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Validating a novel three-times-weekly post-hemodialysis ceftriaxone regimen in infected Indigenous Australian patients—a population pharmacokinetic study

Danny Tsai [1,2,3]*, Betty B. Zam[4], Carleigh Tongs[5], Fabian Chiong[6], Cherian Sajiv[7], Basant Pawar[7], Aadith Ashok[8], Brynley P. Cooper[3], Steven Y.C. Tong [9,10], Sonja Janson[11], Steven C. Wallis [2], Jason A. Roberts [2,12,13,14,15] and Suzanne L. Parker [2]

[1]Flinders Health and Medical Research Institute, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia; [2]UQ Centre for Clinical Research, University of Queensland, Brisbane, QLD, Australia; [3]Pharmacy Department, Alice Springs Hospital, Alice Springs, NT, Australia; [4]Pharmacy Department, Alfred Health, Melbourne, VIC, Australia; [5]Northern Territory Medical Program, College of Medicine and Public Health, Flinders University, Darwin, NT, Australia; [6]Department of Medicine, Alice Springs Hospital, Alice Springs, NT, Australia; [7]Department of Nephrology, Alice Springs Hospital, Alice Springs, NT, Australia; [8]Department of Infectious Diseases, Alfred Health, Melbourne, VIC, Australia; [9]Victorian Infectious Diseases Service, The Royal Melbourne Hospital at the Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia; [10]Department of Infectious Diseases, The University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia; [11]Department of Infectious Diseases, Royal Darwin Hospital, Darwin, NT, Australia; [12]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [13]Department of Pharmacy, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [14]Herston Infectious Diseases Institute (HeIDI), Metro North Health, Brisbane, QLD, Australia; [15]Division of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes, France

*Corresponding author. E-mail: danny.tsai@flinders.edu.au

@DannyTsai83, @jasonroberts_pk, @SuzieParker_CMG, @syctong

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Objectives: To describe the total and unbound population pharmacokinetics of a 2 g three-times-weekly post-dialysis ceftriaxone regimen in Indigenous Australian patients requiring hemodialysis.

Methods: A pharmacokinetic study was carried out in the dialysis unit of a remote Australian hospital. Adult Indigenous patients on intermittent hemodialysis (using a high-flux dialyzer) and treated with a 2 g three-times-weekly ceftriaxone regimen were recruited. Plasma samples were serially collected over two dosing intervals and assayed using validated methodology. Population pharmacokinetic analysis and Monte Carlo simulations were performed using Pmetrics in R. The probability of pharmacokinetic/pharmacodynamic target attainment (unbound trough concentrations ≥1 mg/L) and toxicity [trough concentrations (total) ≥100 mg/L] were simulated for various dosing strategies.

Results: Total and unbound concentrations were measured in 122 plasma samples collected from 16 patients (13 female) with median age 57 years. A two-compartment model including protein-binding adequately described the data, with serum bilirubin concentrations associated (inversely) with ceftriaxone clearance. The 2 g three-times-weekly regimen achieved 98% probability to maintain unbound ceftriaxone concentrations ≥1 mg/L for a serum bilirubin of 5 μmol/L. Incremental accumulation of ceftriaxone was observed in those with bilirubin concentrations >5 μmol/L. Three-times-weekly regimens were less probable to achieve toxic exposures compared with once-daily regimens. Ceftriaxone clearance was increased by >10-fold during dialysis.

Conclusions: A novel 2 g three-times-weekly post-dialysis ceftriaxone regimen can be recommended for a bacterial infection with an MIC ≤1 mg/L. A 1 g three-times-weekly post-dialysis regimen is recommended for those with serum bilirubin ≥10 μmol/L. Administration of ceftriaxone during dialysis is not recommended.

Introduction

End-stage renal disease (ESRD) is highly prevalent in indigenous populations across the world and is often associated with socio-economic disadvantages and a high chronic disease burden.[1–3] The prevalence of ESRD among Indigenous Australians is 5.26 (95% CI 4.44–6.08) per 1000 population compared with 0.36 (95% CI 0.25–0.47) in non-Indigenous Australians,[4] resulting in a disproportionately high number of Indigenous people requiring chronic hemodialysis.[5,6] High rates of hospitalization due to infection are reported for this population.[7]

Ceftriaxone is a third-generation cephalosporin antibiotic commonly used in severe infections due to its broad-spectrum Gram-negative and streptococcal pathogen coverage.[8,9] Cephalosporins have time-dependent (time unbound drug concentration remains above MIC, $fT_{>MIC}$) bacterial-kill characteristics.[10] In healthy individuals ceftriaxone has high and variable protein binding (approximately 83%–95%).[11] Hypoalbuminemia and uremia commonly associate with ESRD and can significantly alter the unbound ceftriaxone concentration.[12] Consequently, the measurement of unbound concentrations for a pharmacokinetic study of ceftriaxone in this patient population would be highly desirable to accurately characterize the impact of renal dysfunction and dialysis on pharmacologically active drug exposure.

Ceftriaxone is eliminated by the kidney and biliary routes.[13] In normal renal function, ceftriaxone has a half-life of 6–9 h,[11] which allows for the use of a once-daily regimen for many indications. In ESRD patients, ceftriaxone clearance is significantly reduced,[14] which provides the potential to extend the dosing interval beyond 24 h. An infrequently used antibiotic dosing regimen in patients receiving hemodialysis is a three-times-weekly schedule. For convenience, a fistula is commonly used for drug administration after or during the last 0.5 to 1 h of a dialysis session. For ceftriaxone, a three-times-weekly post-dialysis regimen may be preferable to minimize the vein trauma from repeated cannulation with daily regimens, thereby preserving veins for future vascular access needs.[15,16] A previous study described the pharmacokinetics of dialysis patients receiving post-dialysis doses of ceftriaxone.[13] This study used total ceftriaxone concentrations to develop the pharmacokinetic model and applied a pharmacokinetic/pharmacodynamic target attainment assessment based on protein-binding estimates obtained from healthy volunteers.[17] However, this has been shown to be fraught with inaccuracy in other patient populations.[18]

There is a paucity of adequate dosing data for ceftriaxone in patients requiring hemodialysis, particularly in Indigenous Australians. In this study, we aimed to describe the population pharmacokinetics using total and unbound ceftriaxone plasma concentrations during a three-times-weekly post-dialysis ceftriaxone regimen in non-critically ill Indigenous Australian patients requiring hemodialysis.

Materials and methods

Ethics

Ethics clearance was obtained from The University of Queensland Human Research Ethics Committee (project code 2019/HE002332) and Central Australian Human Research Ethics Committee (project code CA-19-3345). All participants provided written consent upon recruitment. The study was conducted in accordance with the Declaration of Helsinki and national standards.

Setting and study population

A prospective population pharmacokinetic study was conducted in the renal dialysis unit of a primary referral centre in remote Australia. Inclusion criteria were Indigenous Australians (identified by electronic health record) aged ≥18, who were on a three-times-weekly hemodialysis regimen and were prescribed ceftriaxone 2 g three times weekly (administered within 5 min post dialysis session). The exclusion criterion was pregnancy. Demographics and clinical characteristics of study participants were collected.

Dosing regimen and blood sampling

Each 2 g ceftriaxone dose (Ceftriaxone-AFT™; AFT Pharmaceuticals, NSW, Australia) was dissolved in 10 mL of water-for-injection and slowly injected into the patient's fistula or central venous cannula within 5 min after the conclusion of dialysis. Blood samples (0.5 mL) were collected in lithium-heparin tubes over two dosing intervals at the following times: immediately before and after dialysis, and then 5, 15, 60 and 1440 min (24 h) after the administration of ceftriaxone, then at 2880 min (48 h) (or immediately before the next dialysis session if the inter-dialysis interval was 48 h), and immediately before the next dialysis session (if the inter-dialysis interval was 72 h). Sampling times were adjusted based on clinical management and availability of each patient. The dialyzers used were documented: FX80, FX100 and FX120 (Fresenius Medical Care, Hesse, Germany).

Sample handling and storage

Blood samples were stored at 2–8°C immediately after collection and centrifuged at 5300 rpm for 5 min at 2–8°C within 4 h of collection. The plasma supernatant of each sample was collected into cryovials and stored at −80°C. Effect of freezing and thawing on the stability of ceftriaxone is negligible.[19,20] Sample analysis was conducted by the University of Queensland Centre for Clinical Research Antimicrobial Optimisation bioanalytical laboratory.

Drug assay

The plasma total and unbound concentrations of ceftriaxone were measured by a validated UPLC coupled with tandem MS (see Table S1, available as Supplementary data at *JAC* Online). The unbound fraction was isolated by ultracentrifugation at 37°C with Centrifree devices (Merck Millipore, Tullagreen, Ireland). Test samples were assayed in batches alongside calibrators and quality controls, and results were subject to batch acceptance criteria.[21]

Population pharmacokinetic modelling

Total and unbound ceftriaxone concentrations, blood-sampling time data, dose and hemodialysis intervals and timing were used to construct population pharmacokinetic models. Model development was performed using Pmetrics® software package for R® v.3.5.3, which employed the non-parametric adaptive grid algorithm. One- and two-compartment structural models, which include a protein-binding exchange, with first-order elimination were tested against additive and multiplicative error models.[22]

Hemodialysis was included in the model using selective execution of a logical-expression statement. Simple and complex protein-binding models previously published were adapted for ceftriaxone and assessed.[23] In the simple binding models, the linear relationship between the unbound

and total ceftriaxone concentrations was described as follows:

$$C_{unbound} = C_{total} \times FF \times \frac{36}{Alb}$$

$C_{unbound}$ and C_{total} are the unbound and total ceftriaxone concentrations in mg/L, respectively; FF is the unbound fraction of ceftriaxone; Alb is the serum albumin concentration in g/L.

A complex binding model was described by the following equations:

$$C_{unbound} = C_{total} - \frac{B_{max} \times C_{unbound}}{K_D + C_{unbound}}$$

$$B_{max} = Alb \times N \times \frac{M_{CTX}}{M_{Alb}} \times 1000$$

$$K_D = \frac{1}{K_A} = \frac{K_{off}}{K_{on}}$$

B_{max} is the maximum-binding concentration of ceftriaxone in mg/L; K_D is the equilibrium dissociation constant for ceftriaxone binding to albumin in mg/L; N is the number of ceftriaxone-binding sites per albumin molecule; M_{CTX} is the molecular weight of ceftriaxone in g/mol; M_{Alb} is the molecular weight of albumin in g/mol; K_A is the equilibrium association constant in L/mg; K_{off} is the first-order ceftriaxone-binding dissociation rate constant in h^{-1}; and K_{on} is the second-order ceftriaxone-binding association rate constant in L/mg/h.

Model diagnostics

A reduction in the Akaike information criterion, Bayesian information criterion, and a decrease of >3.84 in the comparative log-likelihood (2*LL) between two nested models was considered a statistical improvement with one degree of freedom (level of significance 99%) for both the inclusion of a model parameter or a covariate; an increase of >6.64 (level of significance 99%) was used for backward selection to retain model parameters and covariates in the model. Patient and treatment characteristics with a biologically plausible effect on pharmacokinetic parameters were assessed for linear, exponential or logarithmic relationships and tested for inclusion into the model using the covariate acceptance criteria described above.

Model evaluation was performed by visual assessment of the population and individual goodness-of-fit plots of observed and predicted ceftriaxone concentrations. The predictive performance was also assessed for mean prediction error (bias) and the mean bias-adjusted squared (imprecision) of the population and individual posterior predictions. A visual predictive plot was used to internally determine the validity of the model.

Monte Carlo dosing simulation

A pharmacokinetic/pharmacodynamic target was set as maintenance of unbound ceftriaxone concentrations >1 mg/L (100%$fT_{>MIC}$) for the final 24 h of a 72 h inter-dialysis interval. This target is likely to provide extended microbiological coverage of ceftriaxone and was selected based on the complexity of comorbidities seen in nephrology patients and the high likelihood of healthcare-associated infections.[24,25] Monte Carlo dosing simulations were conducted in Pmetrics® using the final model (n= 1000) with PTA analyses performed for the regimens of 2 g three times weekly; 1 g three times weekly; three-times-weekly dosing of 3, 2 and 2 g; 0.5 g once daily; and 1 g once daily, across serum bilirubin concentrations of 5, 10, 20, 40 and 80 μmol/L for the MIC of 0.125, 0.25, 0.5, 1, 2, 4, 8 and 16 mg/L. The MIC of 1 mg/L was selected as the pharmacokinetic/pharmacodynamic target concentration for these simulations because the clinical breakpoints for most target pathogens (Enterobacterales, *Streptococcus* spp., *Haemophilus influenzae*, *Moraxella catarrhalis* and *Neisseria gonorrhoea*) defined by EUCAST were ≤1 mg/L.[26] The PTA of three-times-weekly regimens was also assessed by simulating the ceftriaxone as a 30 min infusion given during the last 30 min of a hemodialysis session. Due to the high-risk characteristics of the ESRD population,[24,25] we selected a slightly higher PTA of ≥95% in our study than the ≥90% target that is conventionally used.

To evaluate possible toxicities, we performed dosing simulations that tested the probability of attaining a total trough ceftriaxone concentration (C_{min}) of 100 mg/L[27] during the final 24 h of a 72 h and 7 day course of each dosing regimen described above.

Results

Study population

Sixteen patients (13 female) were recruited with a median age (IQR) of 57 (51–64) years. A total of 122 samples were analysed to measure total and unbound ceftriaxone concentrations, and subsequently used in the pharmacokinetic modelling. Only one sample was below the lower limit of quantification (LLOQ); this sample was collected prior to any ceftriaxone being administered. We have included it in the pharmacokinetic analysis as 0.0 mg/L. Patient demographics and clinical characteristics are presented in Table 1. Seven patients had serum bilirubin concentrations >10 μmol/L, all of which were of an acute nature: two cases were considered attributable to cholecystitis and five cases to severe infection. The median (IQR) unbound fraction, pre-dialysis unbound ceftriaxone trough concentration of a 2 day dose interval, pre-dialysis unbound trough concentration of a 3 day dose interval, and unbound concentration reduction during each dialysis session were: 0.29 (0.20–0.40), 18.2 (9.7–25.9) mg/L, 8.8 (7.1–17.7) mg/L, and 70% (64–74%), respectively. The pharmacokinetic model parameter estimates are presented in Table 2.

Table 1. Patient demographics, clinical characteristics and ceftriaxone trough concentration summary data[a]

Parameter	n=16
Age, year (IQR)	57 (51–64)
Female, *n* (%)	13 (81)
Weight, kg (IQR)	71 (59–83)
Source of infection:	Respiratory: 11
	Urinary: 1
	Bacteremia: 1
	Skin and soft tissue: 1
	Intra-abdominal: 1
	Unknown source: 1
Albumin, g/L (IQR)	36 (33–39)
Urea, mmol/L (IQR)	15.1 (12.2–19.2)
Serum bilirubin, μmol/L (IQR)	10 (6–14)
ALP, U/L (IQR)	216 (171–338)
GGT, U/L (IQR)	74 (42–133)
ALT, U/L (IQR)	23 (13–29)
Filter used, *n* (%)	FX80: 3 (19)
	FX100: 10 (63)
	FX120: 3 (19)

[a]Data presented as median (IQR) or counts (%). ALP, serum alkaline phosphatase concentration; ALT, alanine transaminase; GGT, gamma-glutamyl transferase.

Table 2. Ceftriaxone pharmacokinetic model parameter estimates

Parameter	Mean	SD	CV, %	Median	Shrinkage, %
CL_{nHD} (L/h)	0.83	0.28	33.33	0.77	0.43
CL_{HD} (L/h)	8.76	1.85	21.10	9.13	2.12
V_c (L)	2.25	1.71	75.81	1.91	0.14
V_d (L)	36.22	8.26	22.80	33.83	–[a]
$T_{½nHD}$ (h)	38.31	32.78	85.56	30.40	–[a]
$T_{½HD}$ (h)	3.04	1.09	35.91	2.65	–[a]
K_{on} (L/mg/h)	1.18	0.33	27.76	1.18	0.51
K_{off} (h^{-1})	206.37	48.38	23.44	202.36	1.96
K_{cp} (h^{-1})	15.37	7.24	47.10	17.01	0.24
K_{pc} (h^{-1})	0.78	0.50	64.05	0.55	0.13

CL_{HD}, ceftriaxone clearance when dialysis is on; CL_{nHD}: ceftriaxone clearance when dialysis is off; CV, coefficient of variation; K_{cp}, rate transfer constant from the central to peripheral compartment; K_{off}, first-order dissociation rate constant; K_{on}, second-order association rate constant; K_{pc}, rate transfer constant from the peripheral to central compartment; $T_{½HD}$, elimination half-life when dialysis is on; $T_{½nHD}$, elimination half-life when dialysis is off; V_c, central volume of ceftriaxone; V_d, total volume of distribution.

[a]Data not available because the entry is manually calculated.

Population pharmacokinetic model and model diagnostics

A two-compartment model, which includes a protein-binding exchange, described the data adequately (see a compartment diagram in Figure S1), with data initially incorporated as a one-compartment model, with a protein-binding exchange. The diagnostic plots of observed ceftriaxone concentration-time data against the final model for each individual patient are presented in Figure 1. The population and individual observed versus predicted plots for unbound and total ceftriaxone concentrations, as well as the residual diagnostic plots are presented in Figures 2 and 3.

Ceftriaxone clearance and serum bilirubin concentrations demonstrated an inverse-power relationship, with a r^2 of 0.74 (see Figure 4), with serum bilirubin the only covariate retained in the final model. One patient exhibited a high bilirubin concentration of 72 μmol/L; when this data point was removed the inverse-power relationship remained strong ($r^2 = 0.70$). The improvement of 2*LL, Akaike information criterion and Bayesian information criterion during the process of model design and covariate inclusion is presented in Tables S3A and S3B.

Ceftriaxone clearance was >10-fold higher during dialysis. The final clearance model is as follows:

When dialysis is off:

$$CL = CL_{nHD} \times \left(\frac{14.1}{bili}\right)^{0.5}$$

When dialysis is on:

$$CL = CL_{HD}$$

CL is the population parameter estimate of ceftriaxone clearance in L/h, CL_{nHD} is the population parameter estimate of ceftriaxone clearance when dialysis is off in L/h, bili is the serum bilirubin concentration in μmol/L, CL_{HD} is the population parameter estimate of ceftriaxone clearance when dialysis is on in L/h. The differential equations and the final model file are presented in Table S2.

Dosing simulation

Results of the PTA simulation for the last 24 h of a 3 day dosing interval of various regimens against various bilirubin concentrations are presented in Table 3. The 2 g three-times-weekly regimen achieved a PTA of 98% for a target concentration of 1 mg/L with a bilirubin concentration of 5 μmol/L. All tested regimens achieved a PTA >95%, except for the 1 g three-times-weekly regimen (86%). Moreover, all regimens achieved a PTA >95% when bilirubin was ≥10 μmol/L. When simulating the 2 g three-times-weekly model where ceftriaxone was administered during dialysis, a PTA of 0.1% was achieved.

Higher bilirubin concentrations were associated with a higher probability of achieving toxic C_{min} on Day 3 and Day 7 of all regimens (see Tables 4A and 4B). From the simulations with bilirubin concentration of 5 μmol/L, 2 g once daily was the only regimen with >1% probability of achieving toxicity C_{min} on Day 3 (57%). The 1 g three-times-weekly regimen was least likely to reach a toxic C_{min} amongst all regimens.

Discussion

To the best of our knowledge, this is the first study to describe the pharmacokinetics of unbound ceftriaxone in patients requiring intermittent hemodialysis. Based on clearance and protein-binding considerations in this patient population, a 2 g three-times-weekly post-dialysis regimen can be recommended for the treatment of dialysis patients, where ceftriaxone is indicated for a bacterial infection with an MIC ≤1 mg/L. However, for dialysis patients with hyperbilirubinemia (bilirubin concentration ≥10 μmol/L) a 1 g three-times-weekly regimen is recommended. This novel dosing strategy supports optimal treatment of dialysis patients and is likely to help preserve vein integrity by reducing the requirement for repeat cannulation.

The present study described a median ceftriaxone clearance of 0.77 L/h, which is similar to published data in other ESRD populations[28] and lower than healthy volunteers (1.19–1.30 L/h).[29] This decrease in clearance supports the extension of the dosing interval to 72 h. Furthermore, it has been suggested that inter-ethnic pharmacokinetic differences are unlikely for ceftriaxone,[30] and hence results from this study can be justifiably applied to patients of other ethnic origins.

In this study we identified an inverse relationship between ceftriaxone clearance and bilirubin concentrations in ESRD patients. This finding has not been clearly described in the literature; however, because ceftriaxone is cleared by both the renal and biliary routes in healthy individuals,[29] the biliary system will naturally have a greater influence on the clearance of ceftriaxone when renal clearance is negligible. Accumulation of ceftriaxone would be expected if biliary clearance is also reduced. Based on our dosing simulations, we recommend a 1 g three-times-weekly regimen for dialysis patients with hyperbilirubinemia. We would advise against the use of the 2 g daily regimen in ESRD patients, even in absence of hyperbilirubinemia, in view of an increased risk of drug accumulation. There is a paucity of robust data to support

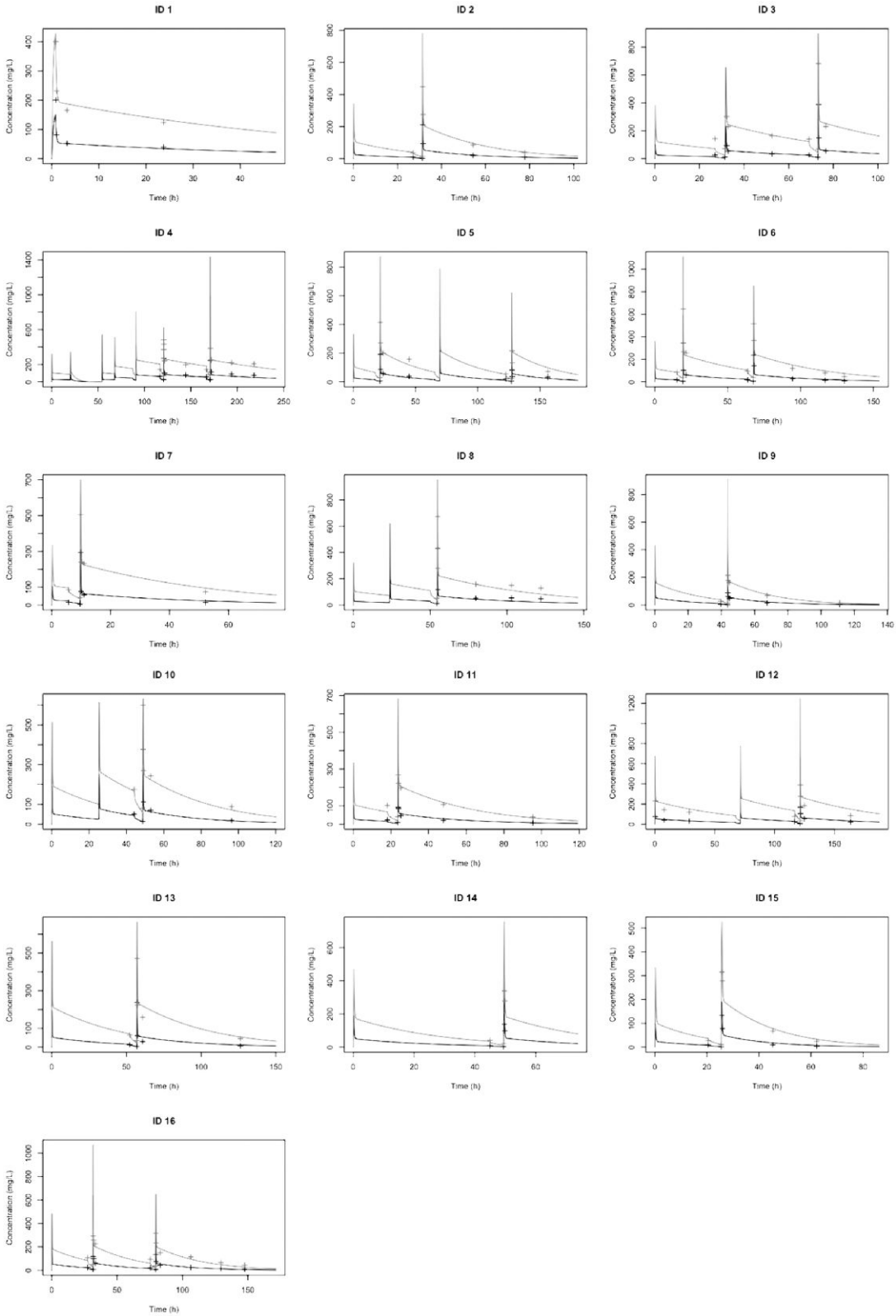

Figure 1. Observed total (grey cross) and unbound (black cross) ceftriaxone concentration-time data are presented with predicted lines of the final model (total, grey line; unbound, black line) for each individual patient.

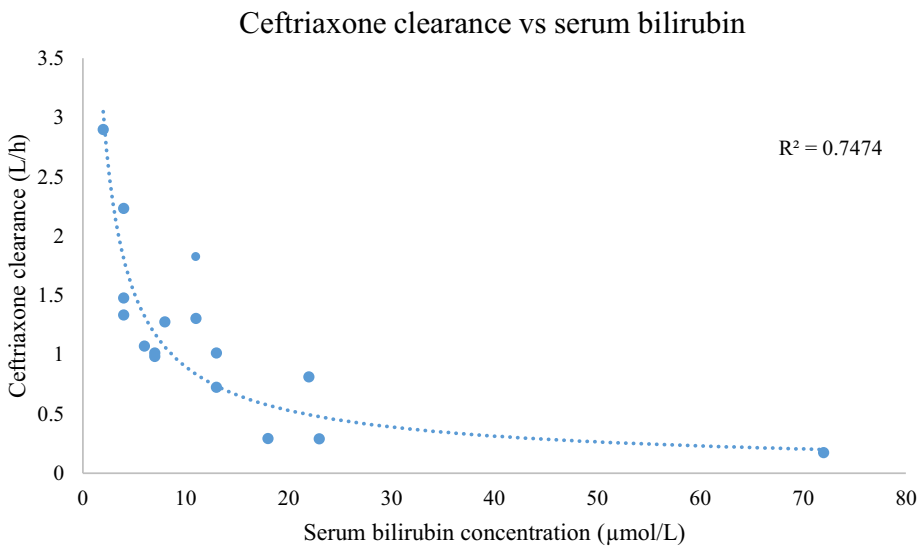

Figure 2. The powered relationship between ceftriaxone clearance and serum bilirubin concentration. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

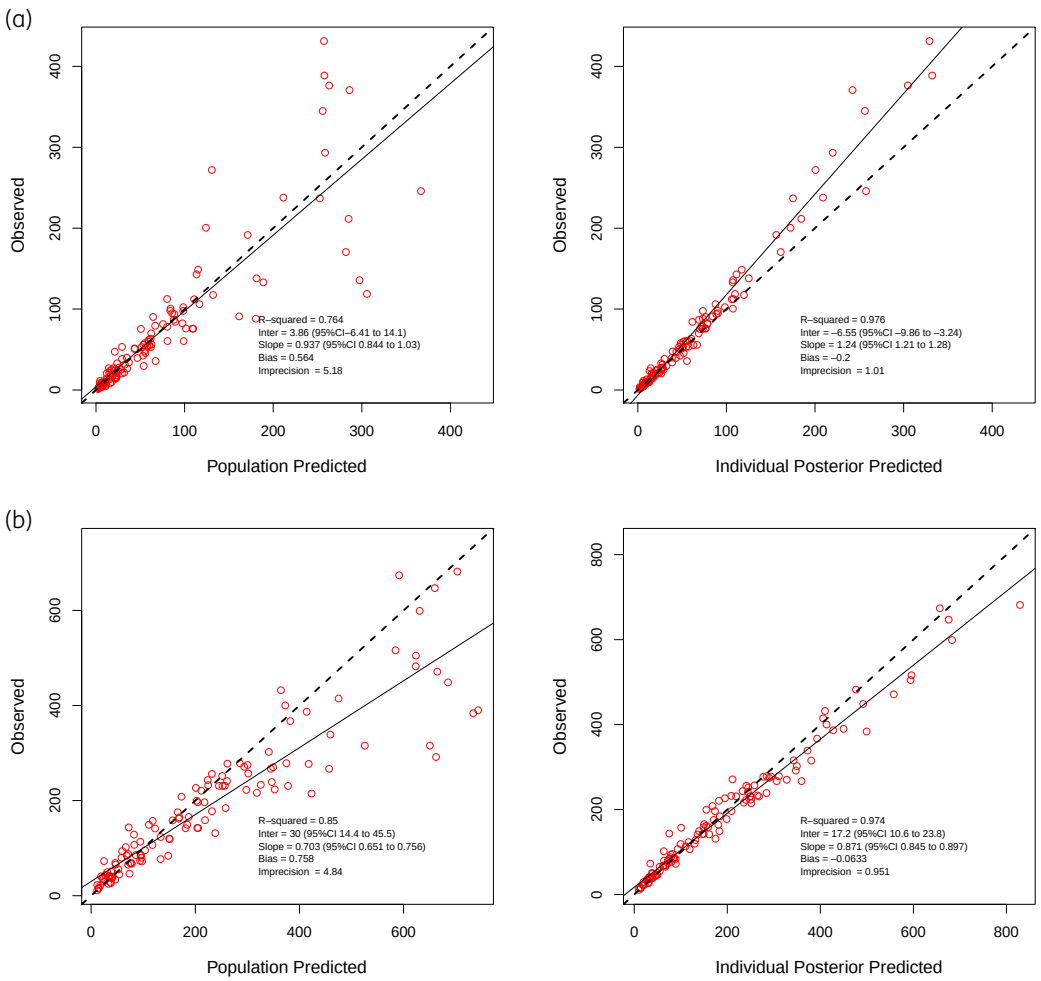

Figure 3. Observed versus predicted goodness-of-fit plots for unbound and total ceftriaxone concentration (open circles). (a) Population and individual predicted unbound ceftriaxone concentration. (b) Population and individual predicted total ceftriaxone concentration. The ceftriaxone concentrations shown are milligrams per litre. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

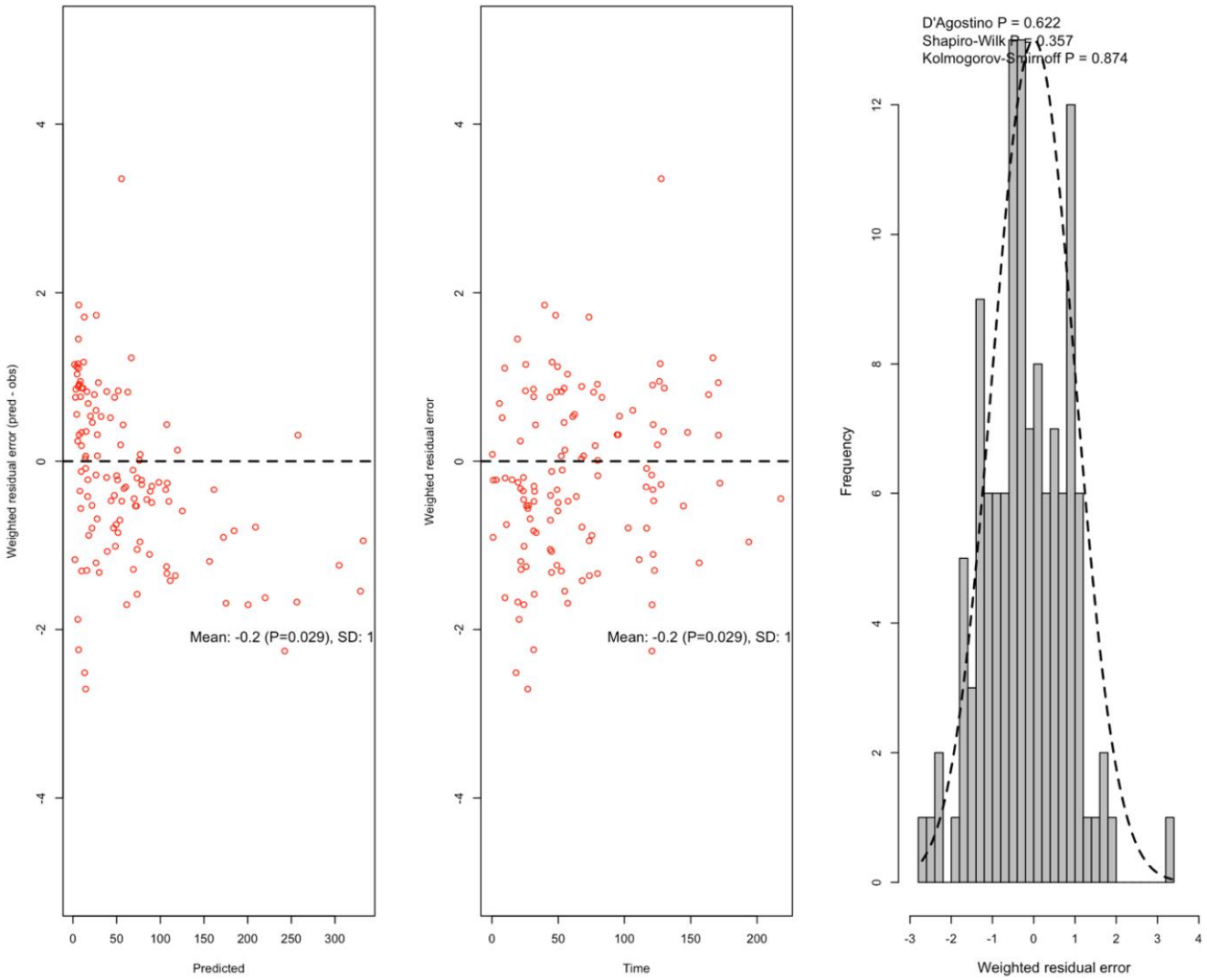

Figure 4. Residual diagnostic plots. From left to right: weighted residual error versus predicted concentration; weighted residual error versus time; weighted residual error frequency histogram. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

and guide dose adjustments in patients with both renal and liver impairment. This is of concern because a case of neurotoxicity has been recently reported in a patient with renal impairment and acute liver injury receiving a 2 g daily regimen.[31] Additionally, associations have been found between prolonged durations of ceftriaxone exposure and amplification of resistance genes in human intestinal flora.[32]

Our study, which used dialyzers with high-flux membranes, observed >10-fold higher ceftriaxone clearance during dialysis compared with non-dialysis periods. Based on dosing simulations, pharmacokinetic/pharmacodynamic targets were not achievable when ceftriaxone was administered during dialysis. Previous publications have reported that the clearance of ceftriaxone was not enhanced by the dialysis modality.[13,28] However, these studies used dialyzers with low-flux membranes. A greater dialysis efficacy and reduced mortality risk was observed in dialyzers with high-flux membranes,[33,34] and hence high-flux dialyzers are now more commonly used in clinical practice. Based on our findings, we strongly advise against the practice of administering ceftriaxone during dialysis.

In our study, the central volume of ceftriaxone (V_c) was lower (2.25 ± 1.71 L) than reported in studies of ESRD patients with similar demographics (4.5 ± 0.8 and 6.5 ± 2.9 L).[13,35] However, our study was the first to estimate V_c using unbound and total ceftriaxone concentrations in dialysis patients. Simon *et al.*[13] and Wise and Wright[35] did not measure unbound ceftriaxone concentrations and have constructed pharmacokinetic models using protein-binding estimates obtained from healthy volunteers. This approach did not account for physiological changes in ESRD that could significantly alter the pharmacokinetics of ceftriaxone.[12] Our study identified a higher unbound ceftriaxone fraction (median 0.29, IQR 0.20–0.40) compared with healthy individuals (0.04–0.17).[29] The binding distribution of ceftriaxone has also been identified as altered in hypoalbuminemia and where there is competitive albumin-binding induced by hyperbilirubinemia.[36] The high unbound fraction observed in this

Table 3. Probability of target attainment of 100% $fT_{>MIC}$ (%) on the last day of a 3 day dose interval for a 2 g post-dialysis dose

		MIC (mg/L)							
Dosing regimen	Bili (μmol/L)	0.125	0.25	0.5	1	2	4	8	16
1 g, 1 g, 1 g	5	**99.8**	**99.5**	**98**	86	54.6	15.6	3.3	0.0
	10	**100**	**100**	**100**	**99.5**	93.1	54.6	7.6	0.2
	20	**100**	**100**	**100**	**100**	**99.8**	92.2	33.7	0.6
	40	**100**	**100**	**100**	**100**	**100**	**100**	73.3	2.2
	80	**100**	**100**	**100**	**100**	**100**	**100**	94.9	6
2 g, 2 g, 2 g	5	**100**	**99.8**	**99.5**	**97.9**	85.5	53.8	15.4	3.2
	10	**100**	**100**	**100**	**100**	**99.5**	92.9	53.6	7.5
	20	**100**	**100**	**100**	**100**	**100**	**99.8**	91.8	32.4
	40	**100**	**100**	**100**	**100**	**100**	**100**	**100**	72.6
	80	**100**	**100**	**100**	**100**	**100**	**100**	**100**	94.9
3 g, 2 g, 2 g	5	**100**	**100**	**99.8**	**98.9**	**95.5**	70.4	37.9	7.4
	10	**100**	**100**	**100**	**100**	**99.8**	**98.5**	77.4	29.8
	20	**100**	**100**	**100**	**100**	**100**	**100**	**99.8**	68
	40	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**96.2**
	80	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
500 mg q24h	5	**100**	**100**	**100**	**100**	**100**	**97.3**	52.3	4
	10	**100**	**100**	**100**	**100**	**100**	**100**	92.3	9.1
	20	**100**	**100**	**100**	**100**	**100**	**100**	**99.8**	48.9
	40	**100**	**100**	**100**	**100**	**100**	**100**	**100**	83.5
	80	**100**	**100**	**100**	**100**	**100**	**100**	**100**	92.5
1 g q24h	5	**100**	**100**	**100**	**100**	**100**	**100**	**97.3**	51.5
	10	**100**	**100**	**100**	**100**	**100**	**100**	**100**	91.5
	20	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**99.8**
	40	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
	80	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

The bold values are >95%.

1 g q24h, a dosing regimen of 1 g once daily; 1 g, 1 g, 1 g, a dosing regimen of 1 g on Day 1, 1 g on Day 4 and 1 g on Day 6; 100% $fT_{>MIC}$, 100% probability to maintain unbound ceftriaxone concentration above the specified MIC; 2 g, 2 g, 2 g, a dosing regimen of 2 g on Day 1, 2 g on Day 4 and 2 g on Day 6 of a 7 day course; 3 g, 2 g, 2 g, a dosing regimen of 3 g on Day 1, 2 g, on Day 4 and 2 g on Day 6 of a 7 day course; 500 mg q24h, a dosing regimen of 500 mg once daily; Bili, serum bilirubin concentration; MIC, pathogenic minimum inhibitory concentration.

population suggests that dosing simulations based on total ceftriaxone concentrations and incorporating protein-binding data obtained from non-ESRD patients may underestimate the unbound ceftriaxone concentrations and increase the risk of toxicity. This finding highlights the value of using measured unbound ceftriaxone concentrations for pharmacokinetic studies in ESRD. Furthermore, the limited influence of serum albumin concentration on the pharmacokinetic model may be contributed by the absence of hypoalbuminemia in our patient cohort (only one patient had an albumin concentration <30 g/L, at 28 g/L).

Indigenous Australians are reported to have earlier onset of chronic kidney diseases and faster progression to ESRD, where 34% of ESRD patients are 50 years or younger, compared with 26% of their non-Indigenous comparators.[5] Consequently, many Indigenous Australians require hemodialysis for long periods of their lives, and this can result in a depletion of accessible veins available for fistula formation in the later stages of their dialysis journey—often leaving the only option for dialysis treatment to be performed using central venous access. The use of central venous catheterization carries a higher risk for line-associated infection and further complications.[16,37] In this light, vein preservation becomes vitally important, and frequent cannulation should be avoided to prevent injuries sustained on the veins. Therefore, post-dialysis doses should be considered so that antibiotics can be administered through a patient's fistula rather than a cannula.

We have identified several limitations in this study. Firstly, only plasma ceftriaxone concentrations were studied, which did not reflect ceftriaxone concentrations achieved in other bodily tissues; hence, results obtained may not be applicable in deep-seated infections such as endocarditis and meningitis. Future studies are needed to investigate the dosing requirement in these settings. Secondly, we were unable to assess the exact renal function of each participant because the serum creatinine concentrations were influenced by when dialysis was last administered. However, all participants had diagnosed ESRD, and this study is representative of a real-life cohort. Finally, we measured unbound ceftriaxone concentrations on plasma samples that had undergone a freeze-thaw process; despite care taken to allow re-equilibrium of the drug-protein binding, this may have impacted on the measurement of unbound concentrations.

In conclusion, we recommend the use of a ceftriaxone 2 g three-times-weekly post-dialysis regimen in patients requiring

Table 4. Probability of target attainment (%) of maintaining a toxicity ceftriaxone (total) concentration on the last day of a (A) 3 day and (B) 7 day ceftriaxone pharmacotherapy course

(A)

		Toxic concentration (mg/L)		
Dosing regimen	Bili (μmol/L)	100	150	200
1 g, 1 g, 1 g	5	0	0	0
	10	0	0	0
	20	0	0	0
	40	0	0	0
	80	0	0	0
2 g, 2 g, 2 g	5	0	0	0
	10	0	0	0
	20	0	0	0
	40	2.1	0	0
	80	33.8	0	0
3 g, 2 g, 2 g	5	0.1	0	0
	10	1.4	0	0
	20	17.6	0	0
	40	63.0	0.4	0
	80	90.5	25.1	0
500 mg q24h	5	0	0	0
	10	0	0	0
	20	0	0	0
	40	0	0	0
	80	1.3	0	0
1 g q24h	5	0.2	0	0
	10	10.7	0	0
	20	38.9	0	0
	40	81.2	5.7	0
	80	94.3	25.1	0.1
2 g daily	5	57.0	4.9	0
	10	93.9	37.2	0.5
	20	99.9	84.1	27.7
	40	100	98.5	67.2
	80	100	99.2	84.3

(B)

		Toxic concentration (mg/L)		
Dosing regimen	Bili (μmol/L)	100	150	200
1 g, 1 g, 1 g	5	0	0	0
	10	0	0	0
	20	0.7	0	0
	40	10.2	0	0
	80	46.1	0	0
2 g, 2 g, 2 g	5	3.5	0.2	0
	10	25.8	1.8	0
	20	73.9	8.2	0.2
	40	97.2	47.1	1.8
	80	100	85.9	33.1
3 g, 2 g, 2 g	5	3.8	0.5	0
	10	28	2.5	0
	20	76.2	11.0	0.7
	40	97.9	51.6	4.2
	80	100	90.2	39.7
500 mg q24h	5	0.2	0	0
	10	1.1	0	0
	20	4.6	0	0
	40	39.6	0.1	0
	80	83.9	1.9	0
1 g q24h	5	14.4	1.8	0
	10	59.6	4.9	0.4
	20	92.2	39.2	1.2
	40	100	86.0	26.3
	80	100	97.9	63.7
2 g daily	5	85.1	36.9	06.7
	10	100	85.8	41.7
	20	100	100	86.8
	40	100	100	100
	80	100	100	100

1 g q24h, a dosing regimen of 1 g once daily; 1 g, 1 g, 1 g, a dosing regimen of 1 g on Day 1, 1 g on Day 4 and 1 g on Day 6; 2 g q24h, a dosing regimen of 2 g once daily; 2 g, 2 g, 2 g, a dosing regimen of 2 g on Day 1, 2 g on Day 4 and 2 g on Day 6 of a 7 day course; 3 g, 2 g, 2 g, a dosing regimen of 3 g on Day 1, 2 g, on Day 4 and 2 g on Day 6 of a 7 day course; 500 mg q24h, a dosing regimen of 500 mg once daily; Bili, serum bilirubin concentration.

intermittent hemodialysis when treating bacterial infections with an MIC ≤1 mg/L. For patients with serum bilirubin concentrations ≥10 μmol/L, we recommend a 1 g three-times-weekly regimen. We do not recommend the administration of ceftriaxone during the dialysis session, particularly when a high-flux dialyzer is used. When compared with conventional daily dosing regimens, a three-times-weekly dosing strategy achieves maximally effective concentrations and exposures associated with a minimal likelihood of drug toxicity. Three-times-weekly dosing minimizes cannulation needs associated with once-daily dosing, which can reduce the longevity of veins required for future vascular access formation.

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Transparency declarations

None to declare.

Author contributions

D.T.: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, software, writing—original draft. B.B.Z.: data curation, investigation, methodology, project administration, writing—review and editing. C.T.: conceptualization, data curation, formal analysis, methodology, writing—review and editing. F.C.: conceptualization, methodology, writing—review and editing. C.S.: conceptualization, methodology, resources, writing—review and editing. B.P.: conceptualization, methodology, resources, writing—review and editing. A.A.: investigation, project administration, writing—review and editing. B.P.C.: conceptualization, data curation, investigation, project administration, writing—review and editing. S.Y.C.T.: conceptualization, methodology, writing—review and editing. S.J.: investigation, methodology, validation, writing—review and editing. S.C.W.: data curation, formal analysis, investigation, methodology, project administration, resources, software, validation, writing—review and editing. J.A.R.: conceptualization, formal analysis, funding acquisition, methodology, resources, software, supervision, validation, writing—review and editing. S.L.P.: conceptualization, data curation, formal analysis, funding acquisition, methodology, software, supervision, validation, writing—original draft, writing—review and editing.

Supplementary data

Tables S1, S2, S3A, S3B and Figure S1 are available as Supplementary data at *JAC* Online.

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