International Journal of Antimicrobial Agents 67 (2026) 107817

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Population Pharmacokinetics of Total and Free Ceftriaxone in Critically Ill and Non-Critically Ill Hospitalised Adult Patients

Eko Setiawan[a,b,c], Alvaro Gonzalez[a,d], Saskia A. Wölky[a,e], Menino Osbert Cotta[a], Xin Liu[a], Hernycane Sosilya[f], Diane Maresco-Pennisi[a], Emmanuel Novy[a,g], Jenny Ordonez[a], Dwi Lily Lukas[h], Steven C. Wallis[a], Jiao Xie[i], Jason A. Roberts[a,j,k,l,#], Mohd H. Abdul-Aziz[a,#,*]

[a] University of Queensland Centre for Clinical Research (UQCCR), Faculty of Medicine, The University of Queensland, Brisbane, Australia
[b] Department of Clinical Pharmacy, Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia
[c] Center for Medicines Information and Pharmaceutical Care (CMIPC), Faculty of Pharmacy, University of Surabaya, Surabaya, Indonesia
[d] Pharmacy Department, Madrid, Spain
[e] Hospital Pharmacy, Heidelberg University Hospital, Heidelberg, Germany
[f] Dr Mohamad Soewandhie Public Hospital, Surabaya, Indonesia
[g] Department of Anesthesiology, Critical Care and Peri-operative Medicine, University Hospital of Nancy, Nancy, France
[h] School of Medicine Ciputra University, Dr Mohamad Soewandhie Regional General Hospital Surabaya, Surabaya, Indonesia
[i] Department of Pharmacy, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China
[j] Herston Infectious Diseases Institute (HeIDI), Metro North Health, Brisbane, Australia
[k] Departments of Pharmacy and Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia
[l] Division of Anesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes, France

ARTICLE INFO

Article history:
Received 13 January 2026
Accepted 15 April 2026

Editor: Dr MH Scheetz

Keywords:
Cephalosporins
Dosing
Pharmacokinetics
Severe pneumonia

ABSTRACT

Objective: To characterise the population pharmacokinetics of total and free ceftriaxone in critically ill and non-critically ill Indonesian patients, define optimised dosing regimens against common hospital pathogens implicated in severe pneumonia and complicated urinary tract infections (UTI), and compare these findings with published data to support broader applicability.

Method: This study recruited critically ill and non-critically ill adults receiving intravenous ceftriaxone. Serial plasma samples were collected over one dosing interval. Total and free ceftriaxone concentrations were measured using a validated UHPLC-MS/MS method. Population pharmacokinetic analysis was performed using Monolix. Dosing simulations were performed to assess the probability of efficacy (100%fT>MIC for a given MIC) and toxicity risk (total trough concentration >100 mg/L) on days 1 and 3 of therapy. Fractional target attainment was evaluated using EUCAST MIC distributions for common pathogens implicated in severe pneumonia and complicated UTI.

Results: Fifty-three patients were recruited (median age, 57 years [IQR 39-65]; median $eGFR_{CKD-EPI}$ 67 mL/min/1.73 m^2 [31.4-92.3]; 26 males; 42% ICU). A two-compartment model with complex protein binding best described the data with $eGFR_{CKD-EPI}$ as the primary determinant of clearance. Once-daily intermittent infusion regimens (1 and 2 g every 24 h) failed to achieve optimal efficacy targets in patients with preserved or augmented renal function ($eGFR_{CKD-EPI}$ ≥60 mL/min/1.73 m^2).

Conclusion: A simplified renal function-stratified dosing strategy provided the best balance between safety and efficacy for empirical treatment; 1 g every 24 h for patients with $eGFR_{CKD-EPI}$ ≤60 mL/min/1.73 m^2 and 1 g every 12 h for patients with $eGFR_{CKD-EPI}$ >60 mL/min/1.73 m^2.

1. Introduction

Ceftriaxone, a third-generation cephalosporin, is widely used as empiric antibiotic therapy for various bacterial infections in both the general and intensive care unit (ICU) wards due to its broad-

* Corresponding author. Mailing address: University of Queensland Centre for Clinical Research (UQCCR), Faculty of Medicine, The University of Queensland, Brisbane, QLD 4029, Australia
E-mail address: h.abdulaziz@uq.edu.au (M.H. Abdul-Aziz).
# Jason A. Roberts and Mohd H. Abdul-Aziz are equal contributors and share senior authorship

https://doi.org/10.1016/j.ijantimicag.2026.107817

spectrum activity. In general wards, ceftriaxone is frequently prescribed for community-acquired pneumonia, urinary tract infections, intra-abdominal infections, and skin and soft tissue infections. In the ICU, its use extends to managing severe infections such as sepsis and complicated intra-abdominal infections where achieving optimal antibiotic exposure is critical for therapeutic success. Ceftriaxone demonstrates unique pharmacokinetic properties, including dual (biliary and renal) elimination pathways, as well as an extended half-life, which allows for flexible dosing regimens such as once- or twice-daily administration [1].

Like other beta-lactam antibiotics, the pharmacokinetic/pharmacodynamic index that best describes ceftriaxone activity is the percentage of time that the free drug concentration remains above the minimum inhibitory concentration (MIC) of the causative pathogen (%$fT_{>MIC}$) [2]. However, achieving optimal pharmacokinetic/pharmacodynamic targets for ceftriaxone (e.g. 100% $fT_{>MIC}$) in severely ill patients is challenging due to acute physiological changes that can significantly alter drug disposition [3–5]. Pathophysiological alterations such as hypoalbuminemia and augmented renal clearance may significantly alter ceftriaxone pharmacokinetics and pharmacokinetic/pharmacodynamic target attainment [6–8], potentially impacting treatment efficacy [9,10]. Inter-ethnic pharmacokinetic differences may further complicate dosing particularly in underrepresented populations such as Indonesians where limited data exist [11]. Most recommended dosing regimens are based on clinical trials primarily involving healthy Caucasian participants, which may not account for inter-ethnic variations in antibiotic pharmacokinetics and exposures. Therefore, characterising the pharmacokinetic of ceftriaxone in specific ethnic groups, including critically ill and non-critically ill patients, is key to optimising dosing in these populations.

The aims of this study were to describe the population pharmacokinetic of total and free ceftriaxone in both critically ill and non-critically ill Indonesian patients and to identify optimised dosing strategies against the most commonly identified hospital pathogens implicated in severe pneumonia and complicated urinary tract infections. Additionally, we compared our findings with previously published data to support broader applicability beyond the Indonesian setting.

2. Methods

2.1. Study design and setting

This prospective observational pharmacokinetic study was conducted at a referral hospital in Indonesia, between November 2018 and November 2019. Adult patients (≥18 years old) admitted to the ICU or non-ICU wards receiving intravenous ceftriaxone were included. Patients were excluded if they were receiving renal replacement therapy (RRT) or were scheduled to commence it at the time of sampling. Pregnant women were also excluded. Ethical approval was obtained from the Ethics Committee of Dr Ramelan Navy Hospital (approval number 76/EC/KERS/2019) and The University of Queensland Human Research Ethics Committee (approval number 2018001592). Written informed consent was obtained from each participant or their legally-authorised representative.

2.2. Drug administration, sampling procedure and data collection

Ceftriaxone was administered over 3 to 60 minutes at a dose of 1 g in 100 mL of normal saline. All other treatments were at the discretion of the treating clinician and were not influenced by study procedures. During one dosing interval, multiple blood samples (~3 mL) were collected into lithium-heparinised tubes at predefined time-points (at 5 min, 20 min, 120 min, and 240 min after injection, as well as immediately before the next dose). Exact sampling times were recorded for each patient. Blood samples were centrifuged at 3000 rpm for 15 minutes to obtain plasma. Plasma samples were stored at –80°C before bioanalysis.

Doses administered, administration times, and the number of doses received prior to sampling were documented at the time of pharmacokinetic sampling. Relevant demographic (age, sex, total body weight, and body mass index), laboratory (serum creatinine and serum albumin), and admission status (ICU or non-ICU) data were collected from the medical records at the time of recruitment. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [12].

2.3. Ceftriaxone assay

Total and free ceftriaxone concentrations in plasma were measured using a validated ultra-high-performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) method on a Shimadzu Nexera UHPLC system coupled to a Shimadzu 8030+ triple quadrupole mass spectrometer (Shimadzu corporation, Kyoto, Japan). The free fraction was isolated by ultrafiltration at 37°C using an Amicon Ultra device (Merck Millipore, Tullagreen, Ireland). $^{13}C_2$ ^{15}N-cefazolin was used as the internal standard for ceftriaxone. Linearity was validated over a concentration range of 2–200 mg/L for total concentrations and 0.2–200 mg/L for free concentrations. Precision and accuracy at three different concentrations were within 6.6% for the analysis of total ceftriaxone concentrations and 12.7% for the analysis of free drug concentrations.

2.4. Population pharmacokinetic modelling

2.4.1. Structural model

Total and free ceftriaxone concentrations in plasma were modelled simultaneously using the non-linear mixed-effects modelling program Monolix version 2023R1 (Lixoft, Antony, France), which implements the stochastic approximation expectation maximisation (SAEM) algorithm. One- and two-compartment models with first-order elimination (and first-order intercompartmental distribution for the two-compartment model) were explored. As described by Byrne et al., both simple and complex protein binding models were assessed to correlate total ceftriaxone concentrations in plasma with free concentrations [13]. The pharmacokinetic disposition model was parameterised on free concentrations. The between-subject variability (BSV) was described using an exponential model with the equation $\theta_j = \theta_p \times \exp(\eta_j)$, where θ_j is the estimated value of a parameter in the j^{th} patient, θ_p is the typical value of this parameter in the population, and η_j is the individual deviation from the typical value, i.e. the BSV, which follows a normal distribution with a mean of zero and a variance of ω^2. Additive, proportional, and combined residual error models were tested to describe residual unexplained variability (ε). Once the structural and error models were determined, covariate analysis was performed to develop the final population pharmacokinetic model for ceftriaxone.

2.4.2. Covariate analysis

The effects of several biologically plausible covariates on individual ceftriaxone pharmacokinetic parameter estimates were assessed. These covariates included age, sex, total body weight, body mass index, serum albumin, $eGFR_{CKD\text{-}EPI}$ [12], and admission status (ICU or non-ICU). The correlation between covariates and individual estimated pharmacokinetic parameters were assessed using Pearson's correlation for continuous covariates and analysis of variance (ANOVA) for categorical covariates. Covariates showing significant correlations ($p < 0.05$) were selected for further evaluation

following a stepwise forward inclusion and backward elimination procedure. A power function was used to describe the impact of the continuous covariate on the pharmacokinetic parameter, while categorical covariates were included as fractional changes relative to the reference category.

2.4.3. Pharmacokinetic model diagnostics

Competing models were evaluated based on visual inspection of goodness-of-fit (GOF) plots, numerical assessment of objective function value (OFV) and corrected Bayesian information criterion (BICc), precision of estimated pharmacokinetic parameters, reductions in BSV, and residual error variances. Once the structural and error models were chosen, each covariate was added separately to the structural model in the forward inclusion step until there was no drop in the OFV greater than 3.84 ($p < 0.05$). In the backward elimination step, covariates were removed from the model unless their exclusion led to an increase in the OFV greater than 6.63 ($p < 0.01$). Internal validation was performed using a visual predictive check (VPC) by simulating 500 patients to assess the predictive performance of the final model. Visual checks were performed by comparing the observed data points with the 95% confidence interval bounds of the simulated 5th, 50th, 95th percentile curves. The final model was considered appropriate if the majority of observed data points fell within the 95% confidence intervals of the simulated 5th, 50th, 95th percentile curves. The robustness of the final model was assessed using a non-parametric bootstrap method. A 1000-run bootstrap resampling procedure was performed in Monolix using the Rsmlx package (R Speaks "Monolix" version 4.0.2) in R software (version 4.1.3). The median, 2.5%, and 97.5% values obtained from the 1000 bootstrap runs for each pharmacokinetic parameter estimate were compared with parameter estimates of the final model.

2.4.4. Monte Carlo dosing simulations

Monte Carlo simulations were performed using Simulx 2023R1 (Lixoft SAS, a Simulation Plus company). The pharmacokinetic parameter estimates of the final model were used to simulate 1000 plasma concentration-time profiles on the first day of treatment and at steady-state for the following dosing regimens: (1) 1 g (administered as a 30-min intermittent infusion) every 8 h; (2) 2 g (administered as a 30-min intermittent infusion) every 8 h; (3) 1 g (administered as a 30-min intermittent infusion) every 12 h; (4) 2 g (administered as a 30-min intermittent infusion) every 12 h; (5) 1 g (administered as a 30-min intermittent infusion) every 24 h; (6) 2 g (administered as a 30-min intermittent infusion) every 24 h; (7) 1 g loading dose followed by 2 g daily as a continuous infusion; and (8) 1 g loading dose followed by 4 g daily as a continuous infusion. Simulations were performed for a typical patient with $eGFR_{CKD\text{-}EPI}$ of 30 mL/min/1.73 m^2, 60 mL/min/1.73 m^2, 90 mL/min/1.73 m^2, and 130 mL/min/1.73 m^2. For each dosing regimen, the probability of target attainment (PTA) was calculated using free ceftriaxone concentrations as the percentage of patients achieving 100% $fT_{>MIC}$ for a given MIC on day 1 and day 3 of therapy. The probability of reaching toxic concentrations, defined as the proportion of simulated patients with total trough concentrations >100 mg/L in this study [14], was also simulated for all scenarios. Dosing regimens that achieved ≥90% PTA for efficacy and ≤25% for toxicity on both days were considered optimal.

Fractional target attainment (FTA) was calculated by comparing the PTA (calculated using free concentrations) against EUCAST MIC distributions for *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae*, and *Klebsiella pneumoniae*, which are commonly implicated in severe pneumonia and complicated urinary tract infections. A dosing regimen was considered optimal if the FTA was ≥95% on both simulated days.

3. Results

3.1. Patient and sampling characteristics

The baseline demographic and clinical characteristics of the study population are presented in Table 1. A total of 53 patients (22 ICU and 31 non-ICU) patients were recruited; 51% were female and 25% were elderly. The $eGFR_{CKD\text{-}EPI}$ ranged from 4.7 to 126.5 mL/min/1.73 m^2. The most common ceftriaxone dosing regimen was 1000 mg every 12 h while only 1 patient received 1000 mg every 8 h.

3.2. Population pharmacokinetic model

A total of 479 ceftriaxone plasma concentrations (240 total and 239 free concentrations) from 53 patients were used for model development. Total concentrations ranged from 10.8 mg/L to 286.58 mg/L, and free concentrations ranged from 2.11 mg/L to 84.8 mg/L. Median (interquartile range, IQR) observed free trough concentration was 9.2 mg/L (5.45 – 20.1). The observed unbound (free) fraction ranged from 5% to 83%.

Free ceftriaxone concentrations (C_{free}) in plasma were best described by a two-compartment model with first-order elimination. The model was parameterised as drug clearance (CL in L/hr), volume of distribution of the central compartment (V_c in L), volume of distribution of the peripheral compartment (V_p in L), intercompartmental clearance (Q in L/hr), maximum binding concentration of ceftriaxone (B_{max} in mg/L), and dissociation constant for ceftriaxone binding to albumin (K_D in mg/L). BSV was estimated for all pharmacokinetic parameters, with the exception of K_D. Residual unexplained variability was best described by a proportional error model. The relationship between total ceftriaxone concentrations (C_{total}) and C_{free} in plasma was best described by a non-linear complex protein binding model using the equation below:

$$C_{total} = C_{free} + \frac{\left(B_{max} \times C_{free}\right)}{\left(K_D + C_{free}\right)}$$

Initial screening identified only $eGFR_{CKD\text{-}EPI}$ as a potential covariate for CL. The inclusion of $eGFR_{CKD\text{-}EPI}$ effect on CL improved the model fit. The influence of $eGFR_{CKD\text{-}EPI}$ on CL of ceftriaxone was best described by the equation below:

$$CL = CL_{pop}\, x \left(\frac{eGFR_{CKD-EPI}}{67}\right)^{0.78}$$

where CL is the estimated ceftriaxone clearance in a given individual (in L/hr), CL_{pop} is the typical value of ceftriaxone clearance in the population (in L/hr), and $eGFR_{CKD\text{-}EPI}$ is the individual's estimated glomerular filtration rate based on the CKD-EPI equation (in mL/min/1.73 m^2).

Typical pharmacokinetic parameter estimates from the final model are presented in Table 2. The pharmacokinetic model building process is summarised in Supplementary Table 1 in Supplementary Materials. The relative standard error (RSE) for all pharmacokinetic parameter estimates was below 30%, indicating good precision. GOF (Fig. 1) and VPC (Fig. 2) plots demonstrated that the final model adequately described the total and free plasma concentration-time data for ceftriaxone. The median values from the bootstrap analysis were in close agreement with the typical pharmacokinetic parameter estimates of the final model (Table 2), with narrow 95% confidence intervals.

3.3. Monte Carlo dosing simulations and probability of target attainment

PTA rates for efficacy and toxicity were comparable between days 1 (Table 3) and 3 (Table 4) of therapy. Across all renal func-

Table 1
Clinical and demographic characteristics of the study population[a].

Patient characteristics	All patients (n = 53)	ICU patients (n = 22)	Non-ICU patients (n = 31)
Age (in years)	55 (39 – 65)	48 (36 – 65)	57 (39 – 65)
Actual bodyweight (in kg)	63 (55 – 70)	64 (59 – 70)	61 (52 – 69)
Male, n (%)	26 (49)	7 (32)	19 (61)
Serum creatinine (in µmol/L)	101.7 (70.7 – 185.7)	92.8 (61.9 – 143.7)	132.6 (82.2 – 238.7)
Estimated CKD-EPI eGFR (in mL/min/1.72 m^2)	67 (31.4 – 92.3)	71.8 (47 – 94.1)	44.9 (23.8 – 92.9)
Serum albumin (in g/dL)[b]	3.2 (2.7 – 3.6)	3.1 (2.7 – 3.6)	3.5 (2.7 – 3.8)
Primary site of infection, n (%)			
Pulmonary	16 (30.2)	6 (27.3)	10 (32.3)
Urinary	12 (22.6)	0 (0.0)	12 (38.7)
Gut	9 (17.0)	4 (18.2)	5 (16.1)
Blood	8 (15.1)	8 (36.4)	0 (0.0)
Skin	1 (1.9)	0 (0.0)	1 (3.2)
Unknown	7 (13.2)	4 (18.2)	3 (9.7)

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; ICU = intensive care unit.
[a] Data are presented as medians (interquartile range) or counts (percentage).
[b] Serum albumin concentrations were only available for 23 patients.

Table 2
Typical population pharmacokinetic parameter estimates of the final model and the 1000 bootstrap runs.

Parameter	Estimate (%RSE)	Bootstrap median (95% CI)
Fixed effect		
CL (L/hr)	4.99 (6.48)	5.1 (4.44 – 5.75)
$eGFR_{CKD-EPI}$ effect on CL	0.78 (10.2)	0.74 (0.58 – 0.94)
V_c (L)	21.64 (12.5)	21.05 (10.72 – 28.33)
V_p (L)	26.75 (10.5)	26.43 (18.44 – 36.32)
Q (L/hr)	16.33 (23.1)	20.19 (9.09 – 34.1)
B_{max} (mg/L)	188.46 (7.89)	195.04 (171.02 – 225.49)
K_D (mg/L)	24.3 (10.4)	25.47 (21.46 – 31.73)
Between-subject variability		
CL (%)	41.15 (13.2)	38.3 (29.6 – 48.5)
V_c (%)	73.87 (18.0)	68.5 (36.1 – 158.3)
V_p (%)	59.45 (29.1)	58.2 (22.3 – 121.1)
Q (%)	129.11 (18.7)	88.4 (31.8 – 322.5)
B_{max} (%)	43.65 (10.2)	43.9 (33.9 – 52.1)
Residual error		
b1	0.12 (6.31)	0.12 (0.09 – 0.16)
b2	0.07 (8.22)	0.07 (0.05 – 0.09)

b1 = proportional error for free drug concentrations; b2 = proportional error for total drug concentrations; B_{max} = maximum binding concentration of ceftriaxone; CI = confidence interval; CL = drug clearance; $eGFR_{CKD-EPI}$ = estimated glomerular filtration rate using CKD-EPI equation; K_D = dissociation constant for ceftriaxone binding to albumin; V_c = volume of distribution of the central compartment; V_p = volume of distribution of the peripheral compartment; Q = intercompartmental clearance; RSE = relative standard error.

tion categories, most dosing regimens achieved ≥90% PTA at MICs ≤1 mg/L (the EUCAST MIC "susceptible" breakpoint for Enterobacterales), although lower attainment rates (32 – 89%) were observed with once-daily intermittent infusion regimens (1 g and 2 g every 24 h), particularly in patients with $eGFR_{CKD-EPI}$ ≥60 mL/min/1.73 m^2. For MIC 2 mg/L (the EUCAST MIC "resistant" breakpoint for Enterobacterales), more frequent intermittent infusion regimens were required to achieve the optimal PTA for efficacy. A regimen of 2 g every 8 h consistently maintained ≥90% PTA across all renal function categories on both simulated days whereas 1 g every 8 h achieved this target only from day 3 onwards in patients with $eGFR_{CKD-EPI}$ 130 mL/min/1.73 m^2. In contrast, once-daily intermittent infusion regimens only maintained optimal PTA in patients with $eGFR_{CKD-EPI}$ ≤30 mL/min/1.73 m^2. Continuous infusion regimens consistently maintained ≥99% PTA against MICs ≤4 mg/L across all simulated renal function categories. The probability of reaching toxic concentrations remained ≤25% for once-daily and 1 g twice-daily intermittent infusion regimens in patients with $eGFR_{CKD-EPI}$ ≥60 mL/min/1.73 m^2 whereas higher toxicity probabilities were generally observed with every 8 hourly and continuous infusion regimens, particularly in those with impaired renal function.

The most favourable balance between safety and efficacy at MICs ≤1 mg/L was achieved with an intermittent infusion regimen of 1 g every 24 h for patients with $eGFR_{CKD-EPI}$ ≤30 mL/min/1.73 m^2, 1 g every 12 h for $eGFR_{CKD-EPI}$ 60 – 90 mL/min/1.73 m^2, and 1 g every 8 h for $eGFR_{CKD-EPI}$ ≥130 mL/min/1.73 m^2 (Figure 3 and Supplementary Figure 1 in Supplementary Materials). For MIC 2 mg/L, the most favourable balance was achieved with intermittent infusion regimens of 1 g every 24 h, 1 g every 12 h, and 1 g every 8 h for patients with $eGFR_{CKD-EPI}$ ≤30 mL/min/1.73 m^2, 60 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2, respectively.

3.4. Fractional target attainment

FTA rates against *S. pneumoniae, E. coli, H. influenzae*, and *K. pneumoniae* are summarised in Table 5. Optimal FTA (≥95%) was attained against *H. influenzae* across all simulated dosing regimens and renal function categories. For *S. pneumoniae, E. coli*, and *K. pneumoniae*, optimal FTA was attained with all dosing regimens in patients with $eGFR_{CKD-EPI}$ ≤60 mL/min/1.73 m^2. Once-daily intermittent infusion regimens failed to achieve the target against these species in patients with $eGFR_{CKD-EPI}$ ≥90 mL/min/1.73 m^2. Taking the toxicity risk into account, the optimal dosing regimen was renal function-dependent. Across all bacterial species, intermittent infusion dosing of 1 g every 24 h provided the best balance between safety and efficacy in patients with $eGFR_{CKD-EPI}$ ≤60 mL/min/1.73 m^2 whereas 1 g every 12 h demonstrated the best balance in patients with $eGFR_{CKD-EPI}$ ≥90 mL/min/1.73 m^2. Although continuous infusion regimens also achieved optimal FTA across all species, these regimens were associated with a relatively higher probability of toxicity, particularly with a loading dose of 2 g followed by 4 g every 24 h (≥56%).

4. Discussion

Optimising ceftriaxone dosing in hospitalised patients remains challenging particularly in resource-limited settings where therapeutic drug monitoring (TDM) is not routinely available. In such settings, a "one-dose-fits-all" approach can be problematic as empirical fixed-dosing may result in subtherapeutic exposures in patients with augmented renal clearance and drug accumulation with potential toxicity in those with impaired renal function. To our knowledge, this study is the first to describe population pharmacokinetics of total and free ceftriaxone in both critically ill and non-critically ill hospitalised adults in Southeast Asia. A key strength of this work was the simultaneous measurement and

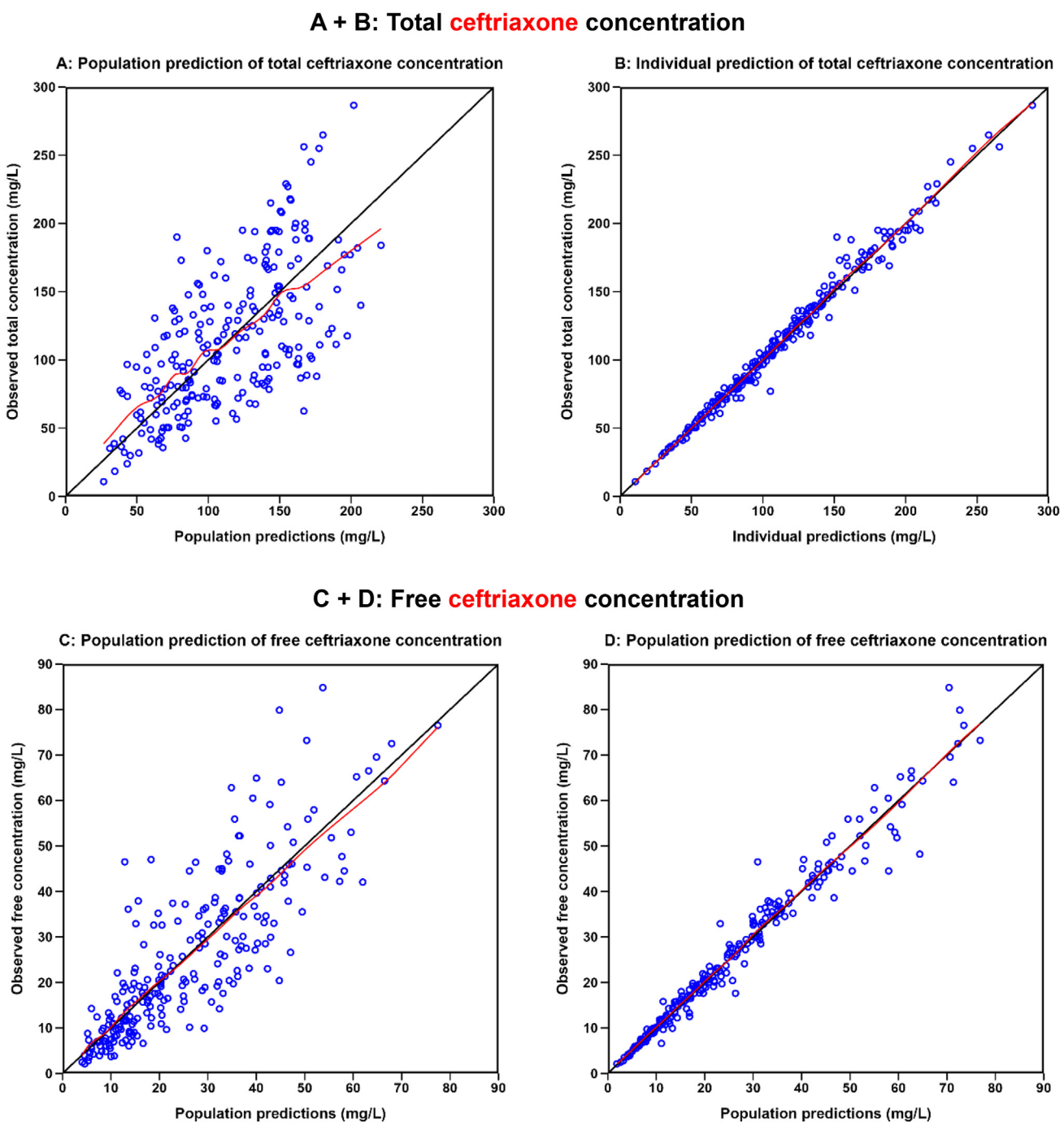

Fig. 1. Goodness of fit plots comparing population (left) and individual (right) predicted concentrations to observed concentrations of ceftriaxone. Blue circles are observed drug concentrations. Red line represents the spline.

modelling of total and free concentrations, which enabled us to directly characterise the complex, non-linear protein binding of ceftriaxone. Notably, with 53 patients, this cohort represents one of the largest adult ceftriaxone pharmacokinetic datasets reported to date, supporting the robustness of the parameter estimates. In this study, renal function estimated using the CKD-EPI equation was the primary determinant of ceftriaxone CL. Neither serum albumin concentrations nor ICU admission status significantly influenced ceftriaxone pharmacokinetics suggesting the dominant role of renal function in influencing total and free drug disposition in this patient cohort. Of note, this study identified significant limitations with standard once-daily intermittent infusion dosing, which failed to achieve optimal efficacy in patients with normal ($eGFR_{CKD\text{-}EPI}$ ≥90 mL/min/1.73 m^2) or augmented renal clearance ($eGFR_{CKD\text{-}EPI}$ ≥130 mL/min/1.73 m^2). Importantly, this study provides practical dosing recommendations for empirical treatment that can be implemented in the absence of TDM; 1 g every 24 h for patients with $eGFR_{CKD\text{-}EPI}$ ≤60 mL/min/1.73 m^2 and 1 g every 12 h for those with $eGFR_{CKD\text{-}EPI}$ >60 mL/min/1.73 m^2. Despite achieving optimal efficacy targets in all simulated scenarios, continuous infusion regimens should be reserved for patients with augmented renal clearance given the higher probability of toxicity in patients with impaired or normal renal function.

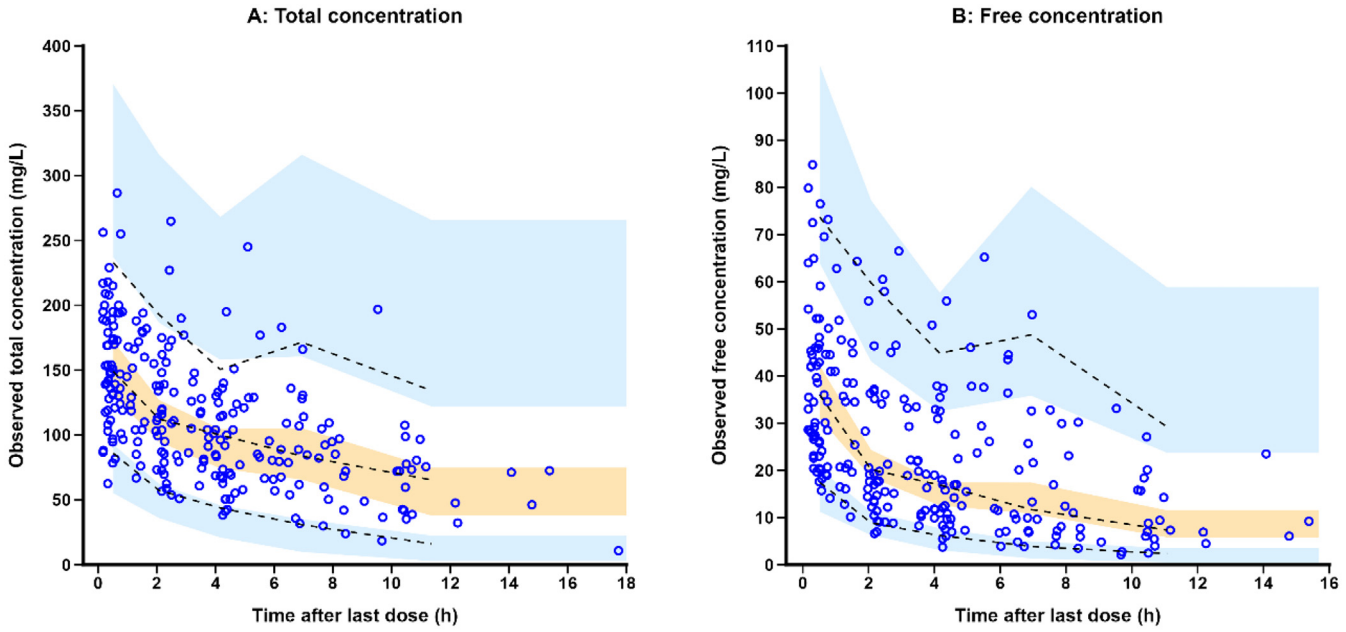

Fig. 2. Visual predictive check (VPC) plot for the final pharmacokinetic model of ceftriaxone.
Blue circles are observed drug concentrations. Dashed black lines represent the empirical 5th, 50th and 95th percentiles. Blue shaded areas represent the 95% confidence interval of the 5th and 95th percentiles and orange shaded areas represent 50th percentile of the simulated data.

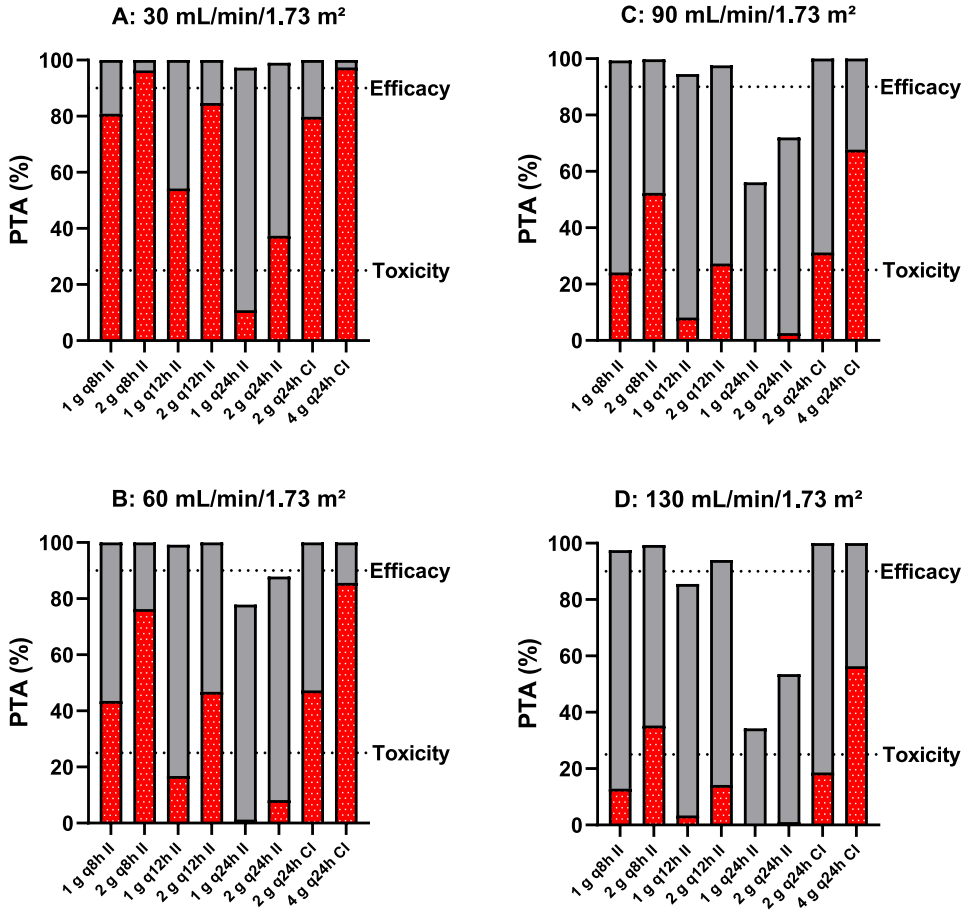

Fig. 3. Probability of target attainment (PTA) for efficacy (100% $fT_{>MIC}$) against MIC of 1 mg/L (the EUCAST MIC "susceptible" breakpoint for Enterobacterales) and toxicity (trough >100 mg/L) for various ceftriaxone dosing regimens across four renal function categories on day 3 of treatment.
Each bar represents the proportion of simulated patients attaining the efficacy target with the embedded red portion representing the proportion of patients exceeding the toxicity threshold. The gray area represents the therapeutic window, which is the difference between the probability of attaining exposures associated with clinical efficacy and toxicity. Dashed lines denote the pre-defined target attainment thresholds (≥90% for efficacy and <25% for toxicity)

Table 3
Probability of target attainment (PTA) for efficacy (100% $fT_{>MIC}$) and toxicity (trough >100 mg/L) for various ceftriaxone dosing regimens across four renal function categories on day 1 of treatment.

Dosing regimens	eGFR (mL/min/1.73m²)	MIC (mg/L)									Tox.
		0.125	0.25	0.5	1	2	4	8	16	32	
1 g q8h II	30	100	100	100	100	100	99	82.3	13.5	0	63.4
	60	100	100	100	100	99	92.6	50.4	1.6	0	31.7
	90	100	100	99.8	98.5	94.3	76.2	22.1	0.1	0	17.5
	130	99.9	99.7	99.2	96.1	88.1	57.3	10.7	0	0	9.5
2 g q8h II	30	100	100	100	100	100	100	99	82.3	13.5	93.4
	60	100	100	100	100	100	99	92.6	50.4	1.6	69.4
	90	100	100	100	99.8	98.5	94.3	76.2	22.1	0.1	46.4
	130	100	99.9	99.7	99.2	96.1	88.1	57.3	10.7	0	30.6
1 g q12h II	30	100	100	100	100	99.3	96	63.1	3.7	0	31.1
	60	100	100	100	99	93.4	75.1	18.7	0.5	0	9.2
	90	99.8	99.5	97.3	93.7	80.1	45.1	5.3	0	0	4
	130	98.8	97.5	93.7	84.2	62.1	22.9	1.5	0	0	2
2 g q12h II	30	100	100	100	100	100	99.3	96	63.1	3.7	71.5
	60	100	100	100	100	99	93.4	75.1	18.7	0.5	37
	90	99.8	99.8	99.5	97.3	93.7	80.1	45.1	5.3	0	20.4
	130	99.6	98.8	97.5	93.7	84.2	62.1	22.9	1.5	0	10.4
1 g q24h II	30	100	99.6	99.1	97.2	91	65.2	12.4	0	0	1.9
	60	97.4	95	88.5	76.9	53	17.3	0.6	0	0	0.3
	90	90.2	83.2	71.9	54.3	28.4	4.8	0	0	0	0
	130	79.4	68.9	52.2	32.1	11.9	0.9	0	0	0	0
2 g q24h II	30	100	100	99.6	99.1	97.2	91	65.2	12.4	0	16.2
	60	98.6	97.4	95	88.5	76.9	53	17.3	0.6	0	3.1
	90	94.8	90.2	83.2	71.9	54.3	28.4	4.8	0	0	0.7
	130	86.8	79.4	68.9	52.2	32.1	11.9	0.9	0	0	0.1
1 g II followed by 2 g q24h CI	30	100	100	100	100	100	100	99.6	71.9	6	72.8
	60	100	100	100	100	100	100	97.2	45.4	1.2	44.2
	90	100	100	100	100	100	100	87.6	18.3	0.1	29.9
	130	100	100	100	100	100	99.4	71.3	8.5	0	18.4
2 g II followed by 4 g q24h CI	30	100	100	100	100	100	100	100	99.6	71.9	96.5
	60	100	100	100	100	100	100	100	97.2	45.4	84.9
	90	100	100	100	100	100	100	100	87.6	18.3	67
	130	100	100	100	100	100	100	99.4	71.3	8.5	56

CI = continuous infusion; eGFR = estimated glomerular filtration rate based on the CKD-EPI equation; II = intermittent infusion over 30 min; MIC = minimal inhibitory concentration; Tox. = percentage of patients reaching total trough concentrations above 100 mg/L (toxicity threshold).
* Efficacy was defined as PTA ≥90%. Dosing regimens which achieved the efficacy target are highlighted in grey.
** Dosing regimens that achieved ≥90% PTA for efficacy and ≤25% for toxicity were considered optimal.

Ceftriaxone is eliminated via both renal and biliary pathways, with approximately 40 – 60% excreted unchanged in urine and the remainder primarily through biliary excretion [1]. While some studies characterised both elimination routes [15–17], most, including ours, did not differentiate between renal and non-renal clearance components. The pharmacokinetic parameter estimates observed in this study are generally consistent with previously published estimates [15–26], although considerable variability exists among studies. The typical CL (4.99 L/hr) and volume of distribution, Vd (48.4 L) from this study were in line with previously reported broad ranges in the literature (CL, 0.35 – 11 L/hr; Vd, 4.3 – 116 L). Comparable CL estimates were described by Dreesen et al. (8.36 L/hr) [23], van den Broek et al. (7.19 L/hr) [24], and Leegwater et al. (6.79 L/hr) [22], whereas higher estimates reported by Bos et al. (11 L/hr) [20] and Heffernan et al. (9.1 L/hr) [16] likely reflecting inclusion of younger patients and/or patients with increased creatinine clearance. Although some studies have reported Vd estimates between 15 and 30 L [15,18,22,26], our estimate aligns more closely with those observed in critically ill populations, such as in Bos et al. [20] and Kumta et al. [25]. These observations suggest that inter-ethnic differences in ceftriaxone disposition are unlikely to be a major contributor to pharmacokinetic variability in this setting, and that variability in pharmacokinetics, and consequently dosing requirements, is driven primarily by renal function and illness-related physiological changes rather than ethnicity.

In contrast to previous studies that reported a significant influence of serum albumin concentrations on ceftriaxone pharmacokinetics [17,20,22,24], we found no significant association between albumin concentrations and ceftriaxone CL. This can be likely explained by the relatively “preserved” and narrow range of albumin concentrations in our cohort. The higher median albumin concentration compared with earlier studies supports that, in patients without marked hypoalbuminemia, renal function rather than albumin binding is the primary determinant of ceftriaxone disposi-

Table 4
Probability of target attainment (PTA) for efficacy (100% $fT_{>MIC}$) and toxicity (trough >100 mg/L) for various ceftriaxone dosing regimens across four renal function categories on day 3 of treatment.

Dosing regimen	eGFR (mL/min/1.73m²)	MIC (mg/L)									Tox.
		0.125	0.25	0.5	1	2	4	8	16	32	
1 g q8h II	30	100	100	100	100	100	100	98.9	91.7	50.4	80.9
	60	100	100	100	100	99.8	97.2	86.4	51.4	8	43.5
	90	100	99.9	99.8	99.4	97	86.9	61.9	24.1	1.4	24.1
	130	99.8	99.7	99.4	97.5	91.3	74	40.3	9.6	0.1	12.9
2 g q8h II	30	100	100	100	100	100	100	100	98.9	91.7	96.4
	60	100	100	100	100	100	99.8	97.2	86.4	51.4	76.3
	90	100	100	99.9	99.8	99.4	97	86.9	61.9	24.1	52.4
	130	100	99.8	99.7	99.4	97.5	91.3	74	40.3	9.6	35.3
1 g q12h II	30	100	100	100	100	99.9	98.8	93.4	64.8	11.6	54.3
	60	100	100	100	99.2	95	84.7	56.8	16.1	0.5	16.8
	90	99.7	99.4	97.6	94.5	83.6	61.4	29.6	4	0	8.1
	130	98.7	97.3	94	85.5	67.6	40	12.3	0.6	0	3.4
2 g q12h II	30	100	100	100	100	100	99.9	98.8	93.4	64.8	84.7
	60	100	100	100	100	99.2	95	84.7	56.8	16.1	46.8
	90	99.8	99.7	99.4	97.6	94.5	83.6	61.4	29.6	4	27.3
	130	99.4	98.7	97.3	94	85.5	67.6	40	12.3	0.6	14.2
1 g q24h II	30	100	99.5	99	97.3	92.8	78.1	43.3	7.5	0	10.9
	60	97	94.7	87.9	77.9	57.4	30.4	6.2	0.2	0	1.3
	90	89.6	82.5	72	56.1	34.5	11.5	1.2	0	0	0.1
	130	78.3	68.1	53.5	34.3	15.5	2.9	0.1	0	0	0
2 g q24h II	30	100	100	99.5	99	97.3	92.8	78.1	43.3	7.5	37.4
	60	98.4	97	94.7	87.9	77.9	57.4	30.4	6.2	0.2	8.2
	90	94.6	89.6	82.5	72	56.1	34.5	11.5	1.2	0	2.6
	130	86	78.3	68.1	53.5	34.3	15.5	2.9	0.1	0	1
1 g II followed by 2g q24h CI	30	100	100	100	100	100	100	100	94.2	36.1	79.8
	60	100	100	100	100	100	100	98.2	60.8	4.6	47.3
	90	100	100	100	100	100	100	89.1	28.3	0.8	31.2
	130	100	100	100	100	100	99.4	71.5	12.1	0	18.6
2 g II followed by 4g q24h CI	30	100	100	100	100	100	100	100	100	94.2	97.4
	60	100	100	100	100	100	100	100	98.2	60.8	85.6
	90	100	100	100	100	100	100	100	89.1	28.3	67.7
	130	100	100	100	100	100	100	99.4	71.5	12.1	56.4

CI = continuous infusion; eGFR = estimated glomerular filtration rate based on the CKD-EPI equation; II = intermittent infusion over 30 min; MIC = minimal inhibitory concentration; Tox. = percentage of patients reaching total trough concentrations above 100 mg/L (toxicity threshold).
* Efficacy was defined as PTA ≥90%. Dosing regimens which achieved the efficacy target are highlighted in grey.
** Dosing regimens that achieved ≥90% PTA for efficacy and ≤25% for toxicity were considered optimal.

tion [16,18,22]. This observation challenges the pervasive and often misguided assumption that hypoalbuminemia alone necessitates dose adjustment for highly-protein bound drugs [27]. Although hypoalbuminemia lowers total ceftriaxone concentrations, the concentration of the pharmacologically active free drug remains unchanged, provided that intrinsic clearance (i.e., renal function) remains stable [28–30]. Consequently, lower total concentrations in patients with hypoalbuminemia should not be misinterpreted as sub-therapeutic exposure and any decision to adjust the dose solely based on albumin or total drug concentrations may be misleading. In this context, the absence of a significant albumin effect in our cohort reinforces the notion that renal function should remain the key determinant for optimising ceftriaxone dosing in clinical practice.

Similarly, ICU admission status did not significantly influence ceftriaxone pharmacokinetics. This may reflect the local healthcare context where ICU capacity is limited and therefore, many severely ill patients are managed in general wards. It is therefore likely that most patients in this study, irrespective of the ward location, were critically ill, which may explain the absence of pharmacokinetic differences between ICU and non-ICU patients. We contend that dosing in such populations should follow regimens that are optimised for critically ill patients, even when treated outside the ICU, given the high illness severity and prevalence of resistant pathogens commonly observed in Indonesian and other resource-constrained settings. Accordingly, a conservative pharmacokinetic/pharmacodynamic target of 100% $fT_{>MIC}$ was applied in our dosing simulations reflecting the importance of sustained drug exposure in high-risk populations where sub-optimal beta-lactam concentrations have been linked with poorer clinical outcomes [3,31,32].

Our dosing simulations integrated the probability of achieving clinical efficacy targets with the risk of exceeding toxicity thresholds to identify optimal dosing regimens specifically for this patient population, and others in settings where TDM is unavailable. As anticipated, PTA for efficacy declined with increasing MIC

Table 5
Fractional target attainment (FTA) for various ceftriaxone dosing regimens across four renal function categories at day 1 and day 3 of treatment against *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae, and Klebsiella pneumoniae.*

Dosing regimen	eGFR (mL/min/1.73 m^2)	S. pneumoniae		E. coli		H. influenzae		K. pneumoniae	
		Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 1	Day 3
1 g q8h II	30	100	100	99.2	99.4	100	100	100	100
	60	99.9	100	99.1	99.2	100	100	100	100
	90	99.7	99.8	99.0	99.1	100	100	100	100
	130	99.3	99.5	98.9	99.0	100	100	99.9	99.9
2 g q8h II	30	100	100	99.3	99.5	100	100	100	100
	60	100	100	99.2	99.4	100	100	100	100
	90	99.9	99.9	99.2	99.3	100	100	100	100
	130	99.8	99.9	99.1	99.2	100	100	100	100
1 g q12h II	30	99.9	100	99.1	99.3	100	100	100	100
	60	99.7	99.8	99.0	99.1	100	100	100	100
	90	98.8	99.0	98.7	98.8	100	100	99.8	99.8
	130	97.4	97.6	98.4	98.4	100	99.9	99.3	99.2
2 g q12h II	30	100	100	99.2	99.4	100	100	100	100
	60	99.9	100	99.2	99.2	100	100	100	100
	90	99.5	99.6	99.0	99.0	100	100	99.9	99.9
	130	98.8	98.9	98.7	98.7	100	100	99.6	99.6
1 g q24h II	30	99.5	99.5	98.9	99.0	100	100	99.9	99.9
	60	96.1	96.2	97.8	97.8	99.9	99.9	98.4	98.2
	90	90.4	90.4	94.5	94.2	98.7	98.4	93.6	93.2
	130	83.0	82.9	88.8	88.2	96.7	96.2	86.2	85.5
2 g q24h II	30	99.8	99.8	99.1	99.2	100	100	100	100
	60	98.0	98.0	98.4	98.5	100	100	99.2	99.1
	90	93.9	93.8	96.0	95.8	99.3	99.2	96.0	95.8
	130	88.2	88.0	92.0	91.6	97.6	97.4	90.8	90.2
1 g II followed by 2 g q24h CI	30	100	100	99.2	99.3	100	100	100	100
	60	100	100	99.2	99.2	100	100	100	100
	90	100	100	99.2	99.2	100	100	100	100
	130	100	100	99.2	99.2	100	100	100	100
2 g II followed by 4 g q24h CI	30	100	100	99.5	99.5	100	100	100	100
	60	100	100	99.4	99.4	100	100	100	100
	90	100	100	99.3	99.3	100	100	100	100
	130	100	100	99.3	99.3	100	100	100	100

CI = continuous infusion; eGFR = estimated glomerular filtration rate based on the CKD-EPI equation; II = intermittent infusion over 30 min.
* A dosing regimen was considered optimal if the FTA was ≥95% on both simulated days. Optimal dosing regimens are highlighted in grey.

and renal function whereas the probability of toxicity increased as renal function decreased. Consistent with previous studies in critically ill populations [16–18,20,22,23], our dosing simulations demonstrated that the contemporary once-daily intermittent infusion regimens (1 – 2 g every 24 h) failed to achieve adequate exposures in patients with augmented renal clearance ($eGFR_{CKD-EPI}$ ≥130 mL/min/1.73 m^2). Notably, our findings extend these concerns to patients with preserved renal function ($eGFR_{CKD-EPI}$ 60 – 90 mL/min/1.73 m^2) in whom these dosing regimens failed to achieve adequate exposures even at MICs ≤1 mg/L (the EUCAST MIC "susceptible" breakpoint for Enterobacterales). Additionally, optimal empirical coverage against common hospital pathogens often implicated in severe pneumonia and complicated urinary tract infections, including *S. pneumoniae, E. coli, and K. pneumoniae*, was compromised particularly in patients with normal renal function ($eGFR_{CKD-EPI}$ 90 mL/min/1.73 m^2). To address these limitations, we propose a simplified renal function-stratified dosing strategy for empirical treatment; 1 g every 24 h for patients with $eGFR_{CKD-EPI}$ ≤60 mL/min/1.73 m^2 and 1 g every 12 h for patients with $eGFR_{CKD-EPI}$ >60 mL/min/1.73 m^2.

These findings reinforce the growing evidence that once-daily ceftriaxone dosing is potentially sub-optimal in patients with preserved renal function, a limitation that has been highlighted consistently in recent pharmacokinetic/pharmacodynamic studies [6,16–18,20,22,23]. Despite these concerns, clinical practice has been slow to adopt intensified dosing strategies. This is likely because the direct clinical impact of failing to achieve pharmacokinetic/pharmacodynamic targets remains debatable and high-quality randomised controlled trials comparing once- versus twice-daily ceftriaxone, particularly in severe Gram-negative infections, are severely lacking. Although some observational studies have reported comparable clinical outcomes between once- and twice-daily dosing in community-acquired pneumonia [33], these cohorts do not reflect critically ill patients or those with severe Gram-negative infections. Therefore, although more frequent dosing is pharmacologically justified and increasingly recognised as necessary, well-designed randomised clinical trials are needed to determine whether intensified dosing (i.e. more frequent dosing) translates to improved patient outcomes. Although continuous infusion regimens achieved optimal PTA and FTA rates across most simulated scenarios, these regimens were associated with a higher probability of reaching toxic concentrations particularly in patients with $eGFR_{CKD-EPI}$ ≤90 mL/min. Despite the proven clinical advantages of continuous beta-lactam infusion [34,35], including for ceftriaxone [36], routine use should be approached with caution. For ceftriaxone specifically, pharmacokinetic/pharmacodynamic studies have predominantly focused on efficacy targets with toxicity risk not routinely integrated into dosing evaluations [15,16,18–20,

22–25]. Instead, a renal function-stratified dosing strategy is recommended to optimise ceftriaxone efficacy while minimising the toxicity risk in this population, where TDM is not available.

This study has several limitations. First, the study was designed as a pharmacokinetic analysis and standardised clinical or microbiological outcomes (e.g. clinical cure, mortality, length of stay, or microbiological cure) were not collected. Therefore, the proposed dosing regimens should be interpreted as recommendations aimed at improving pharmacokinetic/pharmacodynamic target attainment, with targets selected based on the best available evidence, and the clinical benefit of these regimens cannot be directly inferred from this study. Second, the study was conducted at a single centre in Indonesia with a relatively modest sample size. Nonetheless, the consistency of our pharmacokinetic estimates with previously published international data supports the broader applicability of these findings. Third, the EUCAST MIC distribution was used for FTA analysis in the absence of robust local susceptibility data. Therefore, these simulations may not fully reflect the specific resistance patterns in Indonesian hospitals where MIC distributions for Gram-negative pathogens may differ. Fourth, eGFR rather than measured creatinine clearance was used to characterise renal function. Although the CKD-EPI equation was the most appropriate choice given practical constraints, estimation bias may remain, particularly in critically ill patients with dynamic renal function. Fifth, we did not differentiate between renal and biliary elimination pathways and therefore could not quantify variability in non-renal elimination. Sixth, ceftriaxone concentrations at the site of infection (e.g. lungs) were not measured and plasma concentrations may not fully reflect target-site exposure. Finally, the toxicity threshold was based on a single study and therefore, toxicity estimates should be interpreted cautiously given that toxicity is likely multifactorial.

5. Conclusion

Renal function is the primary determinant of ceftriaxone pharmacokinetics in critically ill and non-critically ill hospitalised patients, and the contemporary once-daily intermittent infusion regimens failed to achieve optimal exposures in patients with preserved or augmented renal function. A simplified renal function-stratified dosing strategy provided the most favourable balance between safety and efficacy for empirical treatment of severe pneumonia and complicated urinary tract infections. Specifically, our findings suggest 1 g every 24 h for patients with $eGFR_{CKD\text{-}EPI}$ $\leq$60 mL/min/1.73 m^2 and 1 g every 12 h for patients with $eGFR_{CKD\text{-}EPI}$ >60 mL/min/1.73 m^2.

Funding: J.A. Roberts would like to acknowledge funding from the Australian National Health and Medical Research Council for an Investigator Grant (APP2009736) as well as an Advancing Queensland Clinical Fellowship. J Xie would like to acknowledge funding from National Natural Science Foundation of China (82003860), the Key Research and Development Program of Shaanxi (2024SF-YBXM-277), and the IIT Clinical Research Fund of The Second Affiliated Hospital of Xi'an Jiaotong University (No. M097). The study received financial support from the Centre of Research Excellence – Personalising Antimicrobial Dosing to Reduce Resistance (CRE RESPOND; Australian National Health and Medical Research Council Centre of Research Excellence, APP2007007). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit manuscript for publication.

Ethical approval: Ethical approval was obtained from the Ethics Committee of Dr Ramelan Navy Hospital (approval number 76/EC/KERS/2019) and The University of Queensland Human Research Ethics Committee (approval number 2018001592). Written informed consent was obtained from each participant or their legally-authorised representative.

Sequence information: Not applicable

Declaration of competing interests: None declared.

Author contributions: Dr. Eko Setiawan and Dr. Mohd H. Abdul-Aziz had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis

Concept and design: Setiawan, Cotta, Roberts, Abdul-Aziz; Acquisition, analysis, or interpretation of data: all authors; Drafting of manuscript: Setiawan, Gonzalez, Wölky, Maresco-Pennisi, Abdul-Aziz; Critical review of manuscript for important intellectual content: all authors; Statistical and pharmacokinetic analysis: Gonzalez, Wölky, Liu, Novy, Xie, Abdul-Aziz; Bioanalysis: Setiawan, Ordonez, Wallis; Obtained funding: Roberts; Administrative, technical, or material support: Lukas, Sosilya, Cotta, Roberts, Abdul-Aziz; Supervision: Cotta, Roberts, Abdul-Aziz

Acknowledgements: Given their roles as Editors for IJAA, Mohd Hafiz Abdul-Aziz and Jason A. Roberts, had no involvement in the peer-review of this article and have no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal Editor

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2026.107817.

References

[1] Richards DM, Heel RC, Brogden RN, Speight TM, Avery GS. Ceftriaxone. A review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs 1984;27:469–527.
[2] Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1–10 quiz 11-12.
[3] Roberts JA, Paul SK, Akova M, Bassetti M, De Waele JJ, Dimopoulos G, et al. DALI: defining antibiotic levels in intensive care unit patients: are current beta-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis 2014;58:1072–83.
[4] Abdulla A, Dijkstra A, Hunfeld NGM, Endeman H, Bahmany S, Ewoldt TMJ, et al. Failure of target attainment of beta-lactam antibiotics in critically ill patients and associated risk factors: a two-center prospective study (EXPAT). Crit Care 2020;24:558.
[5] Gijsen M, Dreesen E, Van Daele R, Annaert P, Debaveye Y, Wauters J, Spriet I. Pharmacokinetic/pharmacodynamic target attainment based on measured versus predicted unbound ceftriaxone concentrations in critically ill patients with pneumonia: an observational cohort study. Antibiotics (Basel) 2021;10:557.
[6] Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 2001;47:421–9.
[7] Schleibinger M, Steinbach CL, Topper C, Kratzer A, Liebchen U, Kees F, et al. Protein binding characteristics and pharmacokinetics of ceftriaxone in intensive care unit patients. Br J Clin Pharmacol 2015;80:525–33.
[8] Ollivier J, Carrié C, d'Houdain N, Djabarouti S, Petit L, Xuereb F, et al. Are standard dosing regimens of Ceftriaxone adapted for critically ill patients with augmented creatinine clearance? Antimicrob Agents Chemother 2019;63:e02134-18.
[9] Baalbaki N, Blum S, Akerman M, Johnson D. Ceftriaxone 1 g versus 2 g daily for the treatment of Enterobacterales bacteremia: a retrospective cohort study. J Pharm Technol 2022;38:326–34.
[10] Arensman Hannan K, Draper E, Cole KC, Mc Hugh J, Rivera CG, Abu Saleh O. Impact of hypoalbuminemia on clinical outcomes among patients with obesity treated with ceftriaxone. Antimicrob Agents Chemother 2024;68:e0166323.
[11] Setiawan E, Cotta MO, Roberts JA, MH Abdul-Aziz. A systematic review on antimicrobial pharmacokinetic differences between Asian and Non-Asian adult populations. Antibiotics (Basel) 2023;12:803.
[12] Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.

[13] Byrne CJ, Parton T, McWhinney B, Fennell JP, O'Byrne P, Deasy E, et al. Population pharmacokinetics of total and unbound teicoplanin concentrations and dosing simulations in patients with haematological malignancy. J Antimicrob Chemother 2018;73:995–1003.
[14] Le Turnier P, Navas D, Garot D, Guimard T, Bernard L, Tattevin P, et al. Tolerability of high-dose ceftriaxone in CNS infections: a prospective multicentre cohort study. J Antimicrob Chemother 2019;74:1078–85.
[15] Tan SJ, Cockcroft M, Page-Sharp M, Arendts G, Davis TME, Moore BR, et al. Population pharmacokinetic study of Ceftriaxone in elderly patients, using cystatin C-based estimates of renal function to account for frailty. Antimicrob Agents Chemother 2020;64:e00874-20.
[16] Heffernan AJ, Curran RA, Denny KJ, Sime FB, Stanford CL, McWhinney B, et al. Ceftriaxone dosing in patients admitted from the emergency department with sepsis. Eur J Clin Pharmacol 2021;77:207–14.
[17] Heffernan AJ, Sime FB, Kumta N, Wallis SC, McWhinney B, Ungerer J, et al. Multicenter population pharmacokinetic study of unbound ceftriaxone in critically ill patients. Antimicrob Agents Chemother 2022;66:e0218921.
[18] Garot D, Respaud R, Lanotte P, Simon N, Mercier E, Ehrmann S, et al. Population pharmacokinetics of ceftriaxone in critically ill septic patients: a reappraisal. Br J Clin Pharmacol 2011;72:758–67.
[19] Gergs U, Clauss T, Ihlefeld D, Weiss M, Pönicke K, Hofmann GO, et al. Pharmacokinetics of ceftriaxone in plasma and bone of patients undergoing hip or knee surgery. J Pharm Pharmacol 2014;66:1552–8.
[20] Bos JC, Prins JM, Mistício MC, Nunguiane G, Lang CN, Beirão JC, et al. Pharmacokinetics and pharmacodynamic target attainment of ceftriaxone in adult severely ill sub-Saharan African patients: a population pharmacokinetic modelling study. J Antimicrob Chemother 2018;73:1620–9.
[21] Grégoire M, Dailly E, Le Turnier P, Garot D, Guimard T, Bernard L, et al. High-dose ceftriaxone for bacterial meningitis and optimization of administration scheme based on nomogram. Antimicrob Agents Chemother 2019;63:e00634-19.
[22] Leegwater E, Kraaijenbrink BVC, Moes D, Purmer IM, Wilms EB. Population pharmacokinetics of ceftriaxone administered as continuous or intermittent infusion in critically ill patients. J Antimicrob Chemother 2020;75:1554–8.
[23] Dreesen E, Gijsen M, Elkayal O, Annaert P, Debaveye Y, Wauters J, et al. Ceftriaxone dosing based on the predicted probability of augmented renal clearance in critically ill patients with pneumonia. J Antimicrob Chemother 2022;77:2479–88.
[24] van den Broek AK, van Schip A, Visser CE, Bos JC, Prins JM, van Hest RM. Population pharmacokinetic/pharmacodynamic target attainment of ceftriaxone 2 g once daily in non-critically ill hospitalized adult patients during the acute phase of infection. Br J Clin Pharmacol 2023;89:3262–72.
[25] Kumta N, Heffernan AJ, Liu X, Parker SL, Cotta MO, Wallis SC, et al. Ceftriaxone population pharmacokinetics in plasma and cerebrospinal fluid of neurocritical care patients. Int J Antimicrob Agents 2025;65:107461.
[26] Roubaud-Baudron C, Fauchon H, Stanke-Labesque F, Paccalin M, Breilh D, Grégoire N, et al. Pharmacokinetics of subcutaneous and intravenous ceftriaxone in an older population: the PhASAge study. Open Forum Infect Dis 2025;12:ofaf313.
[27] Gandia P, Decheiver S, Picard M, Guilhaumou R, Baklouti S, Concordet D. Hypoalbuminemia and pharmacokinetics: when the misunderstanding of a fundamental concept leads to repeated errors over decades. Antibiotics (Basel) 2023;12:515.
[28] Rolan PE. Plasma protein binding displacement interactions–why are they still regarded as clinically important? Br J Clin Pharmacol 1994;37:125–8.
[29] Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther 2002;71:115–21.
[30] Toutain PL, Bousquet-Melou A. Free drug fraction vs free drug concentration: a matter of frequent confusion. J Vet Pharmacol Ther 2002;25:460–3.
[31] Roberts JA, Joynt GM, Lee A, Choi G, Bellomo R, Kanji S, et al. The effect of Renal Replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: data from the multinational sampling antibiotics in Renal Replacement Therapy study. Clin Infect Dis 2021;72:1369–78.
[32] Shekar K, Abdul-Aziz MH, Cheng V, Burrows F, Buscher H, Cho YJ, et al. Antimicrobial exposures in critically ill patients receiving extracorporeal membrane oxygenation. Am J Respir Crit Care Med. 2022;207:704–20.
[33] Nakanishi Y, Ito A, Tachibana H, Kawataki M, Ishida T. Comparative prospective cohort study of efficacy and safety according to dosage and administration of ceftriaxone for community-acquired pneumonia. J Infect Chemother 2025;31:102516.
[34] Abdul-Aziz MH, Hammond NE, Brett SJ, Cotta MO, De Waele JJ, Devaux A, et al. Prolonged vs intermittent infusions of β-lactam antibiotics in adults with sepsis or Septic shock: a systematic review and meta-analysis. Jama 2024.
[35] Dulhunty JM, Brett SJ, De Waele JJ, Rajbhandari D, Billot L, Cotta MO, et al. Continuous vs intermittent β-lactam antibiotic infusions in critically ill patients with sepsis: the BLING III randomized clinical trial. Jama 2024.
[36] Roberts JA, Boots R, Rickard CM, Thomas P, Quinn J, Roberts DM, et al. Is continuous infusion ceftriaxone better than once-a-day dosing in intensive care? A randomized controlled pilot study. J Antimicrob Chemother 2007;59:285–91.