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Population pharmacokinetic/pharmacodynamic study suggests continuous infusion of ceftaroline daily dose in ventilated critical care patients with early-onset pneumonia and augmented renal clearance

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Objectives: Ceftaroline could be suitable to treat early-onset ventilator-associated pneumonia (VAP) because of its antibacterial spectrum. However, augmented renal clearance (ARC) is frequent in ICU patients and may affect ceftaroline pharmacokinetics and efficacy. The objective of the study was to explore the impact of ARC on ceftaroline pharmacokinetics and evaluate whether the currently recommended dosing regimen (600 mg every 12 h) is appropriate to treat VAP in ICU patients.

Methods: A population pharmacokinetic model was developed using pharmacokinetic data from 18 patients with measured creatinine clearance (CL_{CR}) ranging between 83 and 309 mL/min. Monte Carlo simulations were conducted to determine the PTA and the cumulative fraction of response (CFR) against *Streptococcus pneumoniae* and MRSA for five dosing regimens. Study registered at ClinicalTrials.gov (NCT03025841).

Results: Ceftaroline clearance increased non-linearly with CL_{CR} , with lower concentrations and lower probability of reaching pharmacokinetic/pharmacodynamic targets when CL_{CR} increases. For the currently recommended dosing regimen, the probability of having unbound ceftaroline concentrations above the MIC over the entire dose range is greater than 90% for MICs below 0.125 mg/L. Considering the distribution of MICs, this regimen would not be effective against MRSA infections (CFR between 21% and 67% depending on CL_{CR}), but would be effective against *S. pneumoniae* infections (CFR >86%).

Conclusions: The recommended dosing regimen of ceftaroline seems sufficient for covering *S. pneumoniae* in ICU patients with ARC, but not for MRSA. Among the dosing regimens tested it appears that a constant infusion (50 mg/h) after a loading dose of 600 mg could be more appropriate for MRSA infections.

Introduction

Ceftaroline is a cephalosporin, administered as a prodrug (ceftaroline fosamil), approved by the US FDA in 2010 and by the EMA in 2012 for the treatment of complicated skin and skin structure infections (cSSSIs)¹ and community-acquired bacterial pneumonia (CABP).² Ceftaroline exhibits broad *in vitro* activity against Gram-positive organisms, including MRSA and penicillin-

resistant *Streptococcus*, as well as common Gram-negative pathogens associated with either cSSSI or CABP.^{3,4}

The pharmacokinetics (PK) of ceftaroline was assessed after single- and multiple-dose studies in healthy volunteers,^{5–7} in different populations of patients^{8,9} with various degrees of renal impairment and also in critically ill patients.¹⁰ After IV administration in healthy adults, ceftaroline fosamil is rapidly converted by plasma phosphatase enzymes into the active ceftaroline that is

essentially (64%) excreted unchanged in urine and to a small extent (6%) as an inactive metabolite, ceftaroline M-1.¹¹ Ceftaroline fosamil has most often been administered at a standard dose of 600 mg every 12 h as a 1 h IV infusion in patients with normal renal function until a higher daily dose (600 mg every 8 h as a 2 h IV infusion) was recently approved for the treatment of cSSSI caused by resistant *Staphylococcus aureus* with a ceftaroline MIC of 2 or 4 mg/L.¹²

Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection in critically ill patients¹³ and many pathophysiological changes occurring in critically ill patients may affect antibiotic PK and thus its efficacy.¹⁴ Augmented renal clearance (ARC), defined as creatinine clearance (CL_{CR}) >130 mL/min/1.73 m², is frequent in ICU patients and contributes to PK alterations in this population.^{15,16} In a multicentre observational study in critically ill patients with normal plasma renal indices at admission, about 65% of patients had ARC on at least one occasion during the first seven study days, leading to sub-therapeutic concentrations for a variety of renally excreted drugs, such as β -lactams, potentially leading to treatment failure.¹⁷

Knowledge of the PK and pharmacodynamic (PD) properties of the antibiotics used for the management of critically ill patients is essential for selecting the antibiotic dosing regimens to optimize patient outcome and minimize antibiotic resistance. The primary objective of the present study was to investigate the impact of ARC on ceftaroline PK in ICU patients. The secondary objective was to evaluate whether the current recommended dosing regimen of ceftaroline (600 mg every 12 h) is appropriate to maintain unbound concentrations above the MIC for pathogens involved in VAP.

Materials and methods

Study design

The study was performed in accordance with the Declaration of Helsinki, approved by the local ethics committee (Comité de Protection des Personnes Ouest III, protocol 16.01.02) and registered at ClinicalTrials.gov (NCT03025841). Written informed consent was obtained from patients or their legal representatives before inclusion. This prospective and open-label PK study was conducted in five university hospital ICUs in France (Poitiers, Tours, Angers, Nantes and Rennes), between February 2017 and May 2018. All patients received 600 mg of ceftaroline fosamil (Zinforo®, PFIZER laboratories, Paris, France) by IV infusion over 1 h, twice a day and for a minimum of 3 days.

Study population

Patients (aged ≥ 18 years) hospitalized in the participating ICUs were eligible if mechanically ventilated, presenting early-onset (i.e. during the 7 days following hospital admission) pneumonia caused by Gram-positive and/or Gram-negative bacteria and a CL_{CR} superior to 80 mL/min/1.73 m² estimated by the Modification of Diet in Renal Disease (MDRD) formula. Estimated CL_{CR} was secondarily confirmed by the measured clearance using creatinine plasma concentrations and amounts excreted in urine over a 24 h period. The measured urinary CL_{CR} values were used for PK analysis. The exclusion criteria were a renal impairment (measured urinary CL_{CR} <80 mL/min/1.73 m²), one or more risk factors of MDR bacteria,¹⁸ septic shock, BMI >40 kg/m², diuretic treatment, ceftaroline contraindications and suspicion or confirmation of pneumonia due to ceftaroline-resistant bacteria. Age, sex, weight, height,

SAPS 2 and SOFA score were collected for each patient at inclusion. Before initiation of ceftaroline treatment, bacteriological samples were obtained by protected distal or tracheal aspiration and antibiotic susceptibility tests were performed for all patients. The MIC of ceftaroline for the different bacterial isolates was determined using the Etest method. Total serum protein, serum albumin, serum and urine creatinine were measured on two occasions [PK1 corresponding to first administration and PK2 corresponding to later (between fifth and ninth) administration].

Blood sampling for PK analysis

Two series of seven blood samples (5 mL per sample, drawn at a distance from the injection site) were taken on PK1 and PK2 for each patient. Samples were collected at the following times: 0 (before administration), 1 (end of infusion), 2, 4, 6, 9 and 12 h. Blood samples were immediately centrifuged and plasma was separated and stored at -80°C until analysis.

Ceftaroline assay

Total plasma concentrations of ceftaroline fosamil, ceftaroline and ceftaroline M-1 were measured by Covance laboratory (Covance Bioanalytical Services, Indianapolis, IN, USA) using an appropriate validated LC-MS/MS method with a limit of quantification (LOQ) of 0.050 mg/L for all analytes.

Population PK analysis

Total plasma concentrations of ceftaroline fosamil, ceftaroline and ceftaroline M-1 were analysed simultaneously using the non-linear mixed-effect modelling approach in NONMEM 7.4 (ICON Development Solutions, Ellicott City, MD, USA). A detailed description of the development, evaluation and the covariate selection is available as [Supplementary data](#) at JAC Online.

PTA and cumulative fraction of response (CFR)

The optimal PK/PD target of β -lactams in ICU patients is an unbound concentration above the MIC for the targeted organism over the entire dosing interval (100% $fT_{>MIC}$).¹⁹ Monte Carlo simulations were performed to evaluate the PTA after repeated administrations of 600 mg of ceftaroline fosamil every 12 h, 400, 600 or 800 mg every 8 h or after a 600 mg loading dose followed by continuous infusion at a rate of 50 mg/h (corresponding to 1200 mg over 24 h). For simulations, CL_{CR} values ranging from 80 to 300 mL/min (10 mL/min increments) were used. Ceftaroline concentration-time profiles of 1000 patients were simulated for each dosing regimen and each CL_{CR} value with the final model. The PTA was calculated as the percentage of simulated patients who met the PK/PD target of 100% $fT_{>MIC}$ at steady state over an MIC range of serial 2-fold dilutions from 0.004 to 32 mg/L. The simulated total drug concentrations were transformed into free drug concentrations assuming an unbound fraction in plasma of 80%.¹²

To evaluate whether the proposed ceftaroline fosamil dosing regimens achieved adequate exposures for maintaining efficacy against MRSA and *Streptococcus pneumoniae* isolates encountered in clinical practice, PTAs were compared with corresponding ceftaroline MIC frequency distributions reported by EUCAST.²⁰ In addition, CFR²¹ was calculated for each dosing regimen as follows:

$$CFR = \sum_{i=1}^n PTA_i \times F_i \quad (1)$$

where i indicates the MIC category ranked from lowest to highest MIC value for a population of microorganisms, PTA _{i} is the PTA of each MIC category and F_i is the fraction of the population of microorganisms in each MIC category.

Results

Patients and data

A total of 18 patients was enrolled in this study, 5 women and 13 men. Their demographic, clinical and biological data are summarized in Table 1 and individual data are presented in Table S1 (available as Supplementary data at JAC Online). Measured urinary CL_{CR} ranged from 83 to 267 mL/min on PK1 and from 100 to 309 mL/min on PK2 (Table S1) and varied both ways by ±20% on average (Figure S1). The most frequent pathogen identified at the infection site was *S. aureus* (8/18). All isolates, except from two patients for which MICs were not available, were susceptible to ceftaroline, according to EUCAST breakpoints,²² with MICs ranging from 0.003 to 0.75 mg/L (Table S1).

Plasma concentrations and population PK model parameters

Ceftaroline fosamil concentrations at the end of infusion were close to 1 mg/L on PK1 and PK2 and were below the LOQ

Table 1. Main demographic, clinical and biological characteristics of patients (mean, SD, min and max values)

	Age (years)	Weight (kg)	Height (m)	BMI (kg/m ²)	SAPS 2	CL _{CR} (mL/min) ^a	
						PK1	PK 2
Mean	46	73	1.71	25.2	45	181.5	180.6
SD	17	12	0.10	4.7	12	52	59
Min	21	53	1.5	19	20	83	100
Max	77	95.6	1.85	38.2	60	267	309

^aCL_{CR} calculated from creatinine concentration in plasma and urine, and urine flow on the first and second PK sampling day (PK1 and PK2, respectively).

(0.050 mg/L) in most patients (16/18 on PK1 and 12/15 on PK2) 1 h later. Measured concentrations of ceftaroline and ceftaroline M-1 are presented in Figure 1.

A model with one compartment for ceftaroline fosamil and two compartments for ceftaroline and for ceftaroline M-1 with linear elimination fitted the data best. The structural model is illustrated in Figure S2. Parameters of the final PK model were well estimated with low relative standard errors (Table S2, Table S3 and Table S4). Individual model predictions of total concentrations versus time properly described the data (Figure S3) with low residual errors. Additionally, the visual predictive checks (VPCs) confirmed that the selected model adequately predicts simultaneously the mean tendency and dispersion of the plasma data for ceftaroline and ceftaroline M-1 (Figure S4).

Clearance of ceftaroline increased less than proportionally with CL_{CR} (Figure 2), according to Equation 2:

$$CL_{\text{ceftaroline}} = CL_{\text{ceftaroline, pop}} \times \left(\frac{CL_{CR}}{180}\right)^{CL_{CR, cov1}} \quad (2)$$

where CL_{ceftaroline, pop} (10.6 L/h) is the ceftaroline clearance for a patient with a CL_{CR} of 180 mL/min, corresponding to the median covariate value, and CL_{CR, cov1} (0.328) is the coefficient describing the impact of CL_{CR} on CL_{ceftaroline}.

The Monte Carlo Mapped Power (MCMP) analysis indicated that a power of 93% (α=0.05 for 1 df) was achieved with 18 patients for the identification of a statistically significant relationship between CL_{ceftaroline} and CL_{CR}.

PTA and CFR

Predicted PTAs of ceftaroline in patients with various CL_{CR} values receiving various dosing regimens, overlaid with ceftaroline MIC distributions, are shown in Figure 3 and Figure S5 for MRSA and Figure S6 and Figure S7 for *S. pneumoniae*. The maximum CL_{CR} values allowing target achievement (fT_{>MIC}=100%) in at least 90% of patients (PTA ≥90%) for various MIC values are shown in

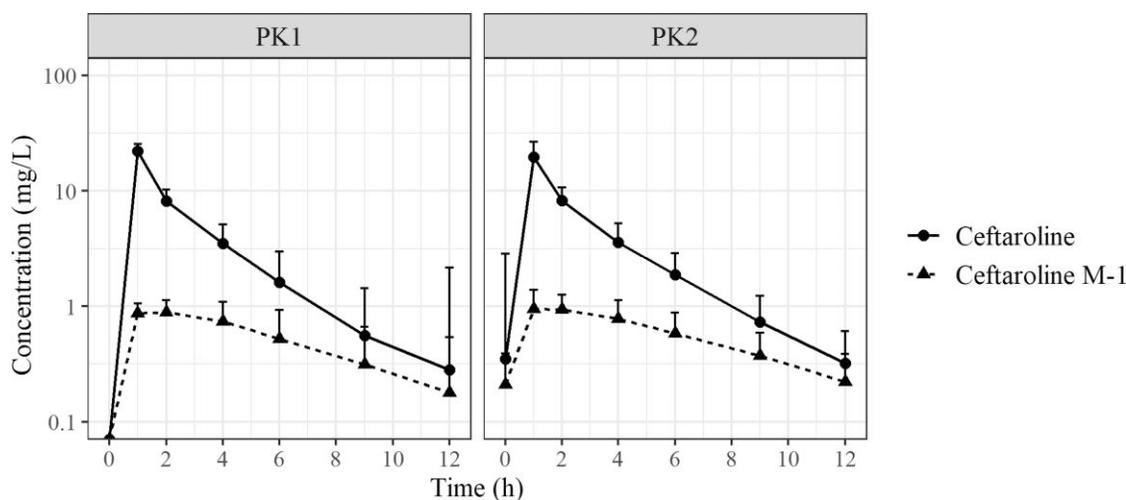


Figure 1. Mean (+SD) plasma concentration of ceftaroline and ceftaroline M-1 following the first administration of 600 mg of ceftaroline fosamil as a 1 h infusion (PK1, left panel) and at least the fifth administration (between fifth and ninth) (PK2, right panel).

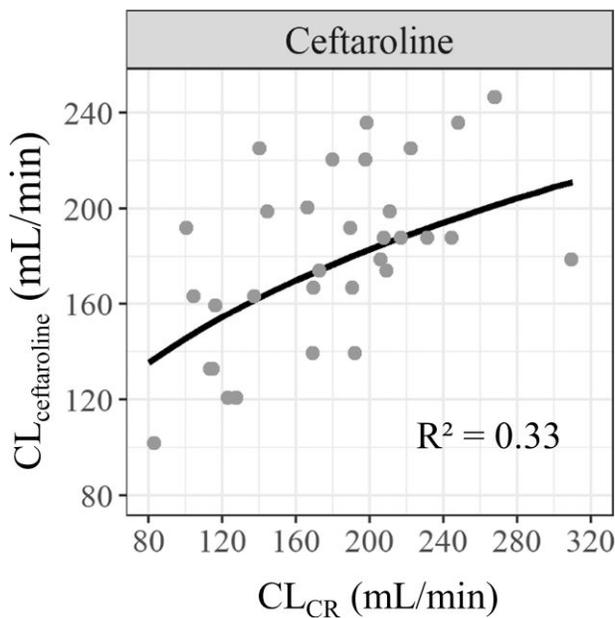


Figure 2. Plot of the predicted clearance of ceftaroline ($CL_{\text{ceftaroline}}$) versus CL_{CR} measured in the patients enrolled in this study. Circles represent the individual predictions for the different CL_{CR} s calculated on the 2 days of PK sampling and lines represent the typical predictions calculated according to the power function used to describe the significant effect of CL_{CR} on the clearance of ceftaroline: $CL_{\text{ceftaroline}} = CL_{\text{ceftaroline, pop}} \times (CL_{\text{CR}}/180)^{CL_{\text{CR, cov1}}}$

Table S5. Table 2 presents ceftaroline CFR against MRSA and *S. pneumoniae*, after each of these dosing regimens. The usually recommended daily dose (1200 mg/24 h) given twice daily (600 mg every 12 h) would allow to reach PTA $\geq 90\%$ for patients with elevated CL_{CR} up to 300 mL/min, only if MIC ≤ 0.032 mg/L (Figure 3 and Table S5). The same daily dose given thrice daily (400 mg every 8 h) would allow to reach PTA $\geq 90\%$ for patients with CL_{CR} up to 300 mL/min, for MIC up to 0.125 mg/L (Figure 3 and Table S5). Increasing the daily dose to 1800 or even 2400 mg while maintaining the same dose interval (600 or 800 mg every 8 h) would allow to obtain PTA $\geq 90\%$ for patients with CL_{CR} up to 300 mL/min for MIC up to 0.25 mg/L (Figure S5 and Table S5). A continuous infusion of 1200 mg over 24 h would allow to achieve unbound steady-state concentrations at least 1.5 times higher than the 90th percentile of the WT distribution (MIC₉₀) for *S. aureus* (1 mg/L) whatever the renal function (Figure 4). Therefore, only continuous infusion would allow PTA $\geq 99\%$ to be achieved against pathogens with MIC up to 2 mg/L in patients with CL_{CR} up to 300 mL/min and thus would allow to cover the entire ceftaroline MIC distribution for MRSA (Figure 3).

Discussion

This study has shown that $CL_{\text{ceftaroline}}$ is increased in patients with ARC, consistent with its decrease in patients with impaired renal function.^{9,23} Although, in clinical practice, CL_{CR} would more likely be estimated by MDRD, it seemed more appropriate here to obtain this parameter value from urine creatinine determination.

Notably, $CL_{\text{ceftaroline}}$ increases less than proportionally with CL_{CR} in ARC. For example, the typical value of $CL_{\text{ceftaroline}}$ would increase by only 25% (183 versus 146 mL/min) when CL_{CR} is doubled from 100 to 200 mL/min (Figure 2). A less than proportional increase in $CL_{\text{ceftaroline}}$ with CL_{CR} has already been observed in a previous PK study gathering data from 21 clinical studies including healthy volunteers and patients with CL_{CR} ranging from 6.7 to 467.4 mL/min, but was not discussed.²³ Yet CL_{CR} only explains part of the inter-individual variability in $CL_{\text{ceftaroline}}$ as attested by the low R^2 value (0.33). The fact that ceftaroline is partly metabolized may contribute to the less than proportional increase in total clearance with CL_{CR} . Notably, according to the model, typical $CL_{\text{ceftaroline}}$ is about 50% higher than CL_{CR} in patients with normal renal function (146 versus 100 mL/min), but roughly similar (183 versus 200 mL/min) and then about 30% lower (209 versus 300 mL/min) for higher CL_{CR} values. This would suggest net reabsorption appearing when CL_{CR} increases in ARC patients. Yet this intriguing hypothetical phenomenon should be further investigated after determining ceftaroline renal and not only total clearance, as well as ceftaroline protein binding in patients. Precise determination of glomerular filtration rate (GFR) using exogenous filtration markers, such as iothexol, should also be preferred to its traditional estimation from creatinine urinary excretion to avoid the uncertainty of GFR estimation by CL_{CR} ^{24–26} and then confirm or rule out the reabsorption hypothesis. In terms of PK/PD, *in vivo* studies performed in murine thigh and lung infection models reported a bactericidal effect of ceftaroline for at least 50% $fT_{>MIC}$ for staphylococci.²⁷ However, in ICU patients treated with β -lactam antibiotics, 100% $fT_{>MIC}$ improved clinical outcome compared with 50% $fT_{>MIC}$.^{19,28} Therefore, a target of 100% $fT_{>MIC}$ was chosen in the present study for PK/PD investigations. Treatment of *S. pneumoniae* and MRSA infections requires to be effective against bacteria with MICs up to 0.125 and 1 mg/L (90th percentiles of WT distributions), respectively (Figure S6 and Figure 3). MICs below 0.125 mg/L should be covered with the usual ceftaroline dosing regimen (600 mg every 12 h) in at least 80% of patients with CL_{CR} values below 200 mL/min. However, the probability of attaining the target if the MIC is 1 mg/L becomes less than 20% when CL_{CR} is higher than 80 mL/min. For *S. pneumoniae* infections, the 600 mg every 12 h dosing regimen should cover the distribution of MICs with CFRs greater than 86% for CL_{CR} values up to 300 mL/min (Table 2). However, for the treatment of MRSA infections, this dosing regimen should not cover the distribution of MICs since CFRs are less than 67% when CL_{CR} values are above 80 mL/min (21% if $CL_{\text{CR}} = 300$ mL/min). To increase PTA and thus CFR in patients infected by MRSA, dose fractionation appears to be much more effective than increasing the daily dose, which would increase the risk of toxicity without covering the entire ceftaroline MIC distributions for MRSA. Continuous infusion of 1200 mg of ceftaroline over 24 h seems more appropriate in terms of efficacy by allowing a CFR of 100% to be achieved in patients with CL_{CR} up to 300 mL/min (Table 2). At treatment initiation, the administration of a 600 mg loading dose allows unbound ceftaroline concentrations to exceed 1 mg/L 30 min earlier than without a loading dose (3 min versus 30 min for a patient with a median CL_{CR} of 180 mL/min). Notably, in the case of continuous infusion, the compound within the infusion bag needs to be stable and, although ceftaroline in 0.9% normal saline or glucose 5% was

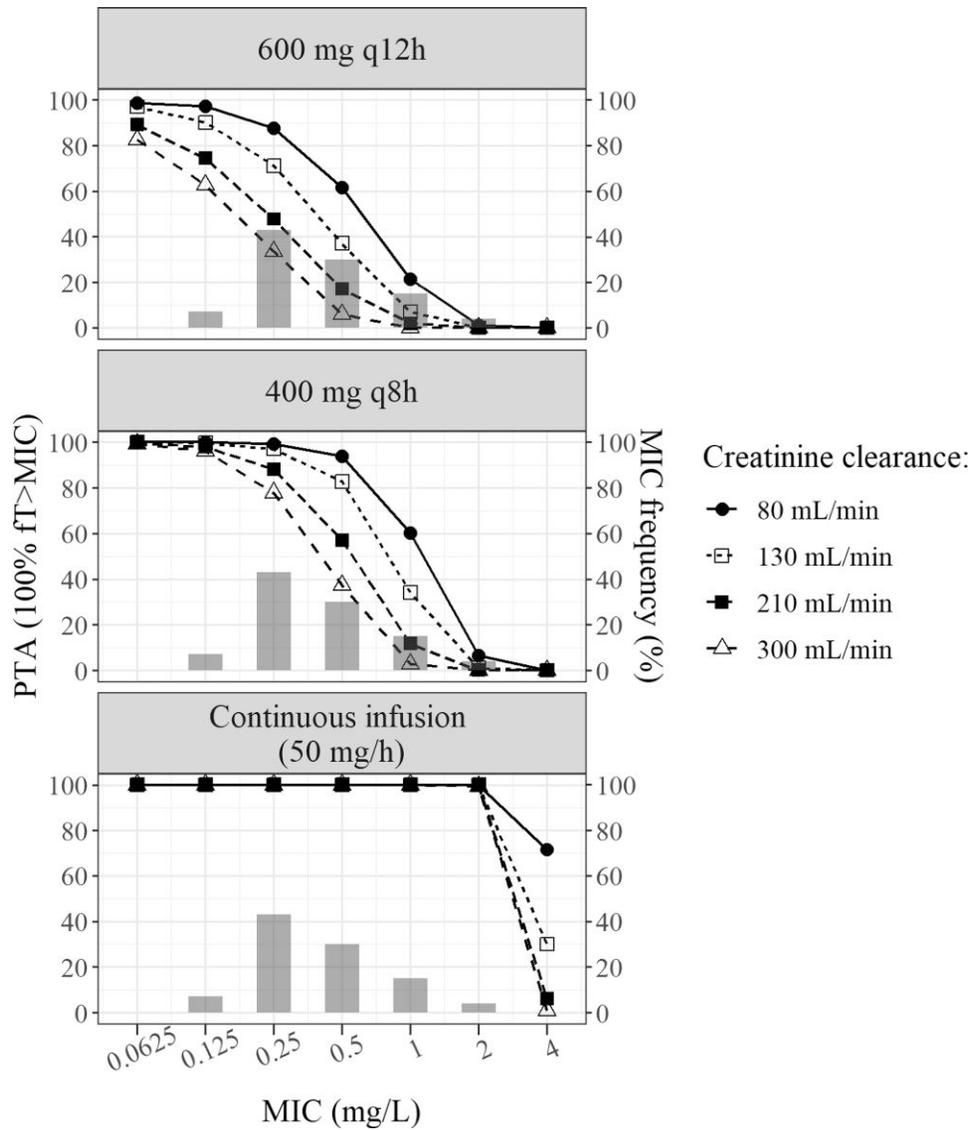


Figure 3. Impact of dose fractionation on PTA ($f_{T > MIC} = 100\%$) in simulated patients with $CL_{CR} = 80, 130, 210$ or 300 mL/min receiving the same daily dose of ceftaroline (1200 mg/24 h), overlaid with ceftaroline MIC distributions for WT MRSA.²⁰

Table 2. CFR (%) of ceftaroline against MRSA and *S. pneumoniae* in simulated patients with different CL_{CR} values following different dosing regimens

Daily dose (mg)	Dosing interval (h)	CL_{CR} (mL/min)							
		MRSA				<i>S. pneumoniae</i>			
		80	130	210	300	80	130	210	300
1200	12	67	50	31	21	98	95	90	86
1200	8	88	79	64	52	100	99	98	97
1800	8	95	88	77	69	100	100	99	98
2400	8	97	93	85	78	100	100	100	99
600+1200	loading dose followed by a continuous infusion over 24 h	100	100	100	100	100	100	100	100

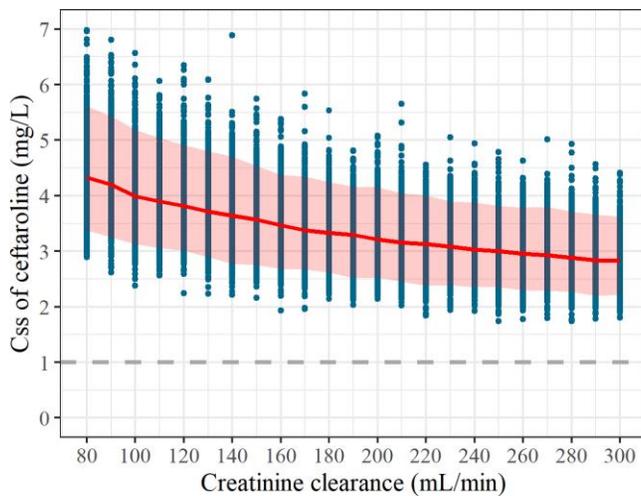


Figure 4. Simulated unbound steady-state concentrations of ceftaroline after a constant infusion of 1200 mg over 24 h for various CL_{CR} values. Circles represent individual simulated concentrations ($n=1000$ for each CL_{CR} value), the red solid line represents the median of the simulated data and the red area represents the 90% prediction interval. The grey dashed line corresponds to the 90th percentile of the WT distribution (MIC_{90}) for *S. aureus*. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

shown to be stable for 24 h at 25°C and for 12 h at 30°C,²⁹ no such data exist for ceftaroline fosamil.

This study has some limitations. Firstly, as previously mentioned, determination of ceftaroline protein binding and a more accurate estimation of GFR than measured urinary CL_{CR} would be necessary to better understand the lower than expected increase in $CL_{ceftaroline}$ and the hypothetical tubular reabsorption issue in patients with ARC. Secondly, efficacy of the dosing regimens tested is based on Monte Carlo simulations and needs to be further evaluated in clinical trials.

Conclusions

This study suggests that the recommended dosing regimen of ceftaroline (600 mg every 12 h) would be appropriate for covering infections due to *S. pneumoniae*, but not MRSA, in ARC patients with CL_{CR} up to 300 mL/min. The most appropriate dosing regimen of ceftaroline for the treatment of MRSA infections is constant infusion of 1200 mg over 24 h (50 mg/h) preceded by a loading dose of 600 mg.

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Transparency declarations

None to declare.

Author contributions

A.C., N.G., W.C., S.M., O.M. and C.D.-F. wrote the article. O.M, C.D.-F., W.C., S.M. and N.G. contributed to conception and design of the study. M.F., S.L., K.A., P.S., M.B. and C.D.-F. performed the research. A.C. and N.G. performed PK/PD modelling. All authors contributed to manuscript revision and read and approved the submitted version.

Supplementary data

Supplementary data, including Tables S1 to S5 and Figures S1 to S7, are available as Supplementary data at *JAC* Online.

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