85 ceftazidime for the empirical treatment of high risk FN in the period between June 2012 and
86 December 2017.

87 Ceftazidime treatment was started with a loading dose (LD) of 60-100 mg/kg infused in 1
88 hour, which was immediately followed by a maintenance dose (MD) of 100-200 mg/kg daily
89 administered by CI. Dosage adjustments were guided by real-time therapeutic drug monitoring
90 (TDM) of ceftazidime steady-state plasma concentrations (C_{ss}), which were assessed after at least 2
91 days from starting therapy. Drug dosages were adjusted using a linear scaling with a minimum dose
92 modification of 500 mg. The desired range of ceftazidime plasma C_{ss} was set between 32 and 64
93 mg/L. The rationale was that of maximizing empirical treatment against *P. aeruginosa* by achieving
94 a C_{ss} between 4-fold and 8-fold the EUCAST clinical breakpoint of ceftazidime versus *P. aeruginosa*
95 which is 8 mg/L.²² This strategy may be especially helpful when in presence of severe infections.^{23,}
96 ²⁴

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

104 The following demographic and clinical data were retrieved from patient clinical records: age,
105 gender, weight, height, body surface area (BSA), duration of therapy, date of HSCT and type of
106 underlying oncological or hematological disease and co-treatment with other antimicrobials. Baseline

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

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

118

119 **Population pharmacokinetic modelling**

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

130 Initially, a base model without covariates was developed and fitted to the data. Subsequently,
131 the relationship between Bayesian estimates of CL and V for each patient and clinically relevant
132 covariates (age, weight, height, sex, BSA, eGFR, time from HSCT, presence of acute leukemia) was

133 assessed. A forward-backward selection process for covariate inclusion was adopted by using the
134 Pmetrics “PMstep” function. A final multivariate model including all the significant covariates was
135 then developed and refitted to the data. The performance of the pharmacokinetic models was assessed
136 by means of visual inspection of the observed-predicted plot, the coefficient of determination of the
137 linear regression of the observed-predicted values and of the likelihood ratio test. Differences in the
138 objective function value (OFV) greater than 3.84 between each pharmacokinetic model and the base
139 model ($p < 0.05$), coupled with evaluation of the Akaike information criteria (AIC), were considered
140 as statistically significant additions to the model. Model performance was evaluated by means of
141 normalized prediction distribution errors (NPDEs), which is a metric design to allow evaluation of
142 non-linear mixed-effect models.

143

144 **Monte Carlo simulation analysis for determining the probability of target attainment for** 145 **empirical treatment against *Pseudomonas aeruginosa***

146 1000-subject Monte Carlo simulations based on the final model were performed for each of
147 six incremental dosing regimens of CI ceftazidime (1g q24h, 2g q24h, 3g q24h, 4g q24h, 5g q24h and
148 6g q24h) for determining the PTA for maximized empirical treatment against *Pseudomonas*
149 *aeruginosa*. Variability of the continuous covariates included in the final model was assessed by
150 splitting each covariate distribution, as observed in our population, into four categories corresponding
151 to four quartiles (0-25th percentile, 25th-50th percentile, 50th-75th percentile, 75th-100th percentile).

152 Ceftazidime C_{ss} were simulated at 48 h by means of the Pmetrics simulation engine. The
153 desired pharmacodynamic target was $C_{ss}/MIC \geq 4$ at the EUCAST clinical breakpoint of 8 mg/L.
154 PTAs were considered acceptable when $\geq 80\%$, and optimal when $\geq 90\%$.²⁹

155 For safety purposes, an upper threshold for simulated ceftazidime C_{ss} was placed at 100 mg/L
156 (potential toxicity threshold). The rationale was based on previous studies suggesting that this choice
157 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 EUCAST³¹ (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 **Ethics**

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 \pm standard deviation or median with
176 25th-75th 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

181 **Results**

182 **Patient characteristics**

183 A total of 46 HSCT children with high risk FN were included in this study. Table 1
184 summarizes patient clinical and demographic characteristics. The median (min-max range) age, BSA
185 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),
186 respectively.

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

190 Ceftazidime treatment was started after a median (IQR) of 6.0 (1.0 – 11.75) days from HSCT
191 and had median (IQR) duration of 10.5 (7.0 – 16.0) days. The median (IQR) loading and maintenance
192 doses of ceftazidime were of 80.0 (49.2-139.7) mg/kg and of 145.9 (128.3 – 171.3) mg/kg daily.
193 Median (IQR) total maintenance dose was of 3.5 (2.5 – 5.0) g/day by CI, with a min-max range of 1
194 – 10 g/day. First TDM assessment occurred after a median (IQR) of 3.0 (2.0 – 5.75) days from
195 starting therapy and in that occasion the observed C_{ss} were ≤ 8 mg/L (C_{ss}/MIC≤1) and ≤ 32 mg/L
196 (C_{ss}/MIC≤4) in 1 and in 9 patients, respectively. Among those patients who had ≥ 2 TDM
197 assessments over time (17/46, 36.9%), the ceftazidime dosage was adjusted in 12 cases. All patients
198 received antibiotic combination therapy. Amikacin (38/46, 82.6%) was the most frequently used
199 followed by glycopeptides, either vancomycin or teicoplanin (33/46, 71.7%).

200 No patient had signs of hepatic toxicity. Median baseline versus end of treatment levels were
201 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
202 0.64 mg/dL ($p = 0.791$) for bilirubin. Similarly, no episodes of ceftazidime-related neurotoxicity
203 were reported. ~~Cure was observed in 39% of patients (18/46), whereas clinical conditions did not~~
204 ~~improve in 54.3% (25/46) of cases and an escalation to meropenem was deemed necessary. Three~~
205 ~~patients died from complications directly related to their hematological malignancies.~~

206

207 **Population pharmacokinetic modeling**

208 A total of 70 plasma ceftazidime C_{ss} samples were included in the population pharmacokinetic
209 model. A two-compartment model performed better than a one-compartment model (OFV of 612.9
210 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-
211 compartment model, respectively). An additive lambda term of 4.87 was estimated and included in
212 the error model. Covariates that improved the fit of the model to the data were the patient's BSA and
213 eGFR (when applied to ceftazidime CL), and the patient's height (when applied to ceftazidime V).
214 After the inclusion of these covariates, the OFV and AIC furtherly improved to 578.3 and 596.6,
215 respectively. The final structural model was as follows:

$$216 \text{ CL (L/h)} = \theta_1 \cdot \left(\frac{BSA}{0.88}\right)^{\theta_2} \cdot \left(\frac{eGFR}{200.5}\right)^{\theta_3}$$

$$217 \text{ V (L)} = \theta_4 \cdot \left(\frac{height}{120}\right)^{\theta_5}$$

218 where, BSA, eGFR and height represent the values of body surface area, estimated glomerular
219 filtration rate and patients' height, respectively. Each covariate was normalized by the median of its
220 relative distribution as observed in the population. The performance of the different models built for
221 covariate analysis is reported in Table S1 of the Supplementary Material.

222 There was a good fit of the final model to the observed data (Figure 1). A linear regression
223 of the observed-predicted values before and after the Bayesian step had an R^2 value of 0.216 and of
224 0.877, respectively, with minimal bias and imprecision. The parameter estimates of ceftazidime for
225 the final population Bayesian pharmacokinetic model are summarized in Table 2. The median
226 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
227 – 33.61 L) for V. Distribution of NPDEs followed a gaussian distribution and no trends were evident
228 in the scatterplot of NPDE versus time and versus predicted outcome (Supplementary Figure S1).

229

230 **Monte Carlo simulation**

231 A total of ninety-six Monte Carlo simulations were conducted in order to test six incremental
232 dosing regimens of CI ceftazidime (ranging from 1 g q 24h to 6 g q 24h) across sixteen different
233 clinical scenarios. These clinical scenarios resulted from the combination of four classes of BSA
234 (0.30-0.64, 0.65-0.88, 0.89-1.34 and 1.35-1.88 m²) and of four classes of eGFR (50-145, 145.1-200,
235 200.1-286 and 286.1-422 mL/min/1.73 m²).

236 Figure 2 shows the CI ceftazidime dosages needed for attaining the desired C_{ss}/MIC ratio ≥ 4
237 at the EUCAST clinical breakpoint against *Pseudomonas aeruginosa* (8 mg/L) in the different clinical
238 scenarios. In patients with eGFR of 50-145 mL/min/1.73 m², ceftazidime dosages ranged between 4
239 g q24h CI for BSA ≤ 1.34 m² and 5 g q24h CI for BSA > 1.34 m². Likewise, in patients with eGFR
240 of 145.1-200 mL/min/1.73 m², ceftazidime dosages were 4 g q24h CI for BSA ≤ 0.88, and 5 g q24h
241 CI for BSA > 0.88 m². In patients with eGFR of 200.1-286 mL/min/1.73 m² and 286.1-422
242 mL/min/1.73 m², ceftazidime dosages were 4 g q24h CI for BSA ≤ 0.64, 5 g q24h CI for BSA between
243 0.65 and 1.34 m², and 6 g q24h CI for BSA > 1.34 m².

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

249 The percentages of probability of achieving ceftazidime C_{ss} above the safety threshold of 100
250 mg/L in the different clinical scenarios are reported in Table 3. For safety purposes, CI ceftazidime
251 dosages should not exceed 3g q24h CI in patients with BSA 0.30-0.64 m² and eGFR 50-200
252 mL/min/1.73 m², 4g q24h CI in those with BSA 0.30-0.64 m² and eGFR 200.1-422 mL/min/1.73 m²
253 and in those with BSA 0.65-0.88 m² and eGFR 50-145 mL/min/1.73 m², and 5g q24h CI in those
254 with BSA 0.30-0.64 m² and eGFR 145.1-200 mL/min/1.73 m².

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

257 with CI ceftazidime in HSCT children with high risk FN according to different classes of eGFR and
258 BSA. Advisable dosages should be of 4g q24h CI and of 5g q24h CI in six clinical scenarios each.
259 The highest dose of 6g q24h CI should be advisable only in those patients with the highest classes of
260 BSA and eGFR. In patients having the lowest BSA estimates (0.30-0.64 m²) and decreased renal
261 function (eGFR of 50-145 or 145.1-200 mL/min/1.73 m²), advisable ceftazidime dosages should not
262 exceed 3g q24h CI, but this may allow only suboptimal PTAs (74 and 70%, respectively). However,
263 a dose increase to 3.5 g q24h by CI may be considered in children with eGFR of 145.1-200
264 mL/min/1.73 m², as PTA increases to 85.6% with a probability of toxicity of only 2.1%. In both
265 these scenario, the dose of 3g q24h by CI enabled the attainment of the less aggressive targets of
266 $C_{ss}/MIC \geq 1$ and $C_{ss}/MIC \geq 2$, with PTA > 97.8%.

267 The CFRs against *Pseudomonas aeruginosa* achievable in HSCT children with the advisable
268 CI ceftazidime dosages are summarized in Table 5. Overall, all regimens were associated with CFRs
269 > 87.1% when considering the EUCAST MIC distribution, and > 79.4% when considering our local
270 MIC distribution. CFRs associated with a less aggressive target of $C_{ss}/MIC \geq 1$ are reported in Table
271 S3. CFRs were > 96.2% when considering the EUCAST MIC distribution and > 88.1% when
272 considering our local MIC distribution. The risk-to-benefit ratios for the CFRs that were associated
273 with the target of a $C_{ss}/MIC \geq 4$ are provided in Table S4.

274

275 **Discussion**

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

279 The mean estimated CL (3.18 L/h or 0.14 L/h/kg) in our population was comparable to the
280 values previously observed among hospitalized pediatric patients aged between 6 and 18 years (0.17-
281 0.23 L/h/kg)³² and/or infants aged < 2 years (0.17 L/h/kg).³³ V was also consistent with values
282 reported for patients of similar ages (13.0 – 22.2 L).³²

283 The finding that eGFR was a significant covariate affecting ceftazidime CL is consistent with
284 a population pharmacokinetic study previously conducted in infants.³³ Ceftazidime is predominantly
285 eliminated via the renal route. Dosages should be adjusted according to the degree of renal function.
286 BSA was also a significant covariate of ceftazidime CL in our study population. This finding was not
287 described previously, and seems biologically plausible, as in children renal weight was found to be
288 significantly correlated with BSA.³⁴ Interestingly, guidelines on pediatric dosing of hydrophilic drugs
289 that are renally excreted recommend dose normalization to BSA when children are aged more than 2
290 years.³⁵

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

297 Mortality from *Pseudomonas aeruginosa* bacteremia remains unacceptably high in children
298 and adolescents with FN.⁸ A recent retrospective study conducted among 31 children with FN
299 showed that appropriate antimicrobial treatment and combination therapy of an antipseudomonal

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

302 Preclinical and clinical studies showed that targeting CI ceftazidime C_{ss} at 4 times the MIC
303 was effective against *Pseudomonas aeruginosa* infections.^{18, 37} Our findings suggest that CI
304 ceftazidime dosages of 4-6 g daily may achieve this pharmacodynamic target in most cases.

305 It is worth noting that theoretically, when considering a more conservative pharmacodynamic
306 target of $C_{ss} / MIC \geq 1$, these dosages could be helpful even when in presence of resistant strains of
307 *Pseudomonas aeruginosa* with an MIC up to 32 mg/L. Interestingly, a similar approach was chosen
308 in the treatment of an 18-year-old female with a bacteremia caused by a resistant strain of
309 *Pseudomonas aeruginosa* with an MIC of 64 mg/L. It was shown that high-dose CI ceftazidime (9.6
310 g daily) for 6 consecutive days with a targeted C_{ss} of 80-100 mg/L was successful.¹⁸

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

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

322

323 **Transparency Declaration Section**

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

334

335 **Funding Section**

336 This study was conducted as part of our routine work

337

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435

436

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

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 \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 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%

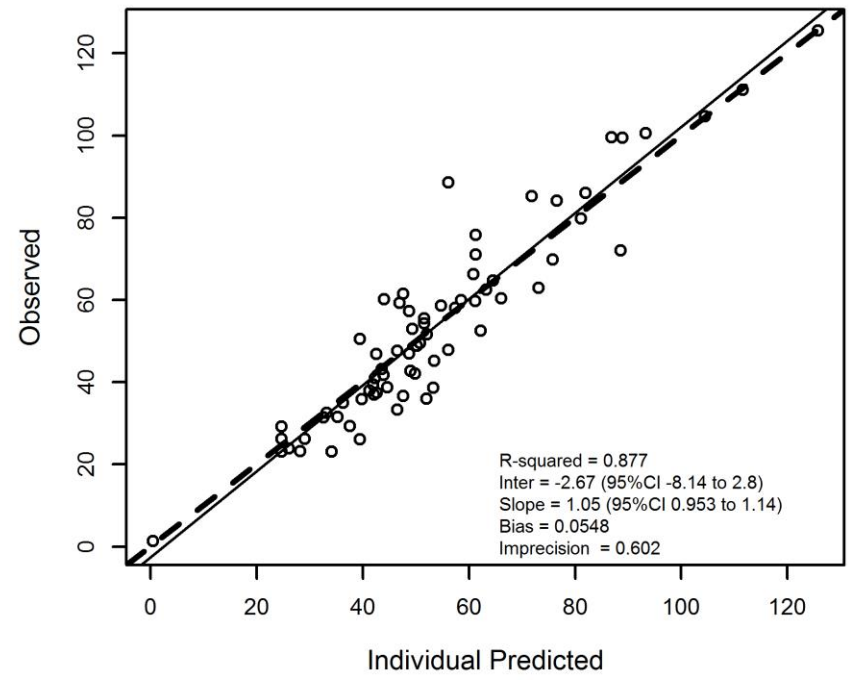
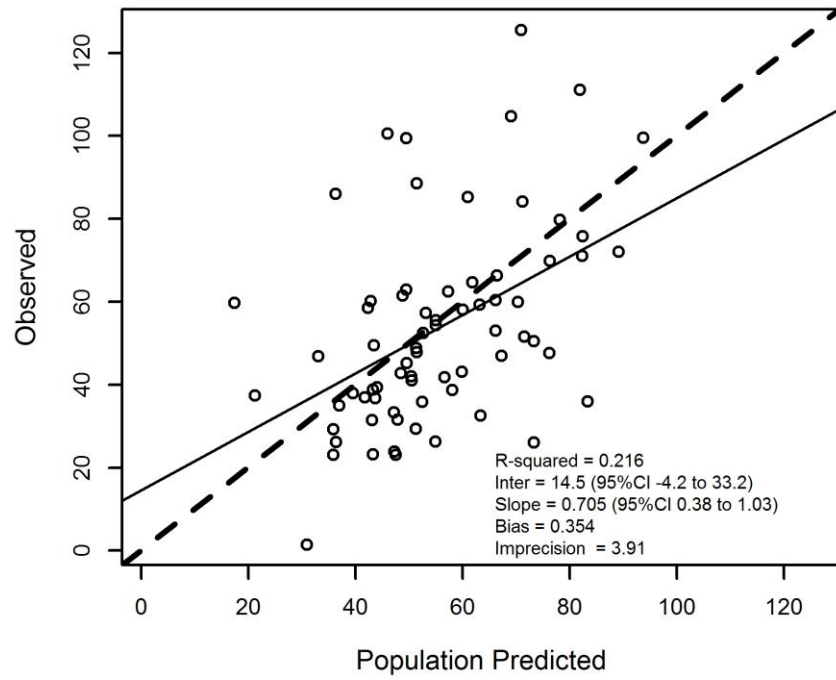
Table 5. Cumulative fraction of response with the advisable continuous infusion (CI) ceftazidime dosages targeting $C_{ss}/MIC \geq 4$ against *Pseudomonas aeruginosa* in relation to the MIC distribution of EUCAST and that observed at our center in HSCT children with high risk FN in relation to different 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

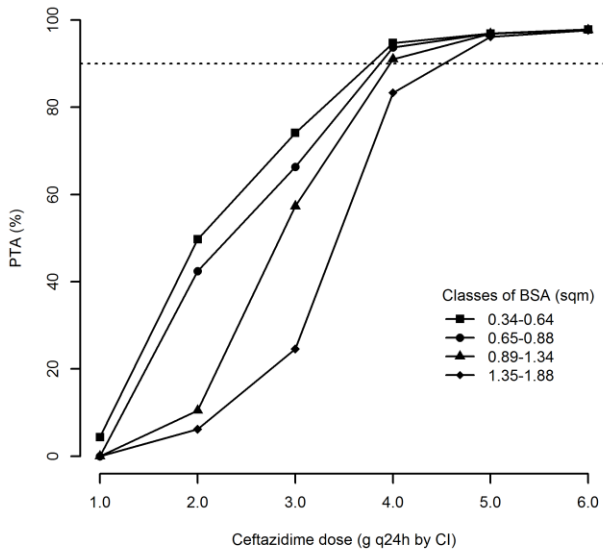
Figure Legend

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.

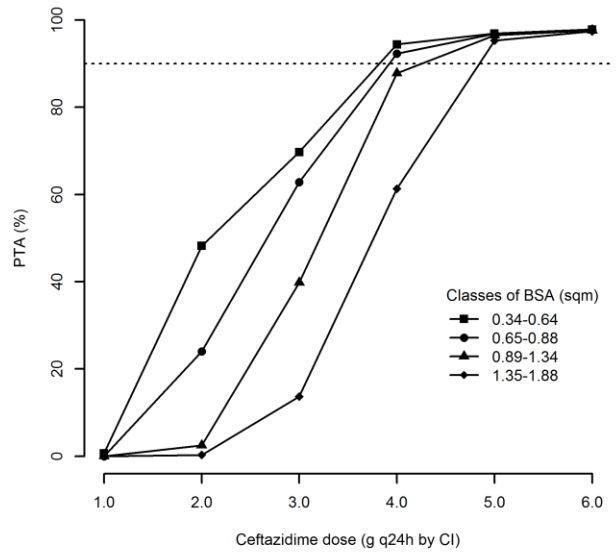
Figure 2. Probability of target attainment (PTA) of $C_{ss}/MIC \geq 4$ at the EUCAST clinical breakpoint of 8 mg/L versus *Pseudomonas aeruginosa* with incremental dosages of continuous infusion (CI) ceftazidime in relation to different classes of estimated glomerular filtration rate (eGFR) and of body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



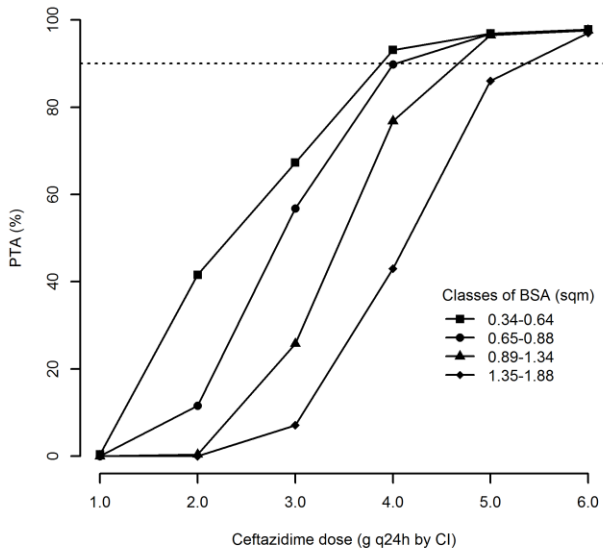
eGFR:50-145 mL/min/1.73 m²



eGFR:145.1-200 mL/min/1.73 m²



eGFR:200.1-286 mL/min/1.73 m²



eGFR:286.1-422 mL/min/1.73 m²

