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Therapeutic drug monitoring of cefepime in a non-critically ill population: retrospective assessment and potential role for model-based dosing

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Objectives: To describe the therapeutic drug monitoring (TDM) of cefepime in non-critically ill adults and compare four different ways of dosing: conventional table-based; empirically adjusted following TDM; individualized based on a population pharmacokinetic (PopPK) model without TDM; and TDM-adjusted with a Bayesian approach integrating TDM and PopPK.

Methods: We conducted a retrospective study in a tertiary centre to examine the current practice of TDM and to evaluate the potential for improvement by PopPK-based software individualization. The prediction of trough concentrations and the total daily doses (TDD) prescribed according to each approach were compared by calculating the mean logarithmic bias and the root mean squared error, complemented by linear regression and variance analysis.

Results: Among 168 trough concentrations in 119 patients (median: 12 mg/L), 38.6% of measurements exceeded 15 mg/L, the reported threshold for neurotoxicity. Nine patients developed neurotoxicity. The prediction performance of PopPK alone for trough concentrations was moderate, but clearly improved after integration of TDM. Accordingly, TDD were significantly lower for *a priori* PopPK-based dosage (mean: 2907 mg/24 h) compared with actual table-based dosage (4625 mg/24 h, $P < 0.001$). They were also lower for *a posteriori* dosage based on PopPK and TDM (3377 mg/24 h) compared with actual dosage after empirical TDM (4233 mg/24 h, $P < 0.001$), as model-based adjustment privileged more frequent administrations.

Conclusions: Our observations support routine TDM of cefepime to prevent overdosing and subsequent toxicity in the non-critically ill. Software-based individualization seems promising to optimize the benefits of TDM, but has little potential to replace it.

Introduction

Cefepime is a fourth-generation extended-spectrum cephalosporin, first approved in 1996 and still a cornerstone in the empirical treatment of neutropenic fever, pneumonia, complicated urinary tract infections and soft tissue infections.[1] It was considered as rather safe until 2006, when a systematic review and meta-analysis warned of increased mortality rates among febrile neutropenic patients receiving this treatment.[2] In 2007, the same research group extended their meta-analysis to all patients treated with cefepime, and still found higher mortality rates compared with patients treated with other broad-spectrum β-lactam antibiotics. The authors warned of unrecognized adverse events such as neurotoxicity and pharmacodynamic issues, possibly with insufficient target attainment for intermittent short infusions.[3] In the subsequent years, the FDA performed its own meta-analyses on both trial-level and patient-level data and could not confirm a statistically significant difference in all-cause 30 day mortality between cefepime and other β-lactams. Dosage recommendations thus remain unchanged to date.[4,5] Meanwhile, our knowledge regarding neurotoxicity has developed further. Pathophysiology studies correlate the pro-

convulsive effect of cephalosporins to concentration-dependent inhibition of GABA-A receptors.[6] Clinically however, neurotoxicity is not limited to convulsions, with the earliest and most prevalent signs being a decreased level of consciousness (80%) followed by delirium (47%), myoclonus (40%) and non-convulsive status epilepticus (31%).[7] Their occurrence is clearly dose-dependent.[8] Lamoth *et al.*[9] demonstrated an association between high cefepime trough concentrations and neurological toxicity in febrile neutropenic patients with only mild renal impairment, with a 50% probability threshold around trough concentrations of 22 mg/L. The authors proposed to avoid intermittent infusion dosages producing trough concentrations above 15 mg/L.[9] Boschung-Pasquier *et al.* similarly found that cefepime plasma trough concentrations were significantly associated with the risk of neurotoxicity [no neurotoxicity 6.3 mg/L (IQR 4.1–8.6) versus neurotoxicity 21.6 mg/L (IQR 17.0–28.6), $P < 0.001$]. This study estimated a probability of neurotoxicity of 25% for trough concentrations ≥12 mg/L, and of 50% for trough concentrations ≥16 mg/L.[10] Other authors found higher threshold values, a study including mostly intensive care patients describes a cefepime trough plasma concentration of ≥36 mg/L to predict cefepime neurotoxicity.[11] Another retrospective cohort study found a threshold of >20 mg/L, noting that almost half of the patients in this cohort were under high-dose cefepime regimens for *Pseudomonas aeruginosa* infections.[12]

On the other hand, the importance of optimizing antibiotic dosing regimens has also been emphasized in light of increasing antimicrobial resistance, together with limited development of novel antibiotics. From a pharmacokinetic and pharmacodynamic (PK/PD) point of view, current perspectives are indeed shifting from a 'one dose fits all' paradigm to a patient-tailored dosing approach in the treatment of infections. Individualized dosing should complement appropriate drug choice (e.g., according to the predicted or observed susceptibility spectrum of infectious agents, together with renal function) to achieve precision antibiotherapy.[13,14]

In brief, PK/PD of antibiotics describe the relationship between efficacy, *in vitro* susceptibility of the microorganism (usually expressed as the MIC) and *in vivo* exposure to the drug (captured by either maximal concentration C_{max}, minimal or trough concentration C_{min}, area under concentration curve AUC, or proportion of time above the MIC). To predict that exposure, which results from both prescribed dosages and patient PK characteristics, population PK (PopPK) models are increasingly advocated.[15]

Therapeutic drug monitoring (TDM) consists of measuring drug concentrations to optimize dosing regimens in individual patients, with the objective to maximize efficacy and minimize toxicity. It has been widely practised for decades for vancomycin and aminoglycosides, due to their narrow therapeutic/toxic margin.[16,17] Nowadays, measurement methods are available for a wide range of antibiotics. Cefepime total concentrations (bound and unbound fractions) can be easily measured using mass spectrometry and its monitoring is now routinely offered in our hospital.[18,19] However, clinicians do not follow stringent rules for TDM interpretation, nor do they routinely rely on a computer tool: they rather tend to adjust dosages empirically with respect to measurement results. This is also anticipated to progress with computer-assisted TDM interpretation connected to electronic medical records.

Advances in PK/PD modelling and TDM software applications are thus expected to both facilitate and standardize such individualization of dosing regimens. These tools may firstly assist prescribers in taking into account individual variables such as age, body weight and renal function, known to affect drug disposition, so as to ensure optimal *a priori* dosage adjustment. Secondly, they may improve the performance of TDM by merging observed concentrations with prior expectations using Bayesian optimization to translate them into proficient dosage adjustment decisions. While TDM software packages using PopPK models are increasingly available nowadays, their clinical validation is still lacking for a number of therapeutic agents.

Since PK/PD challenges are well recognized in critically ill patients, numerous studies on TDM of wide-spectrum antibiotics have been published and are ongoing in this population.[20–25] To date, however, we did not identify studies exploring the potential clinical impact of cefepime dosage individualization in non-critically ill patients.

Considering the aforementioned safety issues regarding cefepime, the dosing recommendations for which have remained unchanged since 1996, and the frequent practice of cefepime TDM in our hospital, we aimed to explore different approaches for cefepime dosing. In particular, we were interested in outlining the potential room for improvement in cefepime prescription brought by a dedicated computer tool for dosage adjustment and TDM assistance that we are currently developing.[26]

In this retrospective study, we describe the TDM of cefepime as practised at-present in non-critically-ill patients in a tertiary hospital. Next, we compared four different methods of cefepime dosing: (1) conventional *table-based a priori dosing*; (2) *empirical TDM-based a posteriori dose adjustment*, as currently practised; (3) *computer-assisted a priori individualized dosing* using predictions derived from a PopPK model without TDM; and (4) *Bayesian a posteriori adjustment* integrating both PopPK and TDM through a maximum likelihood approach. Table-based *a priori* dosing followed by empirical TDM-based *a posteriori* adjustment corresponds to our current practice. Computer-assisted *a priori* and Bayesian *a posteriori* dosing rely on our novel computer tool applied virtually to the study patients.

Materials and methods

We conducted a retrospective study including adult patients (>18 years old) hospitalized between 01/01/2015 and 06/03/2019 in one tertiary centre, who received cefepime by intermittent infusions over 30 min and had at least one residual concentration of cefepime measured at steady-state according to the treating physician's demand. Critically ill, paediatric, haemodialysed patients as well as those receiving continuous cefepime infusions or declining consent to observational studies were excluded. Patients with documented non-steady-state or non-residual concentration measurements of cefepime (>1 h difference between the time of sampling and the time of the residual moment) were also discarded.

Cefepime prescription was initially table-based (according to the institutional recommendations, see Table S1, available as Supplementary data at *JAC-AMR* Online), with a distinction between 'high dose' (2 g q8h) for febrile neutropenia and 'normal dose' (2 g q12h) for other indications in patients with an estimated glomerular filtration rate (eGFR as estimated by the 4-variables MDRD formula[27]) of at least 60 mL/min/1.73 m^2. Dosage adjustments after TDM were guided by advice from

clinical pharmacologists appointed to interpret trough concentrations in real time. Due to the retrospective nature of the current study, the authors had no influence on initial *a priori* dosing or TDM-based *a posteriori* dosage adjustments, performed according to the pharmacologists' educated empiricism.

The institutional recommendations for cefepime TDM propose to measure a trough concentration before administration of the fourth dose of a regular regimen. Indications cited in these recommendations cover rather largely unsatisfactory clinical response, suspicion of toxicity, suspected drug–drug interaction or therapeutic follow-up.

In all study patients, blood samples were collected into 2.6 mL EDTA-K tubes and transported to the laboratory within 30 minutes. Cefepime plasma concentration was measured by high performance liquid chromatography with tandem mass spectrometry. The lower limit of quantification was 0.05–0.08 μg/L. The measurements are accurate (intra-/inter-assay bias ranging from −6.8% to +8.0% according to calibrator's level) and precise (intra-/inter-assay coefficient of variation ranging from 2.2% to 9.7%).[19]

A descriptive analysis was performed for all patients included at this stage. For cefepime trough concentrations exceeding 15 mg/L[9,10] or patients with treatment interruption, electronic patient records were searched for reported side effects and/or neurotoxicity, defined as decreased level of consciousness, delirium, cognitive disturbances, myoclonus, non-convulsive status epilepticus, seizures or hallucinations occurring after ≥2 days of cefepime treatment. Adverse events were graded (possible or probable) using the WHO scale of causality assessment.[28]

Next, measured cefepime trough concentrations were compared with concentration levels predicted by our PopPK software package (Tucuxi®, see Figure S1).[26] The model relies on a systematic review and meta-analysis of 10 PopPK studies of cefepime, summarized in the Appendix available as Supplementary data). The software tool was parametrized to target a minimum acceptable trough concentration of 4 mg/L, a best trough concentration of 8 mg/L and a maximum acceptable trough concentration of 16 mg/L. This target ensures the maintenance of total drug concentration above 4 × MIC over 100% of the dosage interval for most susceptible bacteria, which are those having MICs for cefepime up to 1–2 mg/L according to usual EUCAST breakpoints.[13,29] Considering cefepime's average free fraction of ∼80% in plasma, with a substantial variability between patients, this target ensures the maintenance of free concentrations above 2 × MIC.[30] For patients with documented *P. aeruginosa* infection, the minimum concentration was set at 8 mg/L, best at 12 mg/L and maximum at 16 mg/L according to the recently updated EUCAST criteria.[31]

Predictive performance of the *a priori* model output with regard to actual observations was evaluated by linear regression and calculation of the root mean squared logarithmic error (RMSLE), based on the approach of Sheiner & Beal[32] applied to log-transformed concentration values. This evaluation was extended to the subgroup of patients who had at least two repeated TDM values, to evaluate the performance of Bayesian model-based *a posteriori* predictions. For this comparative analysis, we could only include patients when cefepime treatment was continued after the first residual concentration, for whom a second comparator dosage was available.

We then compared actual table-based dosages to computer-generated *a priori* model-based recommendations, and actual empirical dosage adjustments made after TDM to *a posteriori* model-based Bayesian dosage adjustments. These comparisons were made on cefepime total daily doses (TDD). Our null hypothesis stated that there would be no difference between both approaches, while the alternative hypothesis presumed that use of the modelling software would lead to different TDD, thus indicating room for improvement in current dosing practices. The null hypothesis was tested using a one-way ANOVA. Considering a two-tailed hypothesis, 0.05 type I error and 0.80 power, we calculated a minimal sample size of $n = 134$ TDM values.

Ethics

Ethics clearance was obtained on 9 July 2019 from the ethics commission on human research of the canton of Vaud.

Results

Between 1 January 2015 and 6 March 2019, we identified 195 cefepime TDM values obtained under intermittent infusions in 126 different patients. Of these, 27 TDM values had to be excluded: 26 because of established (as documented on the laboratory request) non-steady-state values and/or non-residual concentration measurement. One additional patient was excluded after starting haemodialysis at the time of TDM. The different levels of analysis (descriptive and comparative) are depicted in the study flow chart (Figure 1). Results are presented accordingly.

Level 1a: descriptive analysis

For the remaining 168 cefepime trough concentrations in 119 different patients, we observed a median value of 12 mg/L (mean 15.5 mg/L). Of these, 38.7% of trough concentrations (65/168) exceeded 15 mg/L, and 10.7% (18/168) were below 4 mg/L. The median *a priori* dosage was 2000 mg twice daily (minimum 1000 mg once daily, maximum 2000 mg thrice daily). The median actual dosage after TDM was 2000 mg twice daily with a minimum of 500 mg twice daily and a maximum of 2000 mg thrice daily.

Adverse events occurred in 9.2% (11/119) of patients. Two patients had possibly drug-related renal impairment, nine presented with a suspicion of neurotoxicity (three probable cases, six possible cases). Details of these patients are summarized in Table 1. The initial table-based prescriptions of cefepime made before the first trough concentration measurement (available in 116 patients) were checked for under- versus over-dosing by comparison with institutional dosage recommendations. We found that 91.4% (106/116) of initial cefepime prescriptions were appropriately dosed. Yet 35% of these (37/106) lead to a trough concentration exceeding 15 mg/L, whereas 13% (14/106) did not reach 4 mg/L. Moreover, 10% of patients (12/116) were underdosed according to their eGFR, but still 25% (3/12) of their trough concentrations exceeded 15 mg/L, against 8% (1/12) found to be <4 mg/L. Finally, 1.7% (2/116) of prescriptions were overdosed, both patients having trough concentrations of >15 mg/L, yet without associated clinical toxicity.

Level 1b: comparison of *a priori* table-based and computer-assisted dosing

We first compared the initial table-based prescriptions of cefepime received by the patients with virtual *a priori* dosing decisions taken with the assistance of our computer tool, aiming at reaching the defined trough concentration target. Total daily doses were significantly lower for the model-based *a priori* dosages (mean 2907 mg/24 h) than for the actual table-based dosages, with a mean of 4625 mg/24 h (linear regression and one-way ANOVA $P < 0.001$, Figure 2a).

The comparison of log-transformed predicted (based on our PopPK model using the real-life prescribed dosage) versus

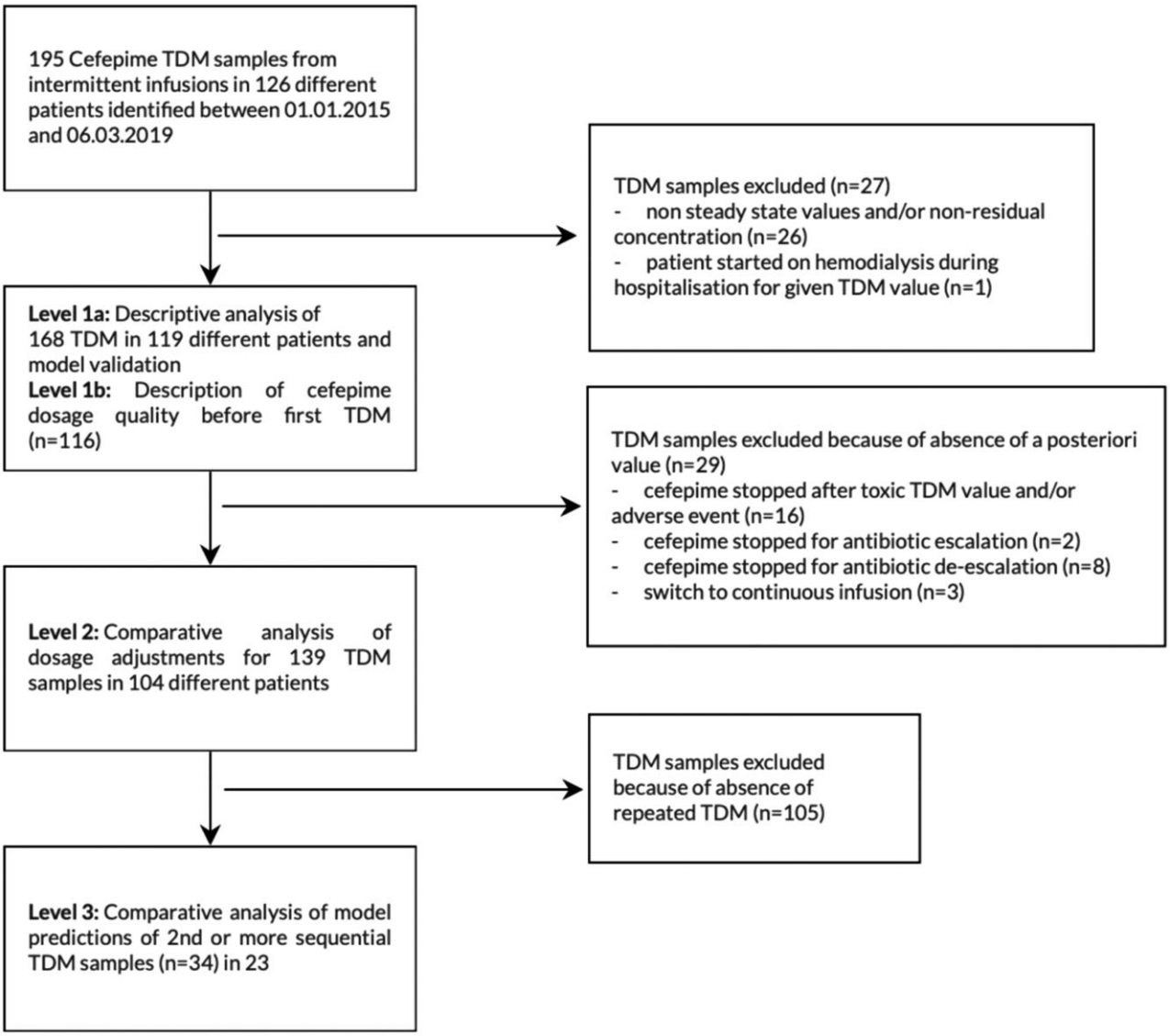

Figure 1. Study flow chart.

measured trough concentrations ($n=168$) is shown in Figure 2(b). Bias on the logarithmic values of predicted versus measured trough concentrations was −0.17, corresponding to a relative bias of −15.7%. A log-linear regression differed significantly from the identity ($P<0.001$).

Level 2: comparison of a posteriori empirical and computer-assisted Bayesian adjustment

After the descriptive analysis, 29 more TDM values in 15 patients were excluded from this comparison because of absence of a comparator dosage. Cefepime was stopped after a first elevated TDM value and/or adverse event ($n=16$), for antibiotic escalation ($n=2$), for antibiotic de-escalation ($n=8$) or switch to continuous infusion ($n=3$). The characteristics of patients included in this comparative analysis are summarized in Table 2.

The total daily doses recommended based on TDM results with our computer-assisted Bayesian tool were again significantly lower (mean 3377 mg/24 h) than the actual empirically individualized dosages after TDM (mean 4233 mg/24 h; one-way ANOVA $P<0.001$, Figure 3a). The overall difference was however less salient than in *a priori* prescriptions. By construction, trough concentrations predicted to result from model-based dosage adjustment were significantly more in the target range than actual dosage adjustments performed empirically (one-way ANOVA $P<0.001$, see Figure S2).

Finally, in three patients the model exclusively proposed prolonged infusions over 120 minutes. One patient was underweight and had a documented invasive *P. aeruginosa* infection and a low first trough concentration despite a cefepime dosage of 2000 mg q12h. The other two patients had a low trough concentration notwithstanding a maximum dose cefepime administration (2000 mg q8h).

Table 1. Summary of suspected neurotoxicity cases ($n = 9$)

Patient characteristics [age (years), sex, ethnicity, weight, baseline eGFR[a]]	Cefepime dosage	Cefepime residual concentration (mg/L)	AE[b] description	Time of AE (days from start of cefepime); eGFR at time of AE	Adverse event category (WHO scale of causality)	Active co-morbidities	Relevant co-medication with potential neurotoxicity at the time of AE	Final assessment; outcome (days after dose adjustment)
66, F, Caucasian, 52 kg, 25 mL/min/1.73 m^2	1 g q12h	33.2	Hypoactive delirium, tremor, myoclonus	4; 24 mL/min/1.73 m^2	Probable	COPD, metastatic pulmonary cancer	Fentanyl	Cefepime discontinuation; improvement of myoclonus (+2) and finally death (+4)
71, F, Caucasian, 59 kg, 36 mL/min/min/1.73 m^2	2 g q12h	27.7	Hyperactive delirium	2; 39 mL/min/1.73 m^2	Probable	Acute myeloid leukaemia, dehydration, mucositis	Morphine, anti-histaminics, low-dose cytarabine[c]	Cefepime discontinuation; complete resolution (+2)
89, M, Caucasian, 77 kg, >60 mL/min/min/1.73 m^2	2 g q12h	12.4	Delirium (unspecified)	2; >60 mL/min/1.73 m^2	Possible	Urinary retention, sepsis, dementia	Benzodiazepines, laxatives, alpha-blocker	Cefepime discontinuation; death (+4)
79, M, Caucasian, 81 kg, 30 mL/min/min/1.73 m^2	1 g q12h	27.9	Hyperactive delirium, hallucinations	3; 26 mL/min/1.73 m^2	Possible	Septic arthritis, mild cognitive impairment	Buprenorphine	Cefepime discontinuation; partial improvement (+2)
86, F, Caucasian, 46 kg, 36 mL/min/min/1.73 m^2	1.5 g q12h	25.6	Hyperactive delirium	2; 33 mL/min/1.73 m^2	Possible	Febrile agranulocytosis (rituximab), cellulitis	Buprenorphine	Cefepime dosage decreased to 1.5 g q24h after 16 h interruption; death (+7)
76, F, Caucasian, 63 kg, >60 mL/min/min/1.73 m^2	2 g q8h	25.6	Hyperactive delirium, hallucinations	2; >60 mL/min/1.73 m^2	Possible	Myelodysplastic syndrome, febrile agranulocytosis	Benzodiazepines	Cefepime discontinuation; partial improvement (+6)
63, M, Caucasian, 90 kg, 37 mL/min/min/1.73 m^2	1.5 g q12h	29.6	Worsening encephalopathy, asterixis	2; 27 mL/min/1.73 m^2	Possible	Hepatic encephalopathy	–	Cefepime dosage decreased to 1 g q12h after 16 h interruption; no improvement
55, M, 54 kg, >60 mL/min/min/1.73 m^2	2 g q8h	26.8	Hypoactive delirium	3; >60 mL/min/1.73 m^2	Possible	Metastatic pulmonary cancer	Fentanyl	Cefepime discontinuation; no improvement and finally death (+13)
56, F, Caucasian, 129 kg, 45 mL/min/min/1.73 m^2	2 g q12h	17.3	Asthenia, loss of coordination, myoclonus, postural tremor	3; 52 mL/min/1.73 m^2	Probable	Acute myeloid leukaemia, acute intermittent porphyria	Low dose cytarabine	Cefepime discontinuation: complete resolution (+2)

[a]eGFR as calculated by the MDRD 4-variables formula.
[b]AE, adverse event.
[c]Low-dose cytarabine of 200 mg/m^2/day for 7 days.

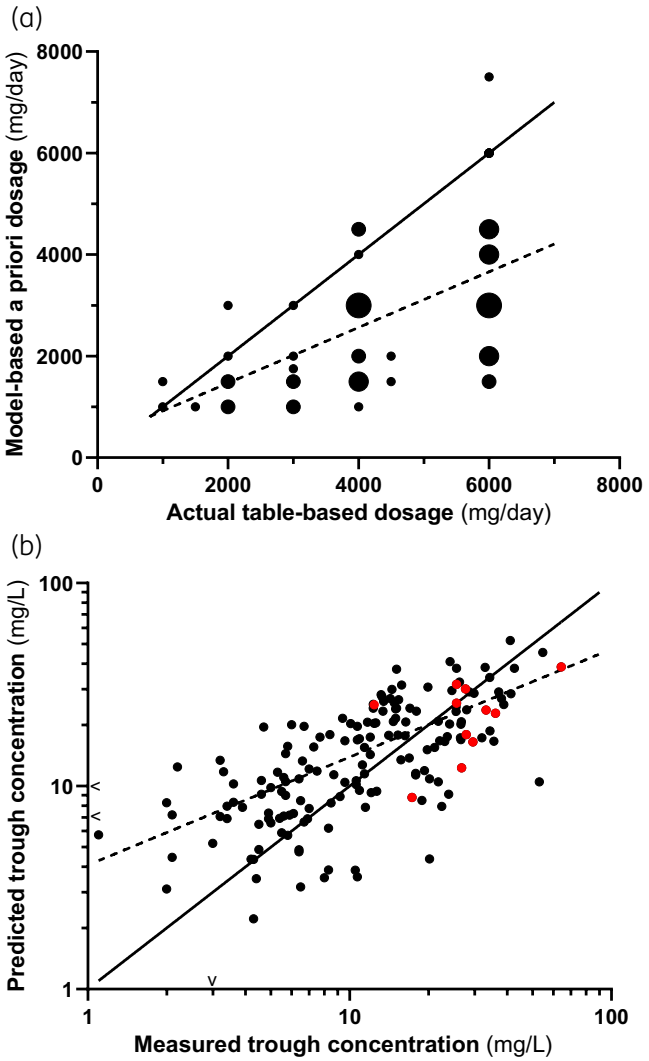

Figure 2. (a) Linear regression (dashed line) and concordance (continuous identity line) of total daily dose (TDD) determined according to conventional tables and *a priori* model-based dosing (without previous TDM) in 116 patients. The size of datapoint markers is proportional to number of cases. (b) Log-linear regression (dashed line) and concordance (continuous identity line) of *a priori* predicted versus measured trough concentrations in 168 samples. The datapoints shown in red are patients with clinical suspicion (possible or probable) of cefepime-related toxicity.

Level 3: comparative analysis for two or more subsequent TDM samples

The same comparison of log-transformed predicted versus measured trough concentrations was applied to 23 patients with repeated TDM values ($n=34$) representing series of 2 ($n=15$), 3 ($n=10$) or 4 ($n=9$) sequential measurements. The corresponding comparison is shown in Figure 3(b) and does not significantly depart from identity. Bias on the logarithmic values was 0.07 (relative bias of 7%). Thirteen predicted trough concentrations were >30% out of range with the measured values: five in patients with suspected pre-analytical error (with a first TDM value particularly high or low compared with the subsequent value), four in patients with ongoing renal function deterioration and four in onco-haematology patients with eGFR estimation possibly biased due to amyotrophy.

Discussion

Our study highlights an important proportion of patients (38.6%) with elevated cefepime trough concentrations and nine cases (7.5%) of suspected neurotoxicity despite appropriate table-based dosing. Given our population with 63% onco-haematology patients undergoing prolonged hospitalization, this probably reflects in part an overestimation of renal function as estimated by serum creatinine values in patients with muscle wasting.[33] Cystatine C level measurement is proposed as an alternative to creatinine as it provides a GFR estimate that is less dependent on a normal muscle mass, and might be beneficial in this population.[34] The incidence of cefepime neurotoxicity that has been reported varies between 1% and 15%, depending on the definition of the syndrome, and typically occurs in older patients with renal failure.[7] In febrile neutropenic patients, high cefepime plasma concentrations are identified as an independent risk factor for developing neurotoxicity, with a neurotoxic threshold proposed starting from 15 mg/L.[9] The current study confirms this threshold with all but one patient with neurotoxicity symptoms actually presenting with trough concentrations between 17.3 and 33 mg/L. The only patient with possible neurotoxicity observed at a trough concentration of 12.4 mg/L had multiple other factors underlying his neurological deterioration (urinary retention, sepsis, benzodiazepine and alpha-blocker use). Interestingly, three out of those nine cases presented with apparently normal renal function (estimated by eGFR according to MDRD formula).

Our evaluation of the PopPK model demonstrated a fairly good fit for in-target values (4–16 mg/L), but the model tended to overestimate the low and to underestimate the very high trough concentrations, eventually failing to predict an elevated trough concentration for two out of nine patients with neurotoxicity. With a closer look at patients who had multiple sequential trough concentrations, pre-analytical error (inadequate timing of sample collection), ongoing renal function deterioration (intra-patient variability) and a high proportion of onco-haematology patients (inter-patient variability) probably contribute to this unsatisfactory model fit. It should be noted that various PopPK modelling studies recognize precisely similar fitting issues.[35,36]

The 37% discrepancy between actual initial dosages and *a priori* model-based dosage propositions results in part from the limitations of the predictive performances of the PopPK model, but also from clinicians often overlooking moderate renal impairment in patients during table-based prescription. Interestingly, *a posteriori* model-based dosage adjustments after TDM also result in significantly (20%) lower total daily doses than empirically defined dosages. The model does so mostly by reducing the dosage interval (e.g. to q6h or q4h) or by proposing prolonged infusions over 120 minutes. This principle makes sense given that cefepime is a time-dependent antibiotic. For example, the impact of continuous versus intermittent infusions on total daily dose requirements is well established for ceftazidime.[37] For cefepime, it has been shown that continuous or prolonged infusions provide the greatest probability of target attainment in terms of protein-

Table 2. Patient characteristics ($n = 104$)

Characteristic	Value
Sex	F 35% (36/104), M 65% (68/104)
Age (years)	Mean 63; min 20; max 92; 36% (38/104) ≥65 years
Body weight (kg)	Mean 73.7; min 31; max 130
Creatinine value (μmol/L)	Mean 87; min 22; max 437
ALAT (U/L)	Mean 42; min 8; max 933
GGT (U/L)	Mean 96; min 8; max 497
Total bilirubin (μmol/L)	Mean 17 (median 9); min 3; max 293
Total leucocyte count (G/L)	Mean 5.4; min 0.1; max 73.9
CRP (mg/L)	Mean 81 (median 44); min <1; max 342
Co-medication at time of TDM (any of the following)	62.2% (64/104)
Systemic corticosteroids	34.6% (36/104)
Systemic antifungals	47.1% (49/104)
Anti-TB drugs (any)	6% (7/104)
Systemic antivirals	58.6% (61/104)
Antineoplastic drugs (any)	19.2% (20/104)
NSAID	0.7% (1/104)
Agranulocytosis	63.5% (66/104)
FUO	18.2% (19/104)
CDI	53.8% (56/104)
MDI	42.2% (29/104)
Site of infection	Skin and soft tissue 0.9% (1/104), ENT 0.9% (1/104), bone and joint 0.9% (1/104), urinary 2.8% (3/104), BSI 14.4% (15/104), gastro-intestinal 25% (26/104), pulmonary 35.6% (37/104).
Type of bacteria	*Pseudomonas* spp. 4.8% (5/104), *E. coli* 5.7% (6/104), streptococcal 5.7% (6/104), Gram-negative (non-*Pseudomonas*, non-*E. coli*) 10.6% (11/104), unknown 73% (76/104).

Please note that albumin values were not available at time of TDM. FUO, fever of unknown origin; CDI, clinically diagnosed infection; MDI, microbiologically diagnosed infection.

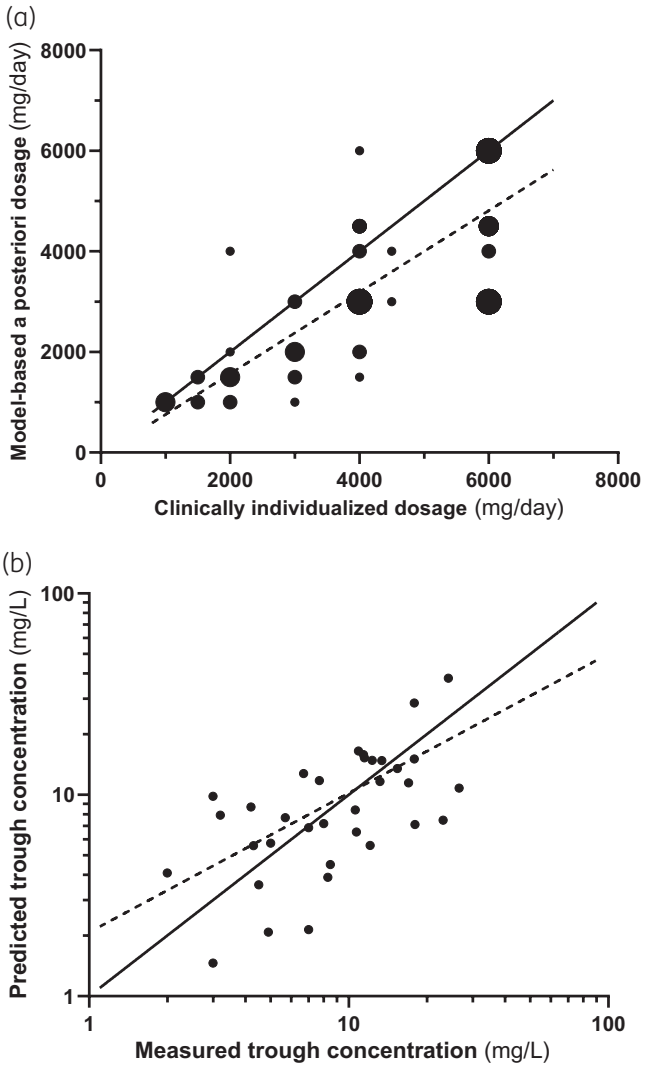

Figure 3. (a) Linear regression (dashed line) and concordance (continuous identity line) of total daily dose (TDD) resulting from empirically individualized adjustment (after TDM, without model) and *a posteriori* model-based Bayesian adaptation (with previous TDM) in 104 patients. The size of datapoints is proportional to the number of cases. (b) Log-linear regression (dashed line) and concordance (continuous identity line) of predicted versus measured trough concentration for repeated TDM values.

corrected trough concentration over MIC (fC_{min}/MIC) ratio.[38] For piperacillin/tazobactam, there is retrospective evidence as well that the use of extended infusions decreases mortality.[39] Our choice of a rather high target for cefepime exposure, while others advocate only fC_{min}/MIC > 1,[40] is motivated by the frequent use of this antibiotic to treat febrile neutropenia and other severe infections in our patients. The fact that predicted trough concentrations reach the target values more systematically with model-proposed dosage adjustments than with the actual dosage adjustments, represents of course merely a model-constructed apparent advantage.

In critically ill patients, real-time TDM of β-lactam antibiotics was shown to prevent both over- and under-dosing, and to increase target concentration attainment.[21,22,25] However, the impact of reaching and maintaining target concentrations on clinical outcomes remains to be determined. One promising multicentre randomized controlled trial comparing survival and length of stay when offering TDM versus no TDM for β-lactam- and fluoroquinolone-treated patients in the ICU is currently ongoing.[41]

Our study is limited firstly by its retrospective nature and more precisely by pre-analytical errors due to inadequate timing of the samples. There is also a non-negligible selection bias taking into account the lack of routine monitoring of cefepime trough concentrations for all patients, as TDM tends to be selected for problematic cases. The model used in our analysis, based on a meta-analysis of ten published PopPK analyses, might not be the most appropriate for our specific population of patients. There are currently no widely accepted standards to run this

type of meta-analysis. However, the fair degree of consistency between the parameters and variabilities extracted from the included studies, regardless of the type of patients investigated, suggests that our simple approach was probably appropriate to capture the essential aspects of cefepime PopPK.

In conclusion, more than a decade after the meta-analyses by Yahav *et al*.[3] and Kim *et al*.[5] on possible cefepime-related increased mortality rates, the issue of how to use this antibiotic with best safety remains a matter of debate. Owing to the small number of expected events, a new prospective safety investigation of cefepime would require a very large sample size and demand substantial resources. We endorse routine therapeutic drug monitoring of cefepime (where available), together with high awareness of subtle forms of cefepime-induced encephalopathy (e.g. hypoactive delirium, non-convulsive status epilepticus) in the non-critically ill to monitor and prevent adverse events. Based on our results, we further suggest that the recognition of high cefepime trough concentration as a predictor of toxicity is clinically more important than in-target concentration as a predictor of success. Repeated TDM measurements might be useful, especially in those patients with muscle wasting where serum creatinine values are an imprecise estimate of kidney function, or in patients with ongoing renal function loss.

Software-assisted dosage individualization based on population pharmacokinetics alone has little chance of replacing TDM, considering the limitations of its predictive performance. Conversely, it appears promising as an approach to improving the efficacy and facilitating the widespread utilization of TDM, therefore deserving further prospective evaluation and clinical validation.

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Transparency declarations

None to declare. The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Supplementary data

Figures S1 and 2, Tables S1 to S4 and the Appendix are available as Supplementary data at *JAC-AMR* Online.

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Supplementary data

Therapeutic drug monitoring of cefepime in a non-critically ill population: retrospective assessment and potential role for model-based dosing.

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Table S1: Institutional dosage recommendations for intermittent IV cefepime.

IV Cefepime (30 minutes infusion)	eGFR >60 mL/min/1.73m²	eGFR 59-30 mL/min/1.73m²	eGFR 29-15 mL/min/1.73m²	eGFR <15 mL/min/1.73m²
Febrile neutropenic patients	2000 mg q8h	2000 mg q12h	1500 mg q12h	1500 mg q24h
Non-neutropenic patients	2000 mg q12h	1500 mg q12h	1000 mg q12h	1000 mg q24h

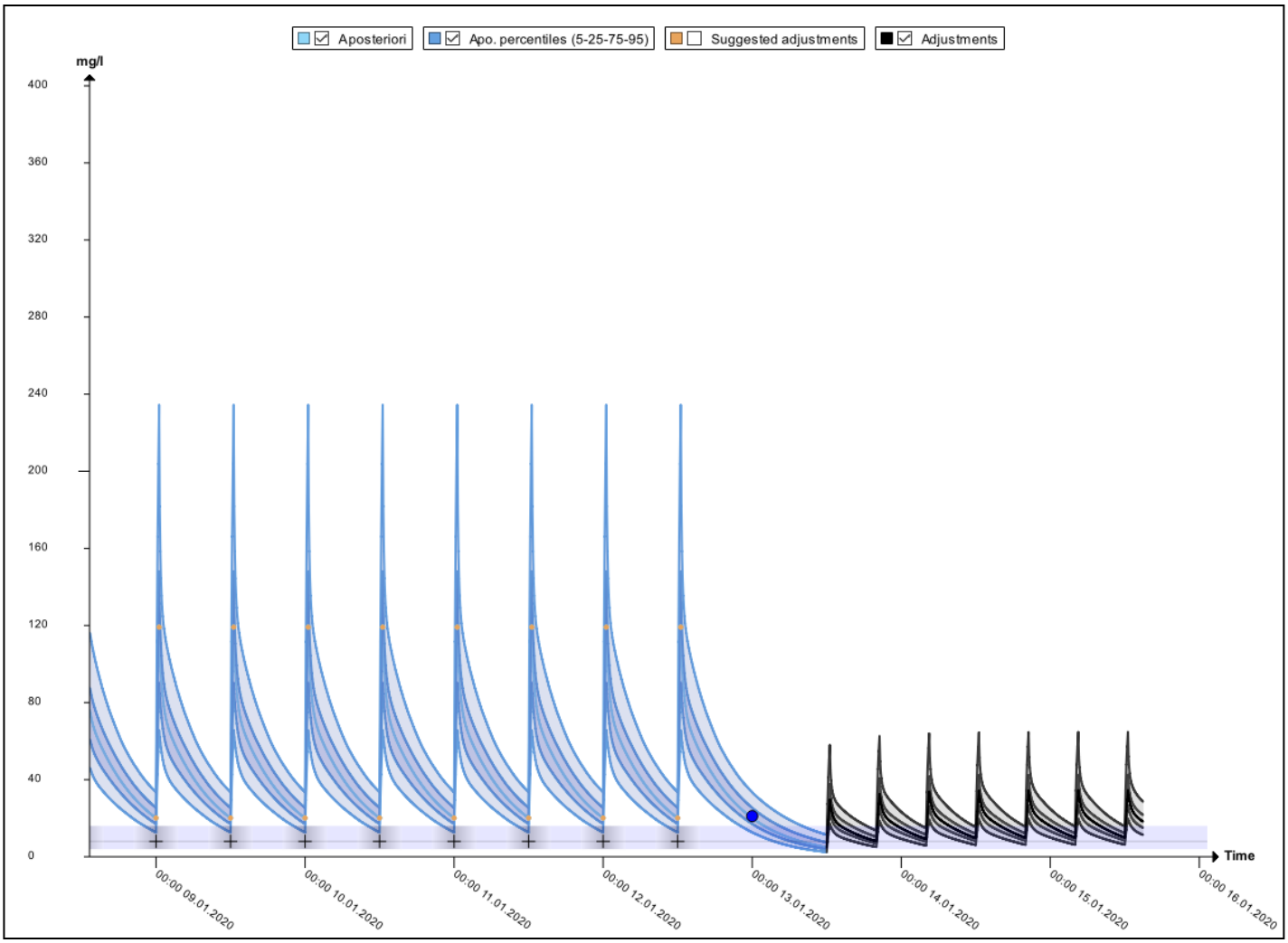

Figure S1: Example of Tucuxi® dosage recommendation after measuring steady state trough cefepime concentration at 21.2 mg/Lin a 74-year-old male patient with normal renal function (creatinine 94 µmol/L, weight 73.7 kg), receiving cefepime 2000 mg q12h for a non-pseudomonal respiratory infection. The model proposed to adjust the dosage to 500 mg q 8h as 30-minutes infusions, predicting a trough concentration of 9.8 mg/L.

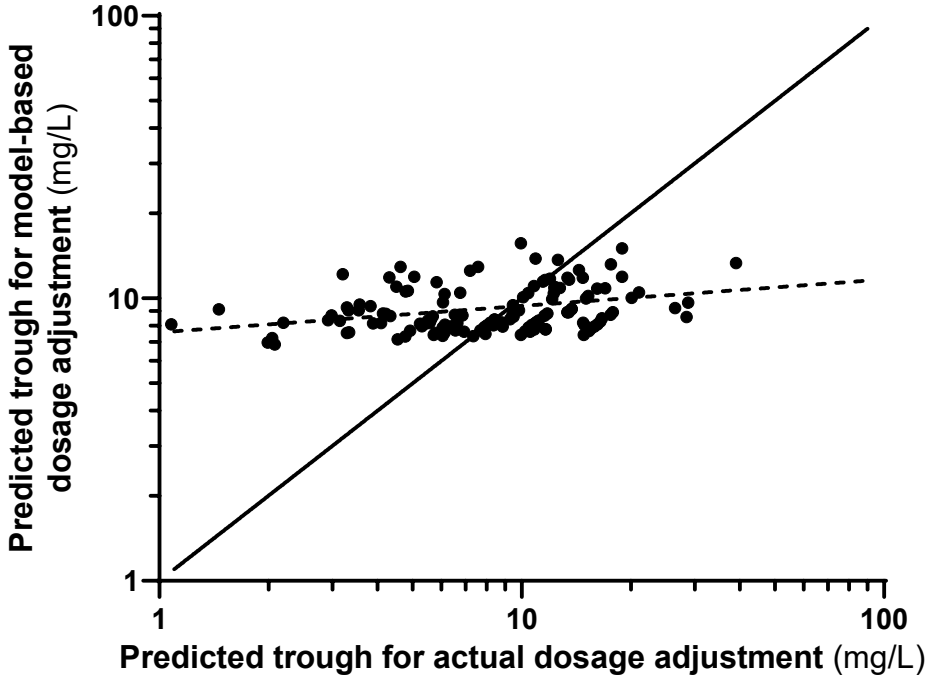

Figure S2: Log-linear regression (dashed line) and concordance (continuous identity line) between actual trough concentrations resulting from real life dosage adjustments and virtual dosage adjustments as proposed by Tucuxi in 104 patients.

Appendix: Systematic review and meta-analysis of cefepime population pharmacokinetic (PopPK) studies

In order to elaborate a PopPK model useable in our software application Tucuxi® (1) to assist the TDM of cefepime, we reviewed systematically the literature to identify PopPK studies providing suitable population parameters describing cefepime disposition in humans.

Our search on PubMed used the terms “cefepime” AND ("population pharmacokinetic" OR "population pharmacokinetics" OR "pharmacometric" OR "pharmacometrics" OR "mixed effect model" OR "mixed effect models" OR "mixed effect modeling" OR "non-linear mixed" OR "non-linear regression" OR "longitudinal analysis" OR "Nonmem" OR "NLME" OR "P-Pharm" OR "Winnonmix" OR "SAS proc mixed" OR "Kinetica" OR "Monolix"). Among the 38 publications found by our query, 9 contained useable PopPK model descriptions and were included in the systematic review. Scanning the bibliography of other articles revealed 2 further publications, among which one brought usable data (4) while the other one did not present a PopPK model with sufficient details (12). Eventually, we identified a conference proceeding bringing one last PopPK parameters set (11). The Table 2 below shows the characteristics of the studies included in our systematic review.

As no single study emerged as clearly superior to all others in this intent, we aggregated the results of the 10 useable studies identified by our literature search, to produce a set of average PopPK parameters according to the structural PK model most commonly used, i.e. a two-compartment disposition. For the only study implementing a 3 compartments model (5), we lumped both peripheral compartments together and kept the highest value of intercompartmental clearances. We decided to retain only the covariates most regularly found to influence PK parameters, i.e. glomerular filtration rate (GFR) on drug clearance and body weight (BW) on central distribution volumes. We recalculated typical parameter values and coefficients for GFR standardized to 6 L/h (i.e. 100 mL/min) and BW standardized to 70 kg. When necessary, we reparametrized the model distribution constants in terms of intercompartmental clearance (3, 4, 7). We averaged subsequently the PK parameter values by weighting them according to a quality score, computed as the sum of logarithms of patients number and samples number. An outlier value of intercompartmental clearance (4) was discarded. Regarding the coefficient of covariates, we retained only those consistent with our decision and averaged them similarly. We computed the weighted quadratic means of coefficients of variation describing inter-patient parameter variability, while lumping it with inter-occasion variability when one had been estimated (5), and ignoring it when the corresponding information was missing in the publication (4, 7). Regarding residual error, we retained the proportional distribution most frequently used in the studies, and we averaged its estimates similarly. The Table 3 show the parameter values extracted from each study, with their weighted average.

We finally retained the components deemed essential for a PopPK model, i.e. 2-compartment disposition, with both a non-renal clearance and a renal clearance correlated to GFR, a central distribution volume linearly dependent on BW, proportional inter-individual variability on clearance, central and peripheral distribution volumes, and proportional residual variability. We rounded the parameters of the aggregated PopPK model as shown in Table 3, which we used as reference in our software tool Tucuxi®.

Table S2. Characteristics of PopPK studies included in the meta-analysis
with their quality score deduced from patients and samples numbers (see text)

Publication			Population				Method		
Author	**Year**	**Ref.**	**Patients**	**Samples**	**Condition**	**Daily dosage**	**Software**	**Model**	**Score**
Ette E I	1995	2	138	2084	Healthy subjects and various patients	NA	Nonmem FO	2-comp	5
Breihl D	2001	3	16	32	Bronchial carcinoma	2 x 2 g	Nonmem FOCE	2-comp	2
Tam V H	2003	4	36	108	Pneumonia and other conditions	2 x 2 g (adjustments)	Adapt MLEM	2-comp	3
Roos J F	2006	5	13	307	ICU patients	2 x 2 g	Nonmem FOCEI	3-comp	3
Georges B	2008	6	55	516	ICU patients with pneumonia requiring artificial ventilation	2 x 2 g intermittently or as continuous infusion	Nonmem FOCE	2-comp	4
Nicasio A M	2009	7	32	88	ICU patients	3 x 2 g (adjustments)	USC-Pack NPML	2-comp	3
Delattre I K	2012	8	19	76	ICU patients with severe sepsis	3 x 2 g	Nonmem FOCEI	2-comp	3
Jonckheere S	2016	9	20	208	ICU patients (some under haemodialysis)	3 x 2 g (adjustments)	Nonmem FOCEI	2-comp	3
Rhodes N J	2017	10	9	93	Neutropenic fever	NA	Pmetrics NPAG	2-comp	2
Ullah S	2019	11	15	387	ICU patients	2 x 2 g	Nonmem (FOCEI?)	2-comp	3
Total		10	353	3899					31

Table S3. **Parameter values extracted from the PopPK studies included in the meta-analysis** with eCLcr standing for estimated creatinine clearance (in L/h, usually derived from serum creatinine with the Cockroft-Gault formula), BW for body weight (kg), BSA for body surface area (m^2), CV for coefficient of variation (quantifying proportional variability), SD for standard deviation (quantifying additive variability). Values in parentheses were not taken into account for average calculation of aggregated parameters. Interrogation marks stands for missing information.

	Clearance [L/h]				**Central distribution volume** [L]			
Ref.	**Typical value**	**Covariate**	**Coefficient**	**CV%**	**Typical value**	**covariate**	**coefficient**	**CV%**
2	6.915	eCLcr	1.1075	25%	10.02	BW	0.43	28%
3	3.65	–	–	50%	15.62	–	–	80%
4	6.669	eCLcr	0.0628	91%	22.97	–	–	68%
5	5.58	eCLcr	1	20%	5.74	–	–	38%
6	6.1425	(Creatinine)	(-0.0133)	45%	16.45	BW	(0.475)	60%
7	6.0	eCLcr	(0.048)	43%	18.41	BW	1	71%
8	6.77	(BW)	(0.75)	47%	17.8	BW	1	39%
		eCLcr	0.41					
9	6.5056	eCLcr	0.0636	50%	18.3	–	–	40%
10	5.275	(BSA)	(1)	17%	14.8	–	–	26%
		eCLcr	1					
11	4.26	eCLcr	0.15	37%	9.39	–	–	71%
Weighted average	5.947	eCLcr	0.66	46%	14.66	BW	0.74	54%

	Peripheral distribution Volume [L]				**Intercompartmental clearance** [L/h]				**Residual variability**	
Ref.	**Typical value**	**Covar.**	**Coeff.**	**CV%**	**Typical value**	**Covar.**	**Coeff.**	**CV%**	**Prop. CV%**	**Add. SD** [mg/L]
2	6.21	(BW)	(0.43)	30%	5.6	(BW)	(1)	15%	11%	0.2
3	17.58	–	–	58%	51.0	–	–	?	10%	0
4	7.22	–	–	?	(257.3)	–	–	?	?	?
5	9.6 + 7.3	–	–	34%	33.8	–	–	0	8%	0.452
6	18.1	–	–	49%	10.5	–	–	9%	16%	0
7	23.53	(BW)	(1)	?	24.6	(BW)	(1)	?	?	?
8	12.2	(BW)	(1)	48%	6.77	(BW)	(0.75)	0	23%	0
9	11.1	–	–	0	6.63	–	–	0	33%	0
10	10.9	–	–	42%	6.87	–	–	40%	?	0
11	18.4	–	–	29%	36.7	–	–	0	50%	?
Weighted average	13.82	–	–	35%	18.3	–	–	12%	22%	–

Table S4. **PopPK model used in this study**

The equation for cefepime clearance is: CL = 0.9 + 0.85·GFR [L/h] ;
for the central distribution volume, the equation is: Vc = 0.2 · BW.
The typical values are for a patient with 6 L/h of GFR and 70 kg of BW.
The peripheral distribution volume and the intercompartmental clearance are not affected by covariates, and the intercompartmental clearance is not assumed to vary among patients.
The residual variability is merely a proportional one.

Clearance [L/h]				**Central distribution volume** [L]			
Typical value	**Covariate**	**Coefficient**	**CV%**	**Typical value**	**covariate**	**coefficient**	**CV%**
6.0	GFR	0.85	45%	14.0	BW	1	50%

Peripheral distribution Volume [L]				**Intercompartmental clearance** [L/h]				**Residual variability**	
Typical value	**Covar.**	**Coeff.**	**CV%**	**Typical value**	**Covar.**	**Coeff.**	**CV%**	**Prop. CV%**	**Add. SD** [mg/L]
14.0	–	–	35%	17.0	–	–	–	25%	–

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