Are Standard Dosing Regimens of Ceftriaxone Adapted for Critically Ill Patients with Augmented Creatinine Clearance?

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ABSTRACT The objective of the present study was to determine whether augmented renal clearance (ARC) impacts negatively on ceftriaxone pharmacokinetic (PK)/pharmacodynamic (PD) target attainment in critically ill patients. Over a 9-month period, all critically ill patients treated with ceftriaxone were eligible. During the first 3 days of antimicrobial therapy, every patient underwent 24-h creatinine clearance (CL_{CR}) measurements and therapeutic drug monitoring of unbound ceftriaxone. ARC was defined by a CL_{CR} of ≥ 150 ml/min. Empirical underdosing was defined by a trough unbound ceftriaxone concentration under 2 mg/liter (percentage of the time that the concentration of the free fraction of drug remained greater than the MIC [$fT_{>MIC}$], 100%). Monte Carlo simulation (MCS) was performed to determine the probability of target attainment (PTA) of different dosing regimens for various MICs and three groups of CL_{CR} (<150, 150 to 200, and >200 ml/min). Twenty-one patients were included. The rate of empirical ceftriaxone underdosing was 62% (39/63). A CL_{CR} of ≥ 150 ml/min was associated with empirical target underdosing with an odds ratio (OR) of 8.8 (95% confidence interval [CI] = 2.5 to 30.7; $P < 0.01$). Ceftriaxone PK concentrations were best described by a two-compartment model. CL_{CR} was associated with unbound ceftriaxone clearance ($P = 0.02$). In the MCS, the proportion of patients who would have failed to achieve a 100% $fT_{>MIC}$ was significantly higher in ARC patients for each dosage regimen (OR = 2.96; 95% CI = 2.74 to 3.19; $P < 0.01$). A dose of 2 g twice a day was best suited to achieve a 100% $fT_{>MIC}$. When targeting a 100% $fT_{>MIC}$ for the less susceptible pathogens, patients with a CL_{CR} of ≥ 150 ml/min remained at risk of empirical ceftriaxone underdosing. These data emphasize the need for therapeutic drug monitoring in ARC patients.

KEYWORDS augmented renal clearance, ceftriaxone, intensive care, pharmacokinetics

In intensive care settings, early initiation of an optimal empirical dosing regimen is one of the major determinants of outcome (1). As MIC data are often not initially available to the clinician, empirical antibiotic therapy should thus aim to inhibit all microorganisms presumed to be susceptible to the drug while limiting antibiotic selection pressure and antibiotic resistance (2).

On the other hand, optimization of antimicrobial therapy remains a complex challenge, given the wide and unpredictable variability of β -lactam antibiotic concentrations (3). A one-dose-fits-all approach could appear to be problematic in critically ill patients with an augmented volume of distribution (V) or augmented renal clearance (ARC) (4). This is a major concern, as ARC has been recognized to be one of the leading

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causes of subtherapeutic antibiotic exposure, which is potentially responsible for poor clinical outcomes in septic patients (5–8).

Ceftriaxone, one of the antibiotics most commonly used for the treatment of community-acquired infections or early health care diseases, has been poorly studied in critically ill patients (9, 10). Its uncommon pharmacokinetic properties (high binding to albumin, mixed biliary and renal elimination, long elimination half-life) might lead to altered trough concentrations in critically ill patients with augmented renal clearance (11, 12).

The primary objective of this study was to determine whether ARC negatively impacts ceftriaxone pharmacokinetic (PK)/pharmacodynamic (PD) target attainment in critically ill patients. The secondary objective was to determine the optimal dosing regimen for empirical antimicrobial therapy in critically ill patients with various renal clearances.

RESULTS

Clinical and pharmacological data. During the study period, 21 patients were treated with ceftriaxone for a first episode of presumed ($n = 3$) or documented ($n = 18$) infection. All patients received ceftriaxone at 2 g once per day. The main characteristics of the population are presented in Table 1.

Moreover, 126 concentration values were used for the empirical PK/PD target attainment analysis and included in the population PK analysis data set. Unbound ceftriaxone concentrations ranged from 17.30 mg/liter to 42.90 mg/liter for peak concentrations and 0.43 mg/liter to 5.21 mg/liter for residual concentrations. The free trough concentrations grouped by clearance quartiles are presented in Fig. 1.

The rate of empirical ceftriaxone underdosing was 62% (39/63), with a strong association with creatinine clearance (CL_{CR}) ($P < 0.0001$). A CL_{CR} of ≥ 150 ml/min was associated with empirical underdosing with an odds ratio (OR) of 8.8 (95% confidence interval [CI], 2.5 to 30.7; $P < 0.0001$).

Considering the 18 patients with documented infection, the rate of documented underdosing was 24% (13/54) when a value of the percentage of the time that the concentration of the free fraction of drug remained greater than the MIC ($fT_{>MIC}$) of 100% was considered and 70% (38/54) when a value of $fT_{>4 \times MIC}$ of 100% was considered. A CL_{CR} of ≥ 150 ml/min remained associated with documented underdosing only when a $fT_{>4 \times MIC}$ of 100% was considered (OR = 7; 95% CI = 1.6 to 30.4%; $P = 0.008$). There was no statistical association between empirical or documented underdosing and therapeutic failure.

Population pharmacokinetic analysis and Monte Carlo simulation. Ceftriaxone PK concentrations were best described by a two-compartment model. The results of graphical exploration of the five covariates (age, sex, total body weight, CL_{CR} , and serum albumin concentration) versus individual model parameter estimates using the base structural model are displayed in Fig. 2. The introduction of CL_{CR} was associated with a decrease in the Akaike information criterion (AIC; 458 versus 472), the Bayes information criterion (BIC; 459 versus 472), and the $-2 \log$ likelihood criterion ($-2LL$; 436 versus 452) ($P = 0.02$). The equation for unbound ceftriaxone clearance was as follows: CL_{u_i} (in liters per hour) = $CL_{u_{pop}} \cdot (CL_{CR_i}/190)^{0.442}$ (where CL_{u_i} is the individual unbound ceftriaxone clearance, $CL_{u_{pop}}$ is the population unbound ceftriaxone clearance, and CL_{CR_i} is the individual CL_{CR}). The residual proportional error described the model with the smallest AIC and BIC values in comparison with those from the additive or combined error model ($P < 0.01$).

The goodness-of-fit plots of the final PK model with covariates are shown in Fig. 3, with good correlations coefficients between individual and population predicted versus observed concentrations ($R^2 = 0.98$ [$P < 0.001$] and $R^2 = 0.95$ [$P < 0.001$], respectively). These plots show no misspecifications in the structural and residual error models. Most residuals were within the expected range (-2 , $+2$). The final ceftriaxone population PK parameter estimates and their associated precisions are provided in Table 2. All were reliably estimated, with the standard error being $< 50\%$. The visual predictive check

TABLE 1 Characteristics of the population^a

Characteristic	Values for all patients (n = 21)
Demographic data	
Median (IQR) age (yr)	36 (27–60)
No. (%) of male patients	17 (81)
Median (IQR) BMI (kg/m ²)	26 (21–29)
No. (%) of patients admitted for:	
Trauma	14 (67)
Nontraumatic surgery	7 (33)
Median (IQR) SAPS 2	32 (27–43)
No. (%) of patients with presumed/confirmed infection at the following site:	
Respiratory tract	11 (52)
Skin/soft tissue	6 (29)
Intra-abdominal region	3 (14)
Urinary tract	1 (5)
No. (%) of patients who used vasopressors	3 (14)
No. (%) of patients infected with the following pathogen:	
<i>Enterobacteriaceae</i>	11 (52)
<i>Streptococcus</i> spp.	6 (29)
<i>Staphylococcus aureus</i>	3 (14)
<i>Haemophilus influenzae</i>	3 (14)
No. (%) of patients with nondocumented infection	3 (14)
Median (IQR) MIC (μ g/ml)	0.5 (0.5–1)
No. (%) of patients receiving the following type of antimicrobial therapy:	
Association with aminoglycoside	5 (24)
Deescalation	8 (38)
Total duration of antimicrobial therapy	8 (6–10)
Median (IQR) measured CL _{CR} from day 1 to 3 (ml/min)	170 (155–225)
No. (%) of patients with the following CL _{CR} :	
CL _{CR} < 150 ml/min	3 (14)
150 ≤ CL _{CR} < 200 ml/min	9 (43)
CL _{CR} ≥ 200 ml/min	9 (43)
Mean (IQR) serum albumin concn from days 1 to 3 (g/liter)	28 (26–32)
No. (%) of patients with therapeutic failure	3 (14)
Median (IQR) MV duration (days)	7 (2–11)
Median (IQR) ICU length of stay (days)	12 (7–22)

^aIQR, 25 to 75% interquartile range; BMI, body mass index; SAPS 2, simplified acute physiology score; MV, mechanical ventilation.

(VPC) plot for the final population PK model is provided in Fig. 4. The majority of the observed concentrations were contained within the prediction interval.

Using the simulated concentration-time profiles at steady state, the probability of target attainment (PTA) (100% $fT_{>MIC}$) was calculated for three categories of CL_{CR} and four dosage regimens (2 and 3 g once a day, 1 and 2 g twice a day). The proportion of patients who failed to achieve a 100% $fT_{>MIC}$ was significantly higher in the group with a CL_{CR} of ≥200 ml/min for each dosing regimen than in the two other groups ($P < 0.01$). For the current dosing regimen (2 g once a day) and for a MIC of 2 mg/liter, the PTA was 76% for a CL_{CR} of <150 ml/min, 55% for 150 ≤ CL_{CR} < 200 ml/min, and only 45% for a CL_{CR} of >200 ml/min. A dose of 2 g twice a day allowed a PTA of 99% to be obtained for a MIC of 2 mg/liter, whatever the clearance group. The PTA (100% $fT_{>MIC}$) calculated for different dosing regimens are shown in Fig. 5.

DISCUSSION

When targeting a theoretical MIC at the upper limit of the susceptibility range, our results demonstrated that desirable PK/PD targets (100% $fT_{>2 \text{ mg/liter}}$) may not be

FIG 1 Trough unbound concentrations grouped by clearance quartiles for ceftriaxone at 2 g/day. The red line represents the non-species-related PK/PD breakpoint for ceftriaxone per the European Committee on Antimicrobial Susceptibility Testing (2 mg/liter).

achieved in patients with of CL_{CR} of ≥ 150 ml/min treated with the standard dosing regimen of ceftriaxone (2 g/day). Higher-than-licensed doses (2 g twice a day) should be necessary in patients with CL_{CR} of ≥ 150 ml/min empirically treated by ceftriaxone.

To our knowledge, very few PK/PD studies have used population PK modeling to optimize the ceftriaxone dosing regimen in critically ill patients with or without ARC. In the present study, the pharmacokinetics of unbound ceftriaxone were best described

FIG 2 Scatterplots of individual parameter estimates versus covariate values using the structural population pharmacokinetic model. CL_u , unbound clearance; $\beta_{CL_{CR}}$, impact of creatinine clearance on unbound fraction; V_{cu} , central volume of distribution of unbound fraction; V_{pu} , peripheral volume of distribution of unbound fraction; Q_u , intercompartmental clearance; CL_{CR} , creatinine clearance; M, male; F, female.

FIG 3 Goodness-of-fit plots of the final pharmacokinetic model. (A) Observed versus population predicted ceftriaxone unbound concentration; (B) observed versus individual predicted ceftriaxone unbound concentration. The solid line in each panel shows y equal to x . The unbound concentrations according to CL_{CR} values are represented by colored circles (green, $CL_{CR} < 150$ ml/min; red, $150 \leq CL_{CR} \leq 200$ ml/min; blue, $CL_{CR} > 200$ ml/min).

by a two-compartment model. First, the volume of distribution was highly increased compared with that in healthy subjects (13). Second, our study confirmed a strong association between ceftriaxone clearance and CL_{CR} (10). Those results are in accordance with the results of previously published studies which reported higher volumes

TABLE 2 Population PK parameters of ceftriaxone in 21 patients^a

Parameter	Value	SE	RSE	P value
Fixed effects				
CL _u (liters/h)	10.61	2.10	0.20	0.001
βCL _{CR}	0.44	0.13	0.31	
VC _u (liters)	57.40	15.00	0.26	
Vp _u (liters)	30.10	12.45	0.41	
Q _u (liters/h)	7.94	3.8	0.48	
Between-subject variability				
CL _u (liter/h)	0.152	0.0509	0.39	
VC _u (liter)	0.267	0.23	0.86	
Residual variability (<i>a</i>)				
	0.11	0.018	0.11	

^aPK, pharmacokinetic; RSE, relative standard error; CL_u , unbound clearance; βCL_{CR} , impact of creatinine clearance on unbound clearance; V_{C_u} , unbound central volume of distribution; V_{p_u} , unbound peripheral volume of distribution; Q_u , unbound intercompartmental clearance.

FIG 4 Visual predictive check (VPC) for the unbound ceftriaxone concentration versus time based on 1,000 Monte Carlo simulations. The solid lines represent the 10th, 50th, and 90th percentiles of the observed data. The shaded regions represent the 90% confidence interval around the 10th, 50th, and 90th percentiles of the simulated data. The observed unbound concentrations according to CL_{CR} values are represented by colored circles (green, $CL_{CR} < 150$ ml/min; red, $150 \leq CL_{CR} \leq 200$ ml/min; blue, $CL_{CR} > 200$ ml/min).

of distribution and increased drug clearance in critically ill patients with normal renal function treated with ceftriaxone (10–12). In nine critically ill patients with high levels of creatinine clearance, Joynt et al. previously documented a significant increase in ceftriaxone clearance, potentially leading to suboptimal plasma ceftriaxone concentrations when administered at 2 g once per day (12). The urinary loss of both free and albumin-bound antimicrobials has been documented and is probably induced by the loss of the permselectivity properties of the glomerular filtration barrier (14).

Our results thus corroborate those of previous studies suggesting a strong association between ARC and subtherapeutic β -lactam plasma concentrations and higher rates of therapeutic failure using conventional dosing regimens (5–8). The overall rate of empirical underexposure in our study (62%) was similar to that reported in ARC patients receiving other β -lactam class antibiotics administered by standard intermittent dosing (15, 16). In a pilot study, Roberts et al. suggested that ceftriaxone administered by continuous infusion (a 500-mg loading dose and then 2 g as a 24-h infusion) presented more clinical advantages (17). That study was, however, impaired by the lack of drug monitoring. Until these results are confirmed, the continuous administration of ceftriaxone should be discouraged, given the poor stability of the molecule after reconstitution (18). Maximizing the quality of antibiotic prescriptions must remain of major importance in terms of adequate preparation and administration modalities.

On the other hand, the MIC of the targeted microorganism is usually not available to the clinician prescribing empirical antibiotic therapy. The empirical PK/PD target was thus defined in terms of the worst-case scenario, taking into account that all microorganisms were presumed to be susceptible to the drug (2). In this context, the rate of underdosing was lower (24%) when a 100% $fT_{>MIC}$ was considered in patients treated by ceftriaxone for a microbiologically documented infection. However, several concerns

FIG 5 Probability of target attainment ($100\% fT_{>MIC}$) for unbound ceftriaxone in patients with a clearance creatinine of <150 ml/min (A), between 150 and 200 ml/min (B), and >200 ml/min (C).

have been raised over the optimal PK/PD target that should be aimed at in critically ill patients. In this context, a PK/PD target greater than four to six times the MIC throughout the dosing period has been suggested to maximize the likelihood of bacterial killing and prevent antibiotic selection pressure on resistant subpopulations (19–22). Moreover, the reduced antibiotic penetration in critically ill patients means that higher blood concentrations should be required to increase concentrations in tissues (23, 24).

A prompt recognition of ARC is thus necessary when antimicrobial adjustments should be considered. On the other hand, commonly used formulas frequently misclassify ARC and may underestimate the risk of β -lactam underdosing (25, 26). As previously reported, the measured CL_{CR} must remain the reference and should be monitored daily in at-risk patients (26). More practical, pragmatic scores may help the clinician to screen for ARC at the bedside, where antimicrobial adjustments should be considered for at-risk populations (27). However, special attention should be granted to detect dose-dependent neurotoxicity, especially when using higher-than-licensed doses of β -lactams (28, 29). Inpatient variability over time must require subsequent dose adjustment guided by CL_{CR} values, pathogen susceptibility, and therapeutic drug monitoring (TDM) (23).

Several limitations should be reported. First, the prevalence of ARC was higher than previously reported in the available literature on septic patients. Indeed, our single-center study included a high-risk population without renal impairment from a group of surgical and trauma intensive care unit (ICU) patients; thus, it is not generalizable to every intensive care setting. Moreover, we acknowledge a limited number of patients, although they contributed numerous samples to provide data with which to build the final model. In addition, the interindividual variability (20% for clearance and 26% for the volume of distribution of the central compartment) limited the predictive performance of the model, although it was comparable to that of previous studies using population PK modeling and Bayesian adaptive feedback control to optimize drug dosing in critically ill patients (30, 31). Variations of PK parameters over time and extrarenal clearance may also have influenced the ceftriaxone concentrations over time. Finally, our primary objective was to determine the likelihood of PK/PD target attainment using theoretical thresholds rather than clinical MIC data. This outcome thus improves the generalizability of the findings for empirical dosing but precludes any

clinical conclusion. Whether those patients would benefit from regimens with increased dosing should be evaluated by the use of clinical outcome studies.

Conclusion. When targeting a 100% $fT_{>MIC}$ for the less susceptible pathogens, adequate target attainment may not be achieved in patients with a CL_{CR} of ≥ 150 ml/min with ceftriaxone administered at 2 g once per day. In this context, a regimen with increased dosing (2 g twice a day) allowed a PTA of 99% to be obtained for a MIC of 2 mg/liter. These data emphasize the need for therapeutic drug monitoring in patients with ARC, especially when targeting less susceptible pathogens or surgical infections with limited penetration of antimicrobial agents.

MATERIALS AND METHODS

Study design and population. This was a prospective, single-center, observational study performed over a 9-month period (December 2016 to August 2017) in a surgical and trauma intensive care unit (ICU) of a university hospital (CHU Pellegrin, Bordeaux, France). The antimicrobial agent assays were performed by the university-affiliated pharmacokinetic laboratory. Ethical approval was obtained from the Institutional Review Board (Comité de Protection des Personnes Sud-Ouest et Outre-Mer III, Bordeaux, France, protocol no. DC 2016/147), which waived the need for written consent. Patients or their next of kin were orally informed of the goal and design of the study.

Patients were eligible for inclusion if they met all the following criteria: (i) the patient was ≥ 18 years of age, (ii) the patient had a first episode of sepsis (defined as presumed or confirmed infection with new organ dysfunction in the previous 48 h), (iii) the patient had been treated with ceftriaxone for less than 24 h at the time of the assessment, and (iv) the patient had an expected ICU stay of greater than 72 h. Secondary exclusion criteria were renal impairment ($CL_{CR} < 60$ ml/min) and/or receipt of renal replacement therapy.

Study protocol. Ceftriaxone was given at 2 g once per day over 30 min (8). Patients were included on their first day of antibiotic therapy (day 1). Therapeutic drug monitoring (TDM) was performed and the serum albumin concentration and creatinine clearance (CL_{CR}) were recorded on days 1 to 3.

During the first 3 days of antimicrobial therapy, every patient underwent 24-h urinary sample collection to calculate the creatinine clearance (CL_{CR}) according to the formula 24-h urinary volume (in liters) $\times$ 24-h urinary creatinine concentration (in nanomoles per liter)/plasma creatinine concentration (in micromoles per liter), which was converted to milliliters per minute. Three groups were defined according to the CL_{CR} values: patients with no ARC ($CL_{CR} < 150$ ml/min), patients with moderate ARC ($150 \leq CL_{CR} < 200$ ml/min), and patients with severe ARC ($CL_{CR} \geq 200$ ml/min) (32).

The rate of therapeutic failure, the duration of mechanical ventilation, the total length of stay, and death in intensive care were recorded for each patient. Therapeutic failure was defined by an impaired clinical response with a need for escalating antibiotics during treatment and/or within 15 days after the end of treatment (EOT). Superinfections due to new causative pathogens with natural resistance to the initial antimicrobial therapy were not considered therapeutic failures (6).

Sample preparation, storage, and quantification. During the first 3 days of antibiotic therapy, blood samples (5 ml placed into lithium heparinized tubes) were collected for each dosing interval to determine maximal and trough concentrations (1 h and 23 h from the time of initiation of the infusion, respectively).

Within 30 min of sampling, all blood samples were centrifuged (3,000 rpm for 15 min at 4°C) and refrigerated, and plasma samples were frozen at -80°C until analysis. As previously published, the unbound fraction was isolated using a 10,000-molecular-weight-cutoff centrifugal filter device (Amicon Ultra; Millipore, Molsheim, France), purified, and extracted using a solid-phase extraction device (Strata-X 33- μm -particle-size polymeric reversed phase; Phenomenex, Le Pecq, France). The mobile phase consisted of a linear gradient of *ortho*-phosphoric acid solution adjusted to pH 2 and acetonitrile from 7% to 50% at a flow rate of 1 ml/min. A UV high-performance liquid chromatography (HPLC-UV) assay was used to isolate unbound plasma ceftriaxone concentrations using a C_{18} column (125 by 4.0 mm; particle size, 3 μm ; ProntoSIL C_{18} ; Bischoff Chromatography, Leonberg, Germany) (33).

As recommended by the FDA bioanalytical method validation guidelines (https://www.ema.europa.eu/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf), accuracy and reproducibility were evaluated for each monitored antibiotic, with the coefficients of variation being below 15% and the accuracy being between 85 and 115%. The linearity of the method was also checked, with the coefficient of regression being >0.99 over the calibration range. The lower limit of quantification for unbound ceftriaxone concentrations was 0.25 mg/liter.

Therapeutic drug monitoring targets. The optimal PK/PD target of β -lactams in critically ill patients is a free drug concentration above the MIC of the targeted organism(s) throughout the dosing interval ($100\% fT_{>MIC}$) (3). The main outcome investigated in this study was thus the rate of ceftriaxone empirical underdosing, defined by a trough unbound concentration of ≤ 2 mg/liter. This represents the non-species-related PK/PD breakpoint for ceftriaxone per the European Committee on Antimicrobial Susceptibility Testing (<http://www.eucast.org>). We aimed to assess the adequacy of dosing in terms of the worst-case scenario, as the type of pathogen and MIC data are often not initially available to the clinician prescribing an empirical (i.e., probabilistic) antimicrobial regimen (30).

For patients with microbiologically documented infection, the MIC of the known pathogen was provided by the local microbiology laboratory. Where the MIC was not available, the MIC of the pathogen was defined by the European Committee on Antimicrobial Susceptibility Testing (<http://www.eucast.org>).

The secondary outcomes investigated in this study were thus the rate of ceftriaxone documented underdosing (i.e., observed), defined by (i) a trough unbound concentration under the MIC of the known pathogen ($fT_{>MIC} < 100\%$) and (ii) a trough unbound concentration under 4 times the MIC ($fT_{>4 \times MIC} < 100\%$).

Population pharmacokinetic modeling. Concentration-time data were analyzed using a nonlinear mixed-effects modeling software program, Monolix (<http://wfn.software.monolix.org>) (31). Unbound plasma ceftriaxone concentrations were fitted to one- and two-compartment models using the stochastic approximation expectation maximization (SAEM) algorithm. Statistical comparison of the nested models was undertaken using log-likelihood ratios. Between-subject variability was evaluated using an exponential variability model. Additive, proportional, and combined error models were tested.

The effect of five covariates (age, sex, total body weight, CL_{CR} and serum albumin concentration) on ceftriaxone pharmacokinetics was tested with a two-consecutive-step approach. Covariates were selected with a forward method using the Bayesian information criterion (BIC) (34). First, a model with several covariates with the smallest BIC was selected. The addition of covariates was stopped when no further decrease of the BIC was obtained. The covariates model was finalized with a backward selection, removing the covariates one by one, using the likelihood ratio test (LRT). A covariate was retained in the model if the LRT was significant ($P < 0.05$) when it was removed from the full model.

The relationship between a covariate and a parameter was defined by the following equation: $CL_i = CL_{pop} \cdot (cov_i / cov_{mean})^\beta \cdot \exp \eta_i$, where CL_i is the individual drug clearance, CL_{pop} is the mean population value for drug clearance, cov_i is the continuous covariate (individual [cov_i] or population centered [cov_{mean}]), β is the fixed-effects parameter in the structural model, and η_i is the interindividual error. The coefficient β was estimated using the stochastic approximation expectation maximization (SAEM) algorithm, and the P value of the Wald test was used to check if this coefficient was different from 0.

Model qualification. Visual inspection of diagnostic scatter plots and the SAEM algorithm objective function value (OFV) were used to assess the goodness of fit. The model was first evaluated using observations versus individual and population prediction plots. It was then assessed using simulation-based plots (visual predictive check [VPC] plot, population weighted residuals [PWRES], individual weighted residuals [IWRES], and normalized prediction distribution error [NPDE] versus time and versus prediction). The VPC plot showed the 5th, 50th, and 95th percentiles of the observed data over time and their corresponding 90% prediction intervals calculated from 1,000 Monte Carlo samples. The NPDE was built from the percentile derived from the VPC prediction. Finally, the most appropriate model was selected on the basis of the smaller value of AIC and BIC, adequate goodness-of-fit plots, and the low relative standard error (RSE) for the estimated PK parameters.

PTA. Probabilistic estimates of different PK/PD target attainments were assessed using a Monte Carlo simulation for various MICs (0.1 to 8.0 mg/liter) and various CL_{CR} values ($CL_{CR} < 150$ ml/min, $150 \leq CL_{CR} < 200$ ml/min, and $CL_{CR} > 200$ ml/min). The probability of target attainment (PTA) was defined by the probability that unbound ceftriaxone plasma concentrations would be maintained above the MIC (in milligrams per liter) during the entire dosing interval ($100\% fT_{>MIC}$). PTA was plotted for usual treatments (2 g every 24 h) and for alternative treatments, defined by (i) increasing the daily prescribed doses (3 g a day), (ii) increasing the frequency of infusion (1 g twice a day), or (iii) increasing both (2 g twice a day).

Statistical analysis. The results are expressed as the mean $\pm$ standard deviation or median (25% to 75% interquartile range) for continuous variables and as the numbers (percentages) of patients for categorical variables. The data distribution was analyzed by the Kolmogorov-Smirnov test. Comparisons between continuous variables were performed using Student's t test or the Mann-Whitney test, and categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. These tests were used to compare clinical outcomes.

We hypothesized that patients with ARC would be four times more likely to experience ceftriaxone empirical underdosing (8). We calculated that 62 samples (21 patients) would be necessary to test our hypothesis, assuming a prevalence of ARC of $\geq 50\%$, a 5% type I error rate, and an 80% power.

A P value of < 0.05 was considered statistically significant. Statistical analyses were performed using XLSTAT 2017 for Windows software (Addinsoft Paris, France).

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