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▶ **To cite this version:**

Matthieu Grégoire, Eric Dailly, Paul Le Turnier, Denis Garot, Thomas Guimard, et al.. High-dose ceftriaxone for bacterial meningitis optimization of administration scheme based on nomogram. Antimicrobial Agents and Chemotherapy, 2019, 63 (9), pp.e00634-19. 10.1128/AAC.00634-19 . hal-02179150

HAL Id: hal-02179150

https://univ-rennes.hal.science/hal-02179150

Submitted on 11 Oct 2019

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

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Running title: pharmacokinetics of high dose ceftriaxone

Key words: Modelling and simulation, Pharmacokinetics, antibiotics, nomogram

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Abstract (225/250)

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

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Introduction

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

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

Materials and methods

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Ethics and patients

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

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

Collection of clinical and therapeutic data

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

Quantification of ceftriaxone concentrations

Plasma samples were obtained by direct venopuncture or thought a catheter and CSF samples by lumbar puncture.

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

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

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

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

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

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

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

Population pharmacokinetics analysis

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

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

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

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

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

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

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

Monte Carlo simulations of dosage regimens and nomogram

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

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

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

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

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

Results

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

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

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

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A two-compartment model was chosen as the basic PK model. K_e was modelled as $K_e1 + \left(\frac{eGFR}{94} \times K_e2\right)$ where 94 was the median value for the population and V was modelled as $V1 \times \left(\frac{WT}{74}\right)^{V2}$ where 74 was the median value for the population.

A gamma error model with a starting value of 2 was chosen, and values for C_0, C_1, C_2 and C_3 were 0.5, 0.05, 0 and 0 for the SD polynomial, respectively. The final cycle value of gamma was 2.45. This indicates an acceptable process noise.

The estimates of the population PK parameters are presented in Table 2. The median value of unbound fraction was calculated from 214 individual observed concomitant data and was 7.57 % (from 1.61 to 49.30 %). Protein binding was saturable, especially when total concentrations exceed 100 mg/L. The relationship between linked and total concentrations was best described by a polynomial model where percentage of protein binding was modelled as $-5E^{-09}x^3 + 6E^{-07}x^2 - 0.0004x + 0.9393$ where x was the total concentration of ceftriaxone (R^2: 0.3224). The median value of CSF/plasma ratio was calculated from 8 individual observed concomitant data and was 14.39 % (from 5.86 to 65.94 %) with a median concentration in CSF of 14.95 mg/L (from 1.65 to 27.1 mg/L), a median total plasma concentration of 63.55 mg/L (from 21.6 to 201.3 mg/L) and a median time after infusion of 12 hours (from 3.67 to 48 hours).

Diagnostic plots are shown in Fig. 1. Equations established by linear regression of observed concentrations versus individual predicted concentrations are close to the identity line and analysis of residuals appears to be satisfactory and VPC plot shows that the model correctly described the observed data (Figure 2).

From the validated model, the dosing nomogram has been constructed. Fig. 3 shows the nomogram according to a twice-daily regimen. eGFR window range from 15 mL/min/1.73 m^2 to 160 mL/min/1.73 m^2 according to our population data.

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Discussion

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

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

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

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

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

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

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

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

Finally, it would have been preferable to evaluate PTA for efficacy in CSF but the number of concentration data in the CSF was insufficient. Nevertheless, the CSF/plasma ratio of 14.39% reported here suggests that when trough plasma concentrations are above 20 mg/L, concentrations in CSF should be higher than the upper bound of ceftriaxone-intermediate strains of *S. pneumoniae* ($0.5<MIC\leq2$mg/L) (18). A recent study showed that during community-acquired pneumococcal meningitis, in which the level of meningeal inflammation is the highest, ceftriaxone diffusion in CSF could be very high (29).

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

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

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

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

For example, a patient with an eGFR of 90 mL/min/1.73 m^2 and weighting 75 Kg (approximatively mean patient eGFR and weight in this study) will require a daily dosage of 47 to 71 mg/Kg (3.5 to 5.3 g) with a twice-daily regimen based on nomogram. In this case,

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

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

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

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

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

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

Conclusion

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

Acknowledgements

This work was supported by a grant from the French Ministry of Health (Interregional French Clinical Hospital Research Program grant PHRCi 2012– API12N037).

All authors declare having no competing interest regarding this work.

Preliminary results of this study were presented at ECCMID Congress, 22-25 April 2017, Vienna, Austria.

The authors want to thank all members of the High-Dose CRO CNS Infections Study Group:

Trial Steering Committee : Pierre Abgueguen, Natahalie Asseray (Principal Investigator), Louis Bernard, David Boutoille, Cédric Bretonnière, Jocelyne Caillon, Anne Chiffoleau, Eric Dailly, Martin Dary, Denis Garot, Thomas Guimard, Jérôme Hoff, Monique Marguerite, Dominique Navas, Maja Ogielska, François Raffi (chair), Véronique Sébille, Pierre Tattevin, Yves-Marie Vandamme

Expert Committee : David Boutoille, Anne Chiffoleau, Martin Dary, Dominique Navas

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347 Cédric Bretonnière, Jocelyne Caillon, Laurent Brisard, Syvie Raoul, Anne-Catherine Di
348 Prizio, Charlotte Biron, Maeva Lefebvre, Magali Brière, Samuel Pineau, Jérémie Orain, Line
349 Happi Djeukou, Laurene Leclair, Arnaud Peyre, Armelle Magot, Guillemette Favet ; *Rennes* :
350 Solène Patrat-Delon, Paul Sauleau, Mathieu Revest, Cédric Arvieux, Caroline Piau-Couapel,
351 Enora Ouamara-Digue, Maja Ratajczak, Adèle Lacroix; *Saint Nazaire* : Céline Chevalier,
352 Patricia Courouble, Alix Phelizot; *Tours* : Frédéric Bastides, Guillaume Gras, Maja Ogielska,
353 Rodolphe Buzele, Emmanuelle Mercier, Pierre-François Dequin, Annick Legras, Antoine
354 Guillon, Youenn Jouan, Stephan Ehrmann, Laeticia Bodet-Contentin, Emmanuelle Rouve,
355 Karine Fevre

356 Contributions of the authors:

357 *Drafting protocol*

358 VS, DN, ED, NA

359 *Funding research*

360 VS, DN, ED, NA

361 *Data collection*

362 MG, ED, DG, TG, LB, PT, YMV, JH, FL, MCV, GD, AC, DB, NA

363 *Concentration measurement*

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Population pharmacokinetic analysis

MG, ED, RB

Drafting of article

MG, ED, PLT, DN, NA

Writing

MG, ED, PLT, NA

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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

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491 **Tables**

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

493 outcomes of studied patients.

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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, 1st quartile, median, 3rd 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, 1st quartile, median, 3rd 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]

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Microbiology (86 isolated pathogens) (n)	
*Streptococcus pneumoniae**	34
**MIC values were determined for *Streptococcus pneumoniae* and ranged from <0.016 to 0.5 mg/L	
Neisseria meningitidis	21
Haemophilus influenzae	8
Other *Streptococci*	10
Enterobacteriaceae	5
Staphylococcus epidermidis	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.

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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 [0.0.065 – 0.186]	0.001 - 1
K_e2 (h^{-1})	0.465 [0.0.367 – 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

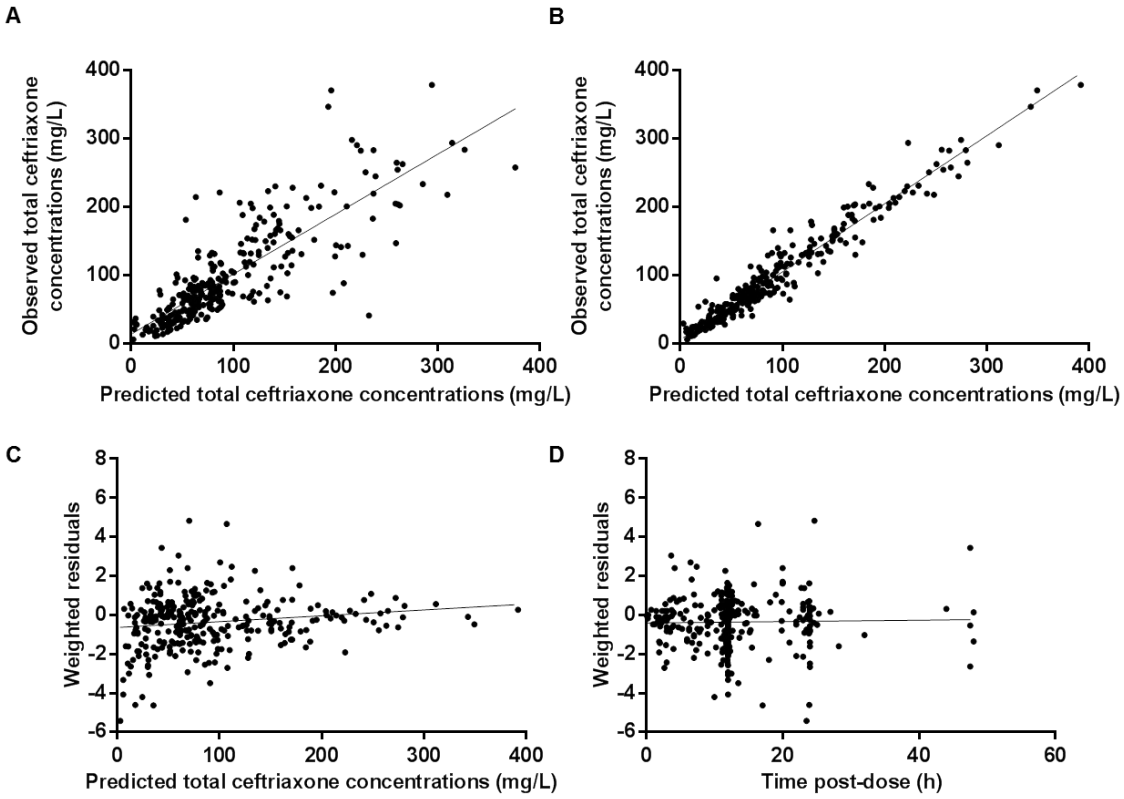
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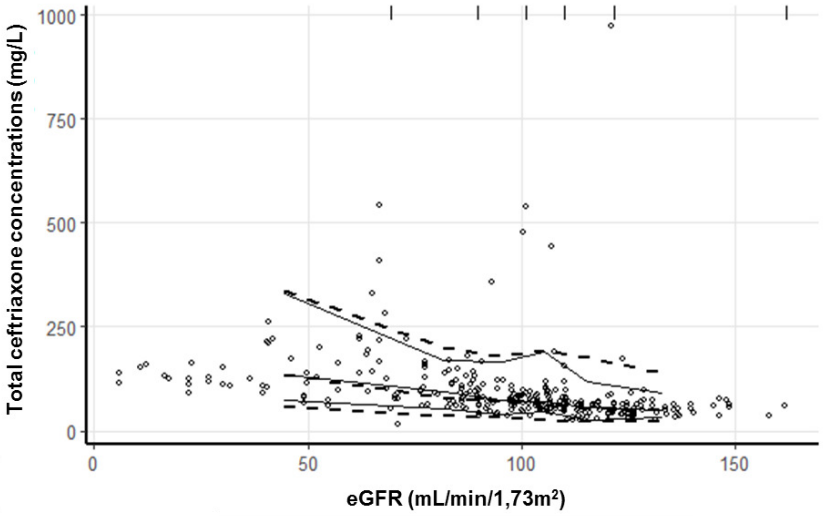
508 Median (Min – Max) value of unbound fraction from 214 individual observed data was 7.57
509 % (1.61 – 49.30 %).
510 Median (Min – Max) value of CSF/plasma diffusion from 8 individual observed data was
511 14.39 % (5.86 – 65.94 %).
512

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