A population pharmacokinetic model-guided evaluation of ceftolozane/tazobactam dosing in critically ill patients undergoing continuous venovenous hemodiafiltration

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Abstract

The aim of this work was to describe optimised dosing regimens of ceftolozane/tazobactam for critically ill patients receiving continuous venovenous hemodiafiltration (CVVHDF). We conducted a prospective observational pharmacokinetic study in adult critically ill patients with clinical indications for ceftolozane/tazobactam and CVVHDF. Unbound drug concentrations were measured from serial pre-filter blood, post-filter blood and ultrafiltrate samples by a chromatographic assay. Population pharmacokinetic modelling and dosing simulations were performed using Pmetrics®. A four compartment pharmacokinetic model adequately described the data from six patients. The mean (± standard deviation [SD]) extraction ratio for ceftolozane and tazobactam were 0.76 ± 0.08 and 0.73 ± 0.1, respectively. The mean ± SD sieving coefficients were 0.94 ± 0.24 and 1.08 ± 0.30 respectively. Model estimated CVVHDF clearances were 2.7 ± 0.8 and 3.0 ± 0.6 L/h respectively. Residual non-CVVHDF clearances were 0.6 ± 0.5 and 3.3 ± 0.9 L/h, respectively. In the initial 24 h, doses as low as 0.75g 8-hourly enable fractional target attainment of ≥ 85% for empiric coverage against Pseudomonas aeruginosa considering 40 % fT>MIC target. For 100 % fT>MIC, at least 1.5 g 8-hourly is required. The median (interquartile range) steady state trough ceftolozane concentrations for simulated 1.5g and 3.0g 8-hourly regimens were 28 (21-42) and 56 (42-84) mg/L, respectively. The corresponding tazobactam concentrations were 6.1 (5.5-6.7) and 12.1 (11.0-13.4) mg/L, respectively. We suggest a front-loaded regimen with a single 3.0 g loading dose followed by 0.75 g 8-hourly for critically ill patients undergoing CVVHDF with study blood and dialysate flow rates.

Keywords: Ceftolozane/tazobactam, pharmacokinetics, renal replacement therapy, hemodiafiltration, CRRT
Introduction

Acute kidney injury (AKI) is a common complication of sepsis necessitating the use of renal replacement therapy (RRT) (1). RRT is delivered either intermittently or continuously. In unstable critically ill patients, continuous RRT (CRRT) in the form of continuous venovenous hemofiltration (CVVHF) or hemodiafiltration (CVVHDF) is commonly used for a better fluid control and hemodynamic stability (2, 3). The CVVHDF modality of CRRT is commonly used in some parts of the world (e.g. 54% in Australian and New Zealand intensive care units) (4).

Antibiotic dosing in critically ill patients undergoing CRRT is considered challenging. The extent of total drug clearance during CRRT is variable not only due to the different modalities and operational settings of CRRT used across different institutions, but also due to the variable residual renal and non-renal clearance pathways (5). The traditional dosing considerations in patients undergoing CRRT mainly focus on the notion of renal impairment and generally consider low doses without appropriately accounting for the substantial extracorporeal clearance, and thus risking under dosing (6-8). The risk of under dosing is particularly high in the initial phase of treatment compared to later in the course of therapy where the drug may accumulate to provide high exposure (9). However, inadequate antibiotic exposure during the initial critical phase of therapy is highly likely to result in treatment failure.

In a recent study (10), the use of CRRT was identified as an independent risk factor for treatment failure of ceftolozane/tazobactam in the treatment of Pseudomonas aeruginosa infections. Although the authors did not investigate why treatment failure was high during CRRT, they alluded to the fact that there is no clearly defined dosing recommendation for ceftolozane/tazobactam in the different forms of CRRT. In their study, all patients received
1.5 g every eight-hourly intermittent infusion, and the authors suggested increasing the dose to minimise risk of treatment failure. However, except few case reports (11-13), there is limited data to answer the question if under dosing was the reason for the increased treatment failure during CRRT, or if higher doses achieve appropriate exposure without risking unnecessary accumulation of the drug.

The aim of this work was, therefore, to describe optimised dosing regimens of ceftolozane/tazobactam in critically ill patients receiving CVVHDF based on a population pharmacokinetic model developed from simultaneous analysis of unbound concentrations in pre-filter patient plasma, post-filter plasma and RRT effluent during CVVHDF.

Results

Demographic and clinical characteristics of each study participant are given in Table 1. All patients received CVVHDF mode of RRT. RRT settings for each participant are summarised in Table 2. The mean (± standard deviation [SD]) extraction ratio for ceftolozane and tazobactam were 0.76 ± 0.08 and 0.73 ± 0.1, respectively. The mean ± SD sieving coefficients were 0.94 ±0.24 and 1.08 ± 0.30 respectively. CVVHDF clearances estimated by non-compartmental method were 2.92 ±0.6 L/h and 2.85 ± 0.6 L/h ceftolozane and tazobactam respectively.

A four-compartment model schematically described in Figure 1, with CVVHDF and non-CVVHD residual clearance from a pre-filter central compartment adequately described the data. This final structural model was used for dosing simulations as none of the available covariates improved model fit. Figures 2 and 3 depict the observed vs predicted plots for ceftolozane and tazobactam respectively. Supplemental figure 1 shows the visual predictive check plot for pre-filter patient plasma concentrations of both ceftolozane and tazobactam. Parameter estimates for the final models are given in Table 3. Model predicted CVVHDF
Filter clearances were similar to values determined from measured cumulative amount of the drugs in effluent bags. For the pharmacokinetic (PK)/pharmacodynamic (PD) target of 40% $fT_{>MAC}$, all simulated dosing regimens achieved PTA of $\geq 0.9$ for MIC values in the susceptible range ($\leq 4$ mg/L) during the first 24 hours of treatment. In addition, at PK steady state, all simulated dosing regimens achieve a PTA of $\geq 0.9$ for all targets when MIC values are $\leq 4$ mg/L (susceptible). However, during the first 24 hours post commencement of dosing, for higher PK/PD targets of 60 and 100% $fT_{>MIC}$ intermittent doses $\geq 0.75$ g q8h and 1.5 g q8h, respectively and continuous infusion doses $\geq 0.375g$ LD + $1.125$ g CI and 1.5g LD + 4.5g CI respectively were required to achieve PTA $\geq 0.9$ for MIC values in the susceptible range ($\leq 4$ mg/L). Extended infusion without a loading dose resulted in significantly lower PTA during the first 24 h compared to the corresponding intermittent infusion across all doses investigated.

Table 4 shows the cumulative fractional response (CFR) for ceftolozane against $P. aeruginosa$ EUCAST MIC distribution for exposure during the first 24 h of treatment. For the PK/PD target of 40% $fT_{>MIC}$, doses as low as 0.75g q8h achieved optimal CFR ($\geq 85$%) for empiric therapy. However, for the higher target of 100% $fT_{>MIC}$, either 1.5 g q8h, 3.0 g q8h, 3.0 g LD + 9.0 g CI or 1.5 g LD + 4.5 g CI was required to achieve optimal CFR for empiric therapy. For directed therapy on the other hand, all simulated doses achieved optimal CFR for up to 60% $fT_{>MIC}$ and doses as low as 0.75 g q8h achieved optimal CFR for 100% $fT_{>MIC}$. At steady state (data not shown), all simulated doses achieved $\geq 85$% CFR for empiric therapy and 100% CFR for directed therapy.

Supplemental table 1 summarises the probability of achieving selected tazobactam exposures of 20% $fT_{>1mg/L}$, 50% $fT_{>2mg/L}$ and 100% $fT_{>4mg/L}$ during the first 24 hours of dosing and at steady state. All simulated doses achieved 20% $fT_{>1mg/L}$. However, at least 0.75 g q8h was
required for 50% $fT_{>2mg/L}$ exposure. On the other hand, at least 1.5 g q8h or 3.0 g LD + 9.0 g CI were required for 100% $fT_{>4mg/L}$ exposures at steady state and during the first 24 hours, respectively.

Maximum concentrations of ceftolozane and tazobactam achieved at steady state from various simulated dosing regimens of ceftolozane/tazobactam in virtual population of critically ill patients (n=1000) receiving CVVHDF are summarised in Table 5. For both ceftolozane and tazobactam, doubling the dose resulted in doubling the steady state concentration.

**Discussion**

This is the first study describing the unbound population pharmacokinetics of ceftolozane and tazobactam in critically ill patients undergoing CVVHDF. We observed sieving coefficients that are consistent with previous findings for continuous hemofiltration and dialysis (14). The observed extraction ratios for unbound ceftolozane (0.76 ± 0.08) and tazobactam (0.73 ± 0.1) were comparable to a previous case report of 0.86 and 0.85 respectively by continuous hemofiltration (11). The model predicted CVVHDF clearance for ceftolozane (2.7± 0.8 L/h) is also in agreement with a previous case report of 2.4 L/h (12) for a patient with comparable RRT settings relative to the study patients (Table 2); blood flow rate of 200 mL/min, pre-dilution rate of 1000 mL/h, post-dilution rate of 750mL/h. The total estimated ceftolozane clearance during CVVHDF (3.3 L/h) is about half of the total ceftolozane clearance we recently described for critically ill patients without renal impairment (7.2 L/h, in press).

The relatively low clearance (longer half-life) during CVVHDF results in a prolonged time-to-pharmacokinetic steady state. Our dosing simulations revealed steady state was achieved only after 4 days for ceftolozane. This is important for dosing evaluation in that adequacy of exposure for PK/PD target attainment should be evaluated during the first 24 hours of
treatment together with assessment of extent of accumulation at steady state to avoid unnecessarily high concentration that potentially risk toxicity. Based on the first 24 h exposure and considering 40% $fT_{\text{MIC}}$ target, 0.75 g q8h is adequate for empiric initiation of therapy (Table 4). For susceptible pathogens (MIC $\leq$ 4 mg/L), this dose is also adequate to provide 100% $fT_{\text{MIC}}$ ceftolozane exposure. In addition, it also achieves (Supplemental table 1) previously recommend tazobactam exposures of 20% $fT_{1\text{mg/L}}$ and 50% $fT_{2\text{mg/L}}$ (14, 15).

These results are concordant with an in silico simulation study based on ex vivo data that recommended 0.75 g q8h dosing as an optimal regimen for continuous hemofiltration and dialysis (14). However, given that susceptibility data is usually not available at the initiation of therapy and that for the critically ill an initial empiric coverage at a higher target for ceftolozane (100% $fT_{\text{MIC}}$) is advantageous, our results (Table 4) suggest that a higher dose of 1.5 g q8h may be advantageous for initiation of therapy. The median (IQR) steady state trough concentrations with 1.5 g q8h dosing was 28 (21-42) mg/L. These concentrations are generally five to ten times the MIC breakpoint for $P. \text{aeruginosa}$ (4 mg/L). Therefore, these concentrations are generally acceptable given most experts consider trough concentrations above 10 times MIC as a cut off point for dose reduction of beta-lactam antibiotics, although not because of significant toxicity concerns, but more so unnecessarily high exposures (16). In addition, keeping concentration above 4 to 5 times the MIC has been shown to maximise the antibacterial effect of beta-lactams (17). Furthermore, given the poor reproducibility of MIC measurements, it is not uncommon to find an isolate considered susceptible at the breakpoint MIC (4 mg/L) is actually be subsequently found to be resistant with re-testing with an MIC higher by up to two dilutions (up to 16 mg/L) (18). Therefore, the steady state concentrations achieved with 1.5 g q8h dosing are generally acceptable.
A 1.5 g LD dose followed by 4.5 g CI may also provide similar exposure, with an added advantage of avoiding higher peak concentration with the intermittent regimen (Table 5) that may have no added benefit in maximising efficacy. This CI regimen achieved a median steady state concentration of 36 mg/L, which is just below the ten-times MIC cut off point. In previous case reports, no ceftolozane related adverse effects were observed at equivalent or higher concentrations (11, 13, 19). Thus, clinicians may choose to use continuous infusion if there is a particular clinical concern with increased peak concentrations during intermittent infusion. An alternative approach to ensure early exposure that maximises efficacy and at the same time minimise amount accumulating at steady state, is to use a front-loaded intermittent regimen with 1.5 g q8h for the first 24 hours followed by 0.75 g q8h that resulted in a median steady state trough concentration of 14 mg/L in our dosing simulation studies. Another convenient approach is also to use 3.0 g initial LD followed by 0.75 g q8h thereafter. These front loaded regimens will ensure adequate initial exposure while minimising unnecessary accumulation of the drug at steady state.

Although there is no clearly defined toxicity threshold for ceftolozane steady state concentration, a high dose of 3.0 g q8h appears to achieve unnecessarily high steady state ceftolozane concentrations in all modes of delivery during CVVHDF (Table 5). Similarly high ceftolozane concentrations were observed in a case study of CVVHDF, a peak and trough total concentrations of 163.9 mg/L (~ 131mg/L unbound concentration) and 79.4 mg/L (~ 64 mg/L unbound) respectively (12).

This study is not without limitations. Firstly, the sample size of six patients is small. We acknowledge that this may have limited the ability to identify covariate relationships with model parameters given the limited spread of covariate values in the data set. Secondly, there is a lack of a well-defined target exposure particularly for tazobactam. We used previously recommended targets 20% $fT_{>1mg/L}$ and 50% $fT_{>2mg/L}$ (14, 15). However, these exposures are
not concordant with the in vitro susceptibility testing protocol for beta-lactam/tazobactam combination antibiotics where tazobactam concentration is fixed at 4 mg/L. This limits the ability to relate in vitro susceptibility (MIC values) to clinical exposure if the targets we aim (20% \( fT_{>1mg/L} \) and 50% \( fT_{>2mg/L} \)) allow exposures less than 4 mg/L. Only 3.0 g q8h intermittent infusion or 3.0 g LD + 9.0 g CI was able to achieve high probability of greater than 4 mg/L exposure during the first 24 hours (Supplemental table 1). Finally, we acknowledge recommendations from this work only relate to similar CVVHDF settings summarised in Table 2.

In conclusion, ceftolozane and tazobactam are efficiently cleared by CVVHDF albeit at a much lower rate compared to patients with normal renal function. A front-loaded intermittent regimen with a single 3.0 g LD followed by 0.75 g q8h, or alternatively 1.5 g q8h for the first 24 hours followed by 0.75 g q8h thereafter would be appropriate to achieve adequate initial exposure and minimise more than necessary drug accumulation at steady state.

Methods

Study design and setting: This was a prospective observational population pharmacokinetic study of ceftolozane/tazobactam in critically ill patients undergoing CRRT. The study was conducted at the University of Queensland Centre for Clinical Research. Patients were recruited from the Royal Brisbane and Women’s Hospital (RBWH) quaternary referral intensive care unit (ICU; RBWH (HREC/16/QRBW/211) and the University of Queensland (No. 2016001368) human research ethics committees provided ethical clearance.

Patients: Adult patients (≥ 18 years) admitted to RBWH ICU, who were prescribed CRRT were enrolled if diagnosed with systemic infection known or suspected to be caused by an organism susceptible to ceftolozane/tazobactam. Patients were excluded if pregnant or had a
documented or suspected allergy to penicillins and cephalosporin. Each study participant or
his or her next of kin provided informed consent prior to enrolment.

**Ceftolozane/tazobactam dosing:** Per protocol, all patients received 1.5 g
ceftolozane/tazobactam (2:1 ratio) administered 8-hourly via intravenous infusion over 1 h.
Any alternative initial dosing or dose adaptation deemed necessary by the attending clinicians
was allowed.

**CRRT procedures:** The standard protocol for CRRT at the Royal Brisbane and Women
Hospital was followed. The general CRRT modality at RBWH was CVVHDF using the
Prismaflex® (Gambro, Lund, Sweden) hemodiafiltration machine with an AN69 ST150 or
ST100 (Gambro, Lund, Sweden) polyacrylonitrile filters (surface areas of 1.50 m² and 0.9 m²
respectively). The dialysis and replacement fluid were either Hemofiltration Solution (HF1)
(Gambro) or lactate-free Hemosol BO (Gambro). Replacement fluid was administered both
pre- and post-filter, or pre-filter only. The blood flow rates were 100 to 200 mL/min. The
dialysate flow rates were 1000 to 1500 mL/h. Replacement fluid rates were adjusted to each
patient’s specific requirements.

**Sample collection:** Blood samples were collected pre and post filter during a dosing interval
in lithium-heparin blood collection tubes. Pre-filter sampling times were, just before the dose,
during ceftolozane/tazobactam infusion at 15 min and 45 min, 15 minutes after end of 1 h
infusion, at 2 h, 3 h, 4 h, 5 h, 6 h, and 7 h post commencement of infusion, and at 8 h just
before the next dose. Post-filter samples were collected at 45 min, 2 h and 6 h after the start
of ceftolozane/tazobactam infusion. Ultrafiltrate samples from the effluent line were collected
at 1 h, 2 h, 4 h, 6 h and 8 h post commencement of ceftolozane/tazobactam infusion. In
addition, the ultrafiltrate volume in the effluent bag was measured at each of these time points
with ultrafiltrate samples taken from the bag for drug concentration measurement.
Ceftolozane and tazobactam assay

Unbound concentrations of ceftolozane and tazobactam in plasma and renal replacement therapy effluent were measured by a UHPLC-MS/MS method on a Shimadzu Nexera2 UHPLC system coupled to a Shimadzu 8050 triple quadrupole mass spectrometer (Kyoto, Japan). The unbound fraction of plasma was isolated by ultracentrifugation using Centrifree devices (Millipore, Tullagreen, Ireland). Sample (10 µL) was spiked with Phosphate Buffered Saline (pH 7.4) and internal standard (sulbactam & L-cefazolin) and acetonitrile. The stationary phase was C18 Ultra IBD, 100 x 2.1 mm, 3 μm column (Restek, Bellefonte, USA) operated at room temperature. Mobile phase A was 0.1% formic acid (v/v) in 10 mM ammonium formate, and mobile phase B was 100% acetonitrile with 0.1% formic acid (v/v). The mobile phase was delivered with gradient from 15% to 50% B at a flow rate of 0.3 mL/min for 5 min run-time and produced a backpressure of approximately 2800 psi. Ceftolozane was monitored by positive mode electrospray at MRMs of 667.00→199.15. Labelled cefazolin was monitored in positive mode at 457.85→326.05. Tazobactam and sulbactam were monitored by negative mode electrospray at MRMs 299.20→138.00 and 232.20→140.00, respectively. The calibration range for ceftolozane was 1 to 100 mg/L and for tazobactam was 0.5 to 100 mg/L. For ceftolozane at total concentrations of 160, 20 and 3 mg/L, the precision of the unbound analysis was 6.3, 6.2 and 8.2% with unbound fractions of 90%, 99% and 101%. For tazobactam at total concentrations of 80, 10 and 1.5 mg/L, the precision of unbound analysis was 6.2, 7.5 and 8.1% with unbound fractions of 89, 91 and 92%. The assay method was validated using the FDA criteria for bioanalysis (20).

Pharmacokinetic analysis

Initially non-compartmental analysis was performed to set the initial boundaries for relevant model parameters during subsequent population pharmacokinetic modelling. The extraction
ratio (ER), sieving coefficient (SC), and extracorporeal clearance by the CVVHDF machine (CL\textsubscript{CVVHDF}) were determined using the equations below based on observed concentrations:

\[
\text{Extraction Ratio} = \frac{\text{Concentration in postfilter blood sample}}{\text{Concentration in prefilter blood sample}} \quad \text{Equation 1}
\]

\[
\text{Sieving Coefficient} = \frac{\text{Effluent drug Concentration}}{\left[\left(\frac{\text{Prefilter plasma concentration}}{}\right) + \left(\frac{\text{Postfilter plasma concentration}}{}\right)\right]/2} \quad \text{Equation 2}
\]

\[
\text{CL}_{\text{CVVHDF}} = \frac{A_{\text{CVVHDF}}}{\text{AUC}_{0-8}} \quad \text{Equation 3}
\]

Where \( A_{\text{CVVHDF}} \) is the total amount of ceftolozane or tazobactam recovered in the ultrafiltrate and \( \text{AUC}_{0-8} \) is the area under the ultrafiltrate concentration-time curve determined by the linear trapezoidal rule.

Subsequently, a non-parametric population pharmacokinetic analysis was performed in R\textsuperscript{*} using the Pmetrics\textsuperscript{*} user interface to describe the unbound concentration-time profiles from pre-filter plasma, post-filter plasma and CVVHDF ultrafiltrate samples simultaneously. Three and four compartment models with first order CVVHDF and residual non-CVVHDF clearance were tested. CVVDHF clearance was from the compartment representing pre-filter samples. Residual clearance was tested on both compartments representing post- and pre-filter samples. All between compartment distributions were modelled as linear processes. Error models were based on standard deviation (SD) of observations [obs] available in Pmetrics as additive (Error= [SD\(^2 + \lambda^2\)]\(^{0.5}\)) and multiplicative (Error=SD*\(\gamma\)) models, where \( \lambda \) and \( \gamma \) represent process noise. In addition assay error was modelled with a first-degree polynomial function (Error= C0 + C1*[obs]). Plausible clinical covariates were tested on residual non-CVVHDF clearance, inter-compartmental clearances and volumes of pre and
post filter compartments. Available covariates considered for analysis include sex, height, weight, body mass index, body surface area, albumin concentration, serum creatinine, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, dialysate flow rate, transmembrane pressure, filter type, and blood flow rate.

Models were evaluated by the combination of diagnostic goodness of fit plots and statistics. Diagnostic plots included scatter plots of observed-versus-predicted concentrations, visual predictive check plots and normalised prediction distribution error (NPDE) versus time and output plots. Statistical evaluation of observed-versus-predicted concentrations was based on regression coefficient $r^2$, bias and imprecision. In Pmetrics, bias is defined as the mean weighted error of predicted minus observed concentrations, $\Sigma(\text{predicted}-\text{observed})/(\text{standard deviation})/N$, and imprecision is defined as the bias-adjusted, mean weighted squared error of predicted minus observed concentration, i.e., $\Sigma((\text{predicted}-\text{observed})^2)/(\text{standard deviation})^2)/N - \Sigma(\text{predicted}-\text{observed})/\text{standard deviations}/N$, where N is the number of observations/predictions. In addition, statistical model evaluation was performed based on objective function values including log-likelihood ratio (LLR), Akaike information criterion (AIC), and Bayesian information criterion (BIC). The LLR chi-squared test within Pmetrics was used for statistical comparison of nested models ($p < 0.05$ considered as significant).

The final model was used to perform Monte Carlo dosing simulations ($n=1000$) and assess the probability of target attainment (PTA) and extent of accumulation for selected dosing regimens. Simulated regimens included $0.75$ g, $1.5$ g and $3.0$ g ceftolozane/tazobactam (2:1 ratio) administered by 1 h intermittent infusion every eight hours (q8h), by 4 h extended infusion q8h and by continuous infusion (CI) of the total daily dose following a single loading dose (LD) given over 1 h. Additional dosing regimens simulated included, a front loaded intermittent regimen of $1.5$ g q8h for 24h followed by $0.75$ g q8h, and a single $3.0$ g LD.
followed by 0.75g q8h. For ceftolozane, the primary target for PTA assessment was 40% $f_{T>MIC}$, which is considered adequate for ~1log kill (21, 22). Secondary targets studied include 60 and 100% $f_{T>MIC}$. For tazobactam, on the other hand, we assessed against previously suggested targets of 20% $f_{T>1mg/L}$ (20% of the time above minimum effective concentration of 1mg/L) (15), and 50% $f_{T>2mg/L}$ (14). In addition, given in vitro susceptibility of beta-lactam/tazobactam combination is tested fixing tazobactam concentration at 4 mg/L (23), we assessed attainment of 100% $f_{T>4mg/L}$. Pre-filter patient plasma exposure was used for all PTA assessments.

CFR was estimated for ceftolozane, using *Pseudomonas aeruginosa* EUCAST MIC distribution (accessed August 2019), for both empiric and directed therapy. A CFR value of ≥85% was considered acceptable. The following equation 4 was used for CFR calculation.

$$\text{CFR} = \sum_{i=0.125}^{n} PTA_i \times F_i \quad \text{(Equation 4)}$$

Where $i$ is MIC category ranging from 0.125 to $n$; $n$ is 64 mg/L for empiric therapy and the EUCAST clinical breakpoint of 4 mg/L for directed therapy; $PTA_i$, PTA at each MIC category; $F_i$, the fraction of the bacterial population at each MIC category.
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Figure legends

Figure 1. Schematics of the structural pharmacokinetic model. $C_{\text{pre-filter}}(t)$, concentration in the pre-filter compartment at time $t$; $C_{\text{post-filter}}(t)$, concentration in the post-filter compartment at time $t$; $C_{\text{peripheral}}(t)$, concentration in the peripheral compartment at time $t$; $C_{\text{effluent}}(t)$, concentration in the effluent compartment at time $t$; $\text{CL}_{\text{CVVHDF}}$, clearance by continuous venovenous hemodiafiltration; $\text{CL}_{\text{residual}}$, residual non-CVVHDF clearance; $V_{\text{post}}$, volume of the post-filter compartment; $V_{\text{pre}}$, volume of the pre-filter compartment; $K_{12}$, rate constant for transfer from pre-filter to post-filter compartment; $K_{21}$, rate constant for transfer from post-filter to pre-filter compartment; $K_d$, rate constant for transfer out of the effluent compartment (‘drainage’); $V_{\text{effluent}}$, volume of the effluent compartment; $Q_{\text{pre, inter}}$ compartmental clearance between pre-filter compartment and the peripheral compartments; $Q_{\text{post, inter}}$ compartmental clearance between post-filter and peripheral compartments; $V_{\text{peripheral}}$, volume of the peripheral compartment.

Figure 2. Observed-versus-predicted concentrations diagnostic plots for ceftolozane.

Figure 3. Observed-versus-predicted concentrations diagnostic plots for tazobactam.
Table 1. Demographic and clinical characteristics of study participants

| Patient No. | Sex | Age (years) | Weight (Kg) | Serum Creatinine (μmol/litre) | Albumin (g/L) | ALT (IU/mL) | AST (IU/mL) | ALP (IU/mL) | Bilirubin (μmol/L) | APACHE II | SOFA | Site of infection | Organism                                      |
|-------------|-----|-------------|-------------|------------------------------|---------------|-------------|-------------|-------------|-------------------|------------|------|----------------|-----------------------------------------------|
| 1           | Male | 23          | 65          | 137                          | 27            | 33          | 35          | 134         | 13                | 40         | 7    | Blood & Lung    | Carbapenem resistant *P. aeruginosa Serratia marcescens Klebsiella pneumoniae |
| 2           | Male | 66          | 65          | 156                          | 32            | 1440        | 762         | 134         | 55                | 29         | 13   | Blood          | *P. aeruginosa Stenotrophomonas maltophilia Candida albicans |
| 3           | Female | 65       | 80          | 77                           | 25            | 44          | 78          | 126         | 10                | 37         | 14   | Unknown        | S. marcescens Staphylococcus epidermidis |
| 4           | Male | 65          | 103         | 139                          | 24            | 39          | 68          | 195         | 36                | 22         | 6    | Blood & Lung    | Staphylococcus cohnii Staphylococcus epidermidis |
| 5           | Male | 58          | 65          | 75                           | 26            | 35          | 19          | 116         | 32                | 35         | 10   | Blood           | Staphylococcus hemolyticus Staphylococcus epidermidis |
| 6           | Male | 58          | 100         | 272                          | 29            | 131         | 569         | 125         | 253               | 24         | 16   | Lung            | Stenotrophomonas maltophilia |

Median: 61.5 72.5 138 26.5 41.5 73 130 34 32 11.5
Q1: 58 65 92 25.25 36 43.25 125.25 17.75 25.25 7.75
Q3: 65 95 151.75 28.5 109.25 446.25 134 50.25 36.5 13.75

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, Alkaline phosphatase; APACHE II, Acute Physiology and Chronic Health Evaluation II Score; SOFA, Sequential Organ Failure Assessment Score; *, suspected; Q1, first quartile; Q3, third quartile
Table 2. Renal replacement therapy settings for the study participants

| Patient No. | Filter type | Filter age (h) | Blood flow rate (mL/min) | Dialysate flow rate (mL/h) | Pre-filter dilution rate (mL/h) | Post-filter dilution rate (mL/h) | Target fluid removal (mL/h) | Haematocrit |
|-------------|-------------|----------------|--------------------------|----------------------------|-------------------------------|-------------------------------|---------------------------|-------------|
| 1           | ST100       | 14             | 150                      | 1000                       | 1800                          | 200                           | 70                        | 0.22        |
| 2           | ST150       | 15             | 100                      | 1000                       | 1167                          | 500                           | 220                       | 0.3         |
| 3           | ST100       | 17            | 200                      | 1500                       | 200                           | 100                           | 30                        | 0.24        |
| 4           | ST150       | 31            | 100                      | 1500                       | 1500                          | 1000                          | 220                       | 0.25        |
| 5           | ST100       | 38             | 150                      | 1500                       | 100                           | 100                           | 200                       | 0.25        |
| 6           | ST150       | 9              | 200                      | 1000                       | 1800                          | 500                           | 70                        | 0.23        |

ST100, AN69 (acrylonitrile and sodium-methallylsulfonate copolymer) hemofilter with surface area of 1m²; ST150, AN69 hemofilter with surface area of 1.5m²

Table 3. Parameter estimates for the final ceftolozane and tazobactam models

| Parameter (unit)          | Ceftolozane | Shrink (%) | Tazobactam | Shrink (%) |
|---------------------------|-------------|------------|------------|------------|
| CL<sub>CVVHDF</sub> (L/h) | 2.659       | 0.783      | 0.00       | 2.973      | 0.603      | 0.06       |
| Cl<sub>residual</sub> (L/h) | 0.596       | 0.504      | 0.00       | 3.254      | 0.867      | 0.011      |
| V<sub>post</sub> (L)      | 17.578      | 10.871     | 0.00       | 19.685     | 14.382     | 0.010      |
| V<sub>pre</sub> (L)       | 25.184      | 7.499      | 0.00       | 28.206     | 6.603      | 0.126      |
| K<sub>12</sub> (h<sup>-1</sup>) | 0.43        | 0.718      | 0.00       | 0.561      | 0.638      | 0.092      |
| K<sub>21</sub> (h<sup>-1</sup>) | 0.676       | 0.908      | 0.00       | 1.01       | 1.01       | 0.013      |
| V<sub>effluent</sub> (L)  | 1.596       | 0.495      | 0.00       | 1.584      | 0.483      | 0.013      |
| Q<sub>pre</sub> (L/h)     | 2.178       | 0.801      | 0.00       | 2.609      | 1.561      | 0.006      |
| Q<sub>post</sub> (L/h)    | 0.834       | 1.863      | 0.00       | 2.547      | 2.455      | 0.009      |
| V<sub>peripheral</sub> (L) | 73.379     | 39.042     | 0.00       | 77.196     | 32.267     | 0.011      |

SD, standard deviation; CL<sub>CVVHDF</sub>, clearance by continuous venovenous hemodiafiltration; Cl<sub>residual</sub>, residual non-CVVHDF clearance; V<sub>post</sub>, volume of the post-filter compartment; V<sub>pre</sub>, volume of the pre-filter compartment; K<sub>12</sub>, rate constant for transfer from pre-filter to post-filter compartment; K<sub>21</sub>, rate constant for transfer from post-filter to pre-filter compartment; K<sub><sub>effluent</sub></sub>, volume of the effluent compartment; Q<sub>pre</sub>, inter compartmental clearance between pre-filter compartment and peripheral compartments; Q<sub>post</sub>, inter compartmental clearance between post-filter and peripheral compartments; V<sub>peripheral</sub>, volume of the peripheral compartment
Table 4. Cumulative fractional response against Pseudomonas aeruginosa EUCAST MIC distribution for exposure during the first 24 hours of treatment

| Dosing regimen      | CFR by PK/PD target for empiric therapy | CFR by PK/PD target for directed therapy |
|---------------------|-----------------------------------------|------------------------------------------|
|                     | 40% T>MIC | 60% T>MIC | 100% T>MIC | 40% T>MIC | 60% T>MIC | 100% T>MIC |
| 0.375 g q8h         | 0.82   | 0.79   | 0.65       | 0.99     | 0.96     | 0.80       |
| 0.375 g 4h EI q8h   | 0.82   | 0.79   | 0.24       | 0.99     | 0.96     | 0.29       |
| 0.375 g LD + 1.125 g CI | 0.83 | 0.83   | 0.68       | 1.00     | 1.00     | 0.83       |
| 0.75 g q8h          | 0.86   | 0.84   | 0.77       | 1.00     | 1.00     | 0.94       |
| 0.75 g 4h EI q8h    | 0.86   | 0.86   | 0.51       | 1.00     | 1.00     | 0.62       |
| 0.75 g LD + 2.25 g CI | 0.86 | 0.86   | 0.79       | 1.00     | 1.00     | 0.96       |
| 1.5 g q8h           | 0.87   | 0.87   | 0.85       | 1.00     | 1.00     | 1.00       |
| 1.5 g 4h EI q8h     | 0.87   | 0.87   | 0.69       | 1.00     | 1.00     | 0.84       |
| 1.5 g LD + 4.5 g CI | 0.87   | 0.87   | 0.86       | 1.00     | 1.00     | 1.00       |
| 1.5 g LD for 24h + 0.75 g q8h | 0.87 | 0.87   | 0.85       | 1.00     | 1.00     | 1.00       |
| 3.0 g q8h           | 0.90   | 0.88   | 0.86       | 1.00     | 1.00     | 1.00       |
| 3.0 g 4h EI q8h     | 0.90   | 0.88   | 0.79       | 1.00     | 1.00     | 0.96       |
| 3.0 g LD+ 9.0 g CI  | 0.92   | 0.91   | 0.87       | 1.00     | 1.00     | 1.00       |
| 3.0 g LD + 0.75 g q8h | 0.87 | 0.87   | 0.86       | 1.00     | 1.00     | 1.00       |

PK, pharmacokinetic; PD, pharmacodynamic; CFR, cumulative fractional response; EI, extended infusion; q8h, every eight hour intermittent infusion (1 hour); % T>MIC, percentage of time free drug concentration is above the minimum inhibitory concentration; *, CFR < 85%; +, CFR ≥ 85%; LD, loading dose over 1 hour; CI, continuous infusion over 24 hours.
Table 5. Maximum concentrations of ceftolozane and tazobactam achieved at steady state from various simulated dosing regimens of ceftolozane/tazobactam in virtual population of critically ill patients receiving continuous venovenous hemodiafiltration.

| Dosing regimens | Median (IQR) steady state ceftolozane concentrations (mg/L) at | Median (IQR) steady state tazobactam concentrations (mg/L) at |
|-----------------|-------------------------------------------------------------|-------------------------------------------------------------|
|                 | End of infusion | Trough /Css | End of infusion | Trough /Css |
| 0.375g q8h      | 13 (12-19)      | 7 (5-10)    | 4.4 (4.1-5.1) | 1.5 (1.3-1.8) |
| 0.375g 4h EI q8h| 11 (9-16)       | 8 (6-11)    | 3.1 (2.8-3.5) | 1.8(1.8-2.0) |
| 0.375g LD + 1.125 g CI | 9 (7-13)    |              | 2.5 (2.2-2.8) |              |
| 0.75g q8h       | 27 (24-39)      | 14 (10-21)  | 8.8 (8.2-10.1)| 3.0 (2.7-3.4) |
| 0.75g 4h EI q8h | 22 (18-31)      | 16 (12-23)  | 5.7 (6.1-7.0) | 3.5 (3.2-3.9) |
| 0.75g LD + 2.25g CI | 18 (14-26) |              | 5 (4.5-5.4)  |              |
| 1.5g q8h        | 54 (47-78)      | 28 (21-42)  | 17.5 (16.4-20.2)| 6.1 (5.5-6.7) |
| 1.5g 4h EI q8h  | 44 (37-63)      | 31 (23-45)  | 12.3 (11.6-14) | 7.0 (6.4-7.8) |
| 1.5g LD + 4.5g CI | 36 (30-53) |              | 9.7 (9.1-10.8) |              |
| 3.0 g q8h       | 107 (95-155)    | 56 (42-84)  | 35.0 (32.8-40.4) | 12.1 (11.0-13.4) |
| 3.0 g 4h EI q8h | 89 (74-126)     | 62 (47-90)  | 24.6(23.3-28.0) | 14.1 (12.9-15.5) |
| 3.0 g LD + 9.0g CI | 73 (59-106) |              | 19.3 (18.2-21.6) |              |

IQR, interquartile range; Css, steady state concentration; q8h, every eight hour intermittent infusion (1hour); EI, extended infusion; LD, loading dose over 1 hour; CI, continuous infusion over 24 hours.
