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1 **High-dose ceftriaxone for bacterial meningitis: optimization of administration scheme**
2 **based on nomogram**

3

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32

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34

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36

37

38 **Abstract (225/250)**

39 High dosages of ceftriaxone are used to treat central nervous system infections (CNSI).
40 Dosage adaptation according to the glomerular filtration rate is currently not recommended.
41 Ceftriaxone pharmacokinetics (PK) was investigated by a population approach in patients
42 enrolled in a French multicenter, prospective cohort study who received high-dose ceftriaxone
43 for CNSI as recommended by the French guidelines (75-100 mg/Kg/day without upper limit).
44 Only suspected bacterial meningitis were included in the PK analysis. A population model
45 was developed using Pmetrics. Based on this model, dosing nomogram was developed, using
46 the estimated glomerular filtration rate (eGFR) and the total body weight as covariates to
47 determine the optimal dosage allowing achieving targeted plasma trough concentrations.
48 Efficacy and toxicity endpoints were based on previous reports as follows: total plasma
49 ceftriaxone greater than or equal to 20 mg/L in more than 90% of patients for efficacy and
50 less than or equal to 100 mg/L in more than 90% of patients for toxicity. Based on 153
51 included patients, a two-compartment model including eGFR and total body weight as
52 covariates was developed. The median value of unbound fraction was 7.57 % and the median
53 value of CSF/plasma ratio 14.39 %. A nomogram was developed according to a twice-daily
54 regimen. High-dose ceftriaxone administration schemes, used to treat meningitis, should be
55 adapted to the eGFR and the weight especially to avoid underdosing using current guidelines.

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59 **Introduction**

60 Ceftriaxone is a broad-spectrum cephalosporin recommended for empiric treatment of
61 bacterial meningitis (1–3). This antibiotic displays original pharmacokinetics (PK) with a dual
62 biliary and renal clearance and an extended half-life allowing a twice-daily or even a once-
63 daily administration scheme. Ceftriaxone recommended dosages for treating meningitis are
64 different from one learned society to another. IDSA (Infectious Diseases Society of America)
65 and ESCMID (European Society for Clinical Microbiology and Infectious Diseases)
66 recommended 4 g per day in adults whatever patients weight (2,3), while French guidelines
67 promote a dose-weighted adjustment in a range of 75 mg/kg to 100 mg/kg per day without
68 upper limit dosage (1). None of them recommends an adaptation according to the glomerular
69 filtration rate (GFR) except French guidelines in case of GFR lower than 10 mL/min.

70 Dosages used in central nervous system (CNS) infections are widely higher than those usually
71 prescribed. Hence, previous studies investigated ceftriaxone population PK after
72 administration of dosage generally equal or lower than 2 g per day (4–8), and no specific
73 study was performed in populations receiving more than 4g per day. High GFR are frequently
74 observed in critically ill patients with community-acquired acute infectious meningitis and are
75 likely to affect ceftriaxone clearance (9,10) These changes, frequently observed during
76 meningitis, justify investigating specifically ceftriaxone PK in this population. The aim of this
77 work was to describe the PK of ceftriaxone in a large cohort of patients treated for suspected
78 bacterial meningitis with a high daily dosage (≥ 75 mg/kg or 4 g per day). Based on the finally
79 developed model, Monte Carlo simulations were performed to propose an optimal ceftriaxone
80 scheme of administration in patients treated for suspected bacterial meningitis according to
81 the renal function and the weight.

82 **Materials and methods**

83 **Ethics and patients**

84 This work is an ancillary population PK study from an open-label prospective,
85 multicenter study entitled “High-Dose Ceftriaxone in Central Nervous System Infections”
86 aiming to determine PK and tolerance of high-dose ceftriaxone in CNS infected patients (11).
87 Written informed consent was obtained from all patients enrolled in the study. The study
88 design and consent form were approved by regulatory authorities and research clinical
89 practices and the study was conducted according to the principles of the Declaration of
90 Helsinki (22 October 2008 version) and to French law. A license was issued by ANSM. This
91 study has been registered at ClinicalTrials.gov under identifier NCT01745679.

92 Patients suffering from suspected or proven CNS infections treated with ceftriaxone daily
93 dosage equal or higher than 4 g or 75 mg/kg were enrolled in 6 French centers in Infectious
94 Diseases departments or intensive care units from the west of France (Nantes University
95 Hospital, Angers University Hospital, Saint-Nazaire Hospital, Tours University Hospital, La
96 Roche-sur-Yon Hospital, Rennes University Hospital) between December 2012 and July 2015
97 and only those suspected of having community or hospital-acquired meningitis were included
98 in the PK analysis.

99 **Collection of clinical and therapeutic data**

100 Clinical evolution during the ceftriaxone treatment was followed by the physician in
101 charge of the patient and clinical and therapeutic data were listed in a case report form.

102 **Quantification of ceftriaxone concentrations**

103 Plasma samples were obtained by direct venopuncture or through a catheter and CSF
104 samples by lumbar puncture.

105 Ceftriaxone plasma concentrations were determined by validated high-performance
106 liquid chromatography methods with UV detection in the pharmacology departments of
107 Nantes and Rennes University Hospital. Concentrations for patients included in Rennes
108 University Hospital were measured using a previously validated assay (12).

109 Total ceftriaxone plasma concentrations for other patients were centralized in the
110 pharmacology department of Nantes University Hospital and consistency of results between
111 the two departments was checked using a similar quality control program (Asqualab, Paris,
112 France). A liquid/liquid extraction procedure was used in Nantes by mixing 1 mL aliquot of
113 plasma with 1 mL acetonitrile. Mixture was centrifuged at 1800 g for 5 min at +4°C.
114 Supernatant layer (1.6 mL) was added to dichloromethane (8 mL). Tubes were horizontally
115 shaken for 10 min and centrifuged at 1800 g for 5 min at +4°C and 50 µL of the upper
116 aqueous layer were injected into the system. Mobile phase (Na_2HPO_4 0.03 M - pH
117 1.9/acetonitrile: 85/15 (v/v)) was delivered at 1.3 mL/min and separation was performed on
118 Waters Symmetry® (5µm C18 column (250 x 4.6 mm ID)), (Waters, Milford, USA).
119 Ceftriaxone plasma concentration was detected by ultraviolet absorbance at 260 nm.

120 Chromatographic conditions defined in this assay were also applied to plasma ultrafiltrates
121 obtained according to a previously validated method using the Amicon Ultra-0.5 mL 30,000
122 molecular weight cut-off centrifugal filter device (Millipore, Cork, Ireland) to measure
123 ceftriaxone unbound plasma concentration (13).

124 These chromatographic conditions were also applied to measure ceftriaxone concentrations
125 into CSF.

126 All unbound plasma and CSF concentrations were determined at the pharmacology
127 department of Nantes University hospital. The limits of quantitation were 1 mg/L in plasma

128 and in CSF. The methods were accurate (inter-day and intra-day inaccuracy <15%) and
129 showed good precision (inter-day and intra-day imprecision <15%).

130 Total ceftriaxone concentrations were the only data used for model building. Unbound and
131 CSF concentrations were used to assay binding and diffusion ratio in our population and to
132 compare these data to those already published and used to build the current guidelines.

133 **Population pharmacokinetics analysis**

134 Ceftriaxone PK analysis was performed using a non-parametric method implemented
135 in Pmetrics (Laboratory of Applied Pharmacokinetics, University of Southern California, CA)
136 (14). Pmetrics is a library package for R using Fortran.

137 Only total plasma concentrations were used to build the model. An initial analysis was
138 conducted to estimate the parameters of the structural model without covariates. Three kinds
139 of structural model were tested: a one-compartment model, a two-compartment model and a
140 three-compartment model.

141 Additive and multiplicative error models were tested, where observations were weighted by
142 $(SD^2 + \lambda^2)^{0.5}$ and $SD \times \gamma$, respectively. Lambda/gamma represented process noise such as
143 sampling time uncertainty and model misspecification. SD was the standard deviation of each
144 observation, modeled by a polynomial equation: $C_0 + C_1 \times [obs] + C_2 \times [obs]^2 + C_3 \times$
145 $[obs]^3$ where [obs] is the observation.

146 The influence of covariates onto parameters was assessed using backward stepwise process
147 and visual examination of the parameter versus covariate plot. Linear, exponential, power
148 associations and allometric scaling were assessed. The following covariates were tested: age,
149 sex, total body weight, creatinine serum concentration measured by enzymatic assay (Roche,
150 Basel, Switzerland), MDRD estimated Glomerular Filtration Rate (eGFR), CKD-EPI eGFR,

151 serum albumin concentration, corticoid use, mechanical ventilation, type of meningitis
152 (community or hospital-acquired).

153 The selection of the best model was based on the Akaike information criterion (AIC value)
154 and Bayesian information criterion (BIC value). The model displaying the lower AIC and BIC
155 values was chosen. Models were also assessed by visual examination of the diagnostic plots
156 (observed concentration versus predicted concentrations, weighted residuals versus time or
157 individual predicted concentrations, visual predictive checks). Bias (mean weighted error of
158 predictions minus observations) and imprecision (bias-adjusted mean weighted squared error
159 of predictions minus observations) were also factored in the model selection.

160 Visual predictive checks (VPC) were performed using Monte Carlo simulations (n = 1,000)
161 from each of the patient to take into account each dose regimen and each time post dose (15).
162 Median, 5th and 95th percentiles for observed and simulated concentrations were then
163 compared visually. Plotting was done using the “vpc” package for R.

164 **Monte Carlo simulations of dosage regimens and nomogram**

165 Based on the parameters of the structural model, Monte Carlo simulations were
166 generated (n = 1,000) from patient profiles with varying eGFR and weights reflective of the
167 population observed. For each of these profiles, exposure to ceftriaxone was assessed for
168 doses ranging from 500 mg/day to 25,000 mg/day according to a twice-daily regimen.

169 Targeted plasma trough concentrations for total ceftriaxone were defined from 20 mg/L to
170 100 mg/L. During bacterial meningitis, no targeted plasma concentration has ever been
171 studied specifically but in severe infections, the unbound trough concentrations should be at
172 least 4 times higher than the MIC (100% fT>4xMIC) to achieve efficacy (16,17). The most
173 resistant bacteria found during community-acquired bacterial meningitis is *Streptococcus*
174 *pneumoniae* with reduced susceptibility to penicillin. Therefore, the EUCAST

175 epidemiological cut-off MIC for *S. pneumoniae* (0.5 mg/L) was used to set the target of
176 efficacy (18). Knowing that a 100% fT>4xMIC was targeted, it correspond to an unbound
177 trough concentration of ceftriaxone in plasma of 2 mg/L. Accounting for the high protein
178 binding of ceftriaxone (around 85-95%) the target of 20 mg/L for total ceftriaxone trough
179 concentration was determined. This cut off was consistent with recent guidelines of the
180 French society of anaesthesia and intensive care/French society of pharmacology (17).

181 The 100 mg/L target was defined as an upper limit beyond which the toxicity risk could be
182 largely increased. This target has been recently reported in the study part investigating
183 tolerability of high-dose ceftriaxone in the same cohort (11).

184 To conceive the dosing nomogram, the lowest dose required to achieve a probability of target
185 attainment (PTA) of at least 90 % was reported on a graph in Microsoft™ Excel (Microsoft
186 Corporation, Redmond Washington, USA) for 20 mg/L as trough targeted concentration while
187 the highest dose allowed to not reach a probability of target attainment (PTA) of more than 10
188 % was reported for 100 mg/L as trough targeted concentration. Confidence intervals (95%)
189 were calculated for each prediction and reported on the graph.

190 **Results**

191 One hundred and fifty three patients were included, 133 for suspected or proven
192 community-acquired meningitis and 20 for suspected or proven hospital-acquired meningitis.

193 Description of study patients, their clinical, microbiological and therapeutic characteristics are
194 reported in Table 1.

195 For each patient, 1 to 4 blood samples were collected at least 23 hours after the beginning of
196 the therapy (mean delay 92 hours (range:23-240)). Three hundred and one total
197 concentrations, 214 unbound concentrations and 11 CSF concentrations were sampled.
198 Elapsed time from last dose to plasma measurement ranges from 5 min to 24 hours.

199 A two-compartment model was chosen as the basic PK model. K_e was modelled as $K_e1 +$

200 $\left(\frac{eGFR}{94} \times K_e2\right)$ where 94 was the median value for the population and V was modelled as

201 $V1 \times \left(\frac{WT}{74}\right)^{V2}$ where 74 was the median value for the population.

202 A gamma error model with a starting value of 2 was chosen, and values for C_0 , C_1 , C_2 and C_3

203 were 0.5, 0.05, 0 and 0 for the SD polynomial, respectively. The final cycle value of gamma

204 was 2.45. This indicates an acceptable process noise.

205 The estimates of the population PK parameters are presented in Table 2. The median value of

206 unbound fraction was calculated from 214 individual observed concomitant data and was 7.57

207 % (from 1.61 to 49.30 %). Protein binding was saturable, especially when total concentrations

208 exceed 100 mg/L. The relationship between linked and total concentrations was best

209 described by a polynomial model where percentage of protein binding was modelled as $-5E^{-}$

210 $09x^3 + 6E^{-07}x^2 - 0.0004x + 0.9393$ where x was the total concentration of ceftriaxone (R^2 :

211 0.3224). The median value of CSF/plasma ratio was calculated from 8 individual observed

212 concomitant data and was 14.39 % (from 5.86 to 65.94 %) with a median concentration in

213 CSF of 14.95 mg/L (from 1.65 to 27.1 mg/L), a median total plasma concentration of 63.55

214 mg/L (from 21.6 to 201.3 mg/L) and a median time after infusion of 12 hours (from 3.67 to 48

215 hours).

216 Diagnostic plots are shown in Fig. 1. Equations established by linear regression of observed

217 concentrations versus individual predicted concentrations are close to the identity line and

218 analysis of residuals appears to be satisfactory and VPC plot shows that the model correctly

219 described the observed data (Figure 2).

220 From the validated model, the dosing nomogram has been constructed. Fig. 3 shows the

221 nomogram according to a twice-daily regimen. eGFR window range from 15 mL/min/1.73 m²

222 to 160 mL/min/1.73 m² according to our population data.

223 **Discussion**

224 This first population PK study in adult patients treated with high doses of ceftriaxone
225 (above 4g or 75 mg/Kg per day) for suspected bacterial meningitis suggests that ceftriaxone
226 administration scheme and posology should be adapted to the eGFR and the weight.

227 However, few obese patients were included in our work and the proposed nomogram was not
228 adapted for these patients. It should therefore be used with caution in this population knowing
229 that, for most beta-lactams, adjustment in proportion to excess weight is not required.

230 Only 86 pathogens were isolated in proven single-strain infections. For the other 67 patients,
231 microbiological research was unable to isolate the pathogen or the infection was not proven. If
232 ceftriaxone was given in the case of a strong suspicion of bacterial meningitis, the absence of
233 infection in some patients could not be excluded.

234 The population modelling results are consistent with previous studies and confirm the
235 influence of the eGFR onto ceftriaxone clearance (7,19,20). According to Schleibinger *et al.*,
236 ceftriaxone concentrations seem to depend only on the clearance of unbound ceftriaxone
237 which depends on renal function but not on unbound fraction (21). Here, influence of renal
238 function was observed whatever the degree of renal insufficiency while not in previous study
239 with lower ceftriaxone regimen but owing to higher concentrations, percentage of binding is
240 very variable (1.6 to 43%) and probably may results in a greater role of the kidney in total
241 elimination (7). According to Heinemeyer *et al.*, this result suggests that biliary ceftriaxone
242 clearance does not compensate the decrease in renal elimination in patients with renal failure
243 (22).

244 In this work, the volume of distribution was correlated to the total body weight and
245 demonstrate the interest to adapt the dosage to the total body weight as suggested by French
246 recommendations (1). Previous study shows similar results where total body weight has been

247 integrated in population modelling (23). Other recent population studies did not integrate
248 body weight in modelling but integrated other covariates such as serum albumin (20).

249 The unbound fraction in our study was heterogeneous compared to healthy volunteers (1.6 -
250 43% vs. 5 - 15%), and seems lower than other published data on critically ill patients (14 – 43
251 %, 33%) (21,24,25). This could be due to the characteristics of our group which was
252 constituted partly of viral meningitis with less systemic inflammation and subsequent
253 hypoalbuminemia.

254 Median value of CSF/plasma ratio of total ceftriaxone was calculated for 8 observed
255 concomitant data and was 14.39 % (from 5.86 to 65.94 %). These data were higher than those
256 observed in previous study (from 0.6 - 1.8% without meningeal inflammation to 2 - 7% in
257 case of meningeal inflammation) (27–29).

258 Finally, it would have been preferable to evaluate PTA for efficacy in CSF but the number of
259 concentration data in the CSF was insufficient. Nevertheless, the CSF/plasma ratio of 14.39%
260 reported here suggests that when trough plasma concentrations are above 20 mg/L,
261 concentrations in CSF should be higher than the upper bound of ceftriaxone-intermediate
262 strains of *S. pneumoniae* ($0.5 < \text{MIC} \leq 2 \text{ mg/L}$) (18). A recent study showed that during
263 community-acquired pneumococcal meningitis, in which the level of meningeal inflammation
264 is the highest, ceftriaxone diffusion in CSF could be very high (29).

265 The first infectious agents found in our population were *Streptococcus pneumoniae* (34/86
266 isolated pathogens) followed by *Neisseria meningitidis* and *Haemophilus influenzae* which is
267 consistent with previous data (30). MIC values were determined for *Streptococcus*
268 *pneumoniae* and ranged from <0.016 to 0.5 mg/L confirming EUCAST epidemiological cut-
269 off values used for determination of the PK-PD target of 20 mg/L (18).

270 The DALI study suggests that the PK-PD target is 100% $fT > MIC$ in critically ill patients (16).
271 Given the severity of these patients, a fixed target for unbound trough plasma concentration
272 higher than 4 times the MIC of the targeted bacteria appears to be reasonable (31). This
273 margin of safety is justified notably by imprecision in the determination of the MIC (32).
274 Moreover, the variability of the diffusion of ceftriaxone in the CNS could justify this margin
275 and an elevated target appears to be more accurate to prevent insufficient level of diffusion
276 and to have a maximum bactericidal rate (31,33). Therefore, a target of 20 mg/L was chosen
277 based on a protein binding around 90% and a maximum MIC value of 0.5 mg/L as confirmed
278 by our results. This target is currently recommended by French guidelines (17).

279 The target for toxicity was fixed at 100 mg/L according to recent published data (11). This
280 plasma concentration threshold could be associated to a higher risk of having ceftriaxone-
281 related adverse drug reaction and, even if it is uncertain, it justifies to monitor clinically the
282 patient especially at the neurological level. In addition, it is unlikely that exceeding these
283 concentrations will provide a benefit in terms of effectiveness. This target has been confirmed
284 by the recent guidelines of the French society of anaesthesia and intensive care/French society
285 of pharmacology (17).

286 Nomogram was developed to propose a twice-daily regimen knowing that more than a quarter
287 of our group received ceftriaxone by a once-daily regimen and more than two thirds by a
288 twice-daily regimen. A once-daily regimen nomogram was not presented here because it
289 failed to allow achieving of sufficient concentrations while being safe in terms of toxicity.
290 Moreover, a once-daily regimen necessitates higher daily dosages than a twice-daily regimen.

291 For example, a patient with an eGFR of 90 mL/min/1.73 m² and weighting 75 Kg
292 (approximately mean patient eGFR and weight in this study) will require a daily dosage of
293 47 to 71 mg/Kg (3.5 to 5.3 g) with a twice-daily regimen based on nomogram. In this case,

294 the proposed posology is consistent with European and American guidelines. In case of higher
295 eGFR ($> 140 \text{ mL/min/m}^2$), a probably frequent and underestimated situation in patients with
296 bacterial meningitis, the same patient weighting 75 Kg, would require at least 78 mg/Kg (5.8
297 g) daily without exceeding 108 mg/kg (8 g) to obtain the same PTA with a twice-daily
298 regimen. This patient would probably be under dosed using European and American
299 guidelines (and potentially with a once-daily regimen). In summary, according to our model,
300 European and American guidelines could increase the risk of subtherapeutic concentrations of
301 ceftriaxone especially in case of increased GFR, obese patients even in the case of susceptible
302 strains of *S. pneumoniae* with MIC of 0.5 mg/L. On the contrary, French guidelines probably
303 overestimate posology in case of renal impairment. Unfortunately, the 3 guidelines neglect the
304 importance of kidney function in dosage adjustment.

305 This work suffers from several limitations. First, population model did not integrate unbound
306 plasma and CSF concentrations because of missing data for many patients. Integration of
307 unbound concentrations has been tested but was not satisfactory and it was chosen to develop
308 the model based only on total plasma concentrations to obtain a reliable model for Monte
309 Carlo simulations. Moreover, targeted concentrations have been defined by French guidelines
310 as total concentrations and modelling on total concentrations allowed being coherent with
311 those.

312 The second limitation of this work is the absence of correction of the eGFR by the body
313 surface area because there are missing data for many patients. Despite this limitation, the
314 model appears to be robust and eGFR not corrected by the body surface area is probably more
315 easily reachable for posology adaptation.

316 Thirdly, the proposed schemes do not take into account the potential excessive peaks that may
317 also lead to toxicity (neurological, renal) and dosage proposals higher than those

318 recommendations are to be used with caution. In this context of high daily dose, the
319 shortening of the dosing interval could be discussed.

320 Finally, two sites were used for quantification of ceftriaxone total plasma concentrations
321 which potentially increased analytical variability. Moreover, for technical reasons, all
322 unbound plasma (and CSF) concentrations were determined in a single site. Knowing that
323 analytical practices, clinical practices and types of patients included were the same in both
324 centers, the authors considered that the impact of this point was negligible.

325 **Conclusion**

326 High-dose ceftriaxone administration schemes, used to treat meningitis, should be
327 adapted to both eGFR and weight but weight adjustment should be discussed in obese patient.

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472

473 **Figure legends**

474 **Fig. 1.** Graphical representations allowing the validation of the population pharmacokinetic
475 model. Observed concentrations were plotted against population (A) or individual (B)
476 predicted concentrations (mg/L), $R^2=0.684$ and 0.947 respectively. (C) Weighted residuals
477 were plotted against individual predicted concentrations (mg/L). (D) Weighted residuals were
478 plotted against time post administration (h).

479 **Fig. 2.** Visual predictive checks of ceftriaxone concentrations against estimated values of
480 glomerular filtration rate (eGFR) by the CKD-EPI. Open circles represent all observed
481 ceftriaxone concentrations included in modelization. Solid lines represent the 5th, 50th and
482 95th percentiles for observed concentrations. Dashed lines represent the 5th, 50th and 95th
483 percentiles for simulated concentrations. Vertical lines at the top of the plots are bin
484 separators.

485 **Fig. 3.** Nomogram of daily dose of ceftriaxone per kilogram of total weight to be administered
486 to achieve trough concentration target of 20 mg/L (full line) and to not exceed 100 mg/L
487 (broken line) with a probability of 0.9, accounting for renal function estimated by the CKD-
488 EPI formula (eGFR) using a twice-daily regimen. Dotted lines represent the 95% confidence
489 interval.

490

491 **Tables**

492 **Table 1.** Baseline demographic and therapeutic characteristics, microbiology and clinical

493 outcomes of studied patients.

Demographic characteristics (unit)	
Number of patients	153
Age (years), mean [SD]	54.8 [19.7]
Male gender, n [%]	88 [57.5]
Weight (Kg), mean [SD; min, 1 st quartile, median, 3 rd quartile, max]	74.33 [16.6; 36.6, 62, 73, 85, 146]
eGFR estimated by CKD-EPI (mL/min/1.73m ²), mean [SD; min, 1 st quartile, median, 3 rd quartile, max]	93.7 [28.6; 7.78, 83.2, 100.07, 113.39, 148.55]
Albuminemia (g/L), mean [SD]	30.4 [6.2]
Community acquired meningitis, n [%]	133 [86.9]
Postoperative hospital-acquired-meningitis, n [%]	20 [13.1]
Corticosteroids, n [%]	102 [66.7]
Therapeutic characteristics (unit)	
Daily ceftriaxone dosage (g), mean [SD]	7 [1.8]
Daily ceftriaxone dosage (mg/kg), mean [SD]	95.7 [16.5]
Once-daily regimen, n [%]	44 [28.8]
Twice-daily regimen, n [%]	107 [69.9]
Three time daily regimen, n [%]	2 [1.3]

 Microbiology (86 isolated pathogens) (n)

<i>Streptococcus pneumoniae</i> *	34
*MIC values were determined for <i>Streptococcus pneumoniae</i> and ranged from <0.016 to 0.5 mg/L	
<i>Neisseria meningitidis</i>	21
<i>Haemophilus influenzae</i>	8
Other <i>Streptococci</i>	10
<i>Enterobacteriaceae</i>	5
<i>Staphylococcus epidermidis</i>	4
Others	4

 Clinical outcomes at ceftriaxone discontinuation

Death, n [%]**	4 [2.6]
**Deaths were caused by septic shock (n=2), stroke (n=1) and cerebral venous thrombosis (n=1)	
No clinical improvement, n [%]	5 [3.3]
Partial clinical improvement, n [%]	19 [12.4]
Total clinical improvement, n [%]	120 [78.4]
Unknown, n [%]	5 [3.3]

494 SD: standard deviation; n: number of patient or isolates; min: minimum; max: maximum;

495 MIC: minimal inhibitory concentration.

496 **Table 2** – Population parameters estimates and pharmacokinetics data

Parameter (unit)	Median [95 % CI]	MAWD [95 % CI]	Range
K_e1 (h^{-1})	0.158 [0.104 – 0.272]	0.119 [0.065 – 0.186]	0.001 - 1
K_e2 (h^{-1})	0.465 [0.0367 – 0.546]	0.138 [0.066 – 0.190]	0.001 - 1
K_{CP} (h^{-1})	72.082 [59.067 – 79.618]	13.154 [8.285 – 21.189]	25 - 100
K_{PC} (h^{-1})	11.127 [7.490 – 12.904]	3.262 [1.279 – 4.830]	5 - 20
$V1$ (L)	3.712 [2.874 – 5.169]	1.595 [0.948 – 2.934]	1 - 20
$V2$ (L)	0.602 [0.204 – 0.993]	0.336 [0.006 – 0.483]	0.001 - 1

497 CI: confidence interval of the estimates; MAWD: median absolute weighted deviation, used
 498 as an estimate of the variance for a nonparametric distribution. Range: interval of values set
 499 before the run.

500 In the model, $K_e = K_e1 + \left(\frac{eGFR}{94} \times K_e2\right)$, where K_e is the elimination rate constant from the
 501 central compartment (h^{-1}), $\frac{aGFR}{94}$ is the estimated glomerular filtration rate (mL/min)
 502 normalized with the population mean; K_{CP} is the constant of transfer from the central
 503 compartment to the peripheral compartment (h^{-1}); K_{PC} is the constant of transfer from the
 504 peripheral compartment to the central compartment (h^{-1}); $V = V1 \times \left(\frac{WT}{74}\right)^{V2}$, where V is the
 505 volume of the central compartment (L), $\left(\frac{WT}{74}\right)$ is the weight (Kg) normalized with the
 506 population mean.

507

508 Median (Min – Max) value of unbound fraction from 214 individual observed data was 7.57

509 % (1.61 – 49.30 %).

510 Median (Min – Max) value of CSF/plasma diffusion from 8 individual observed data was

511 14.39 % (5.86 – 65.94 %).

512





