Population Pharmacokinetics of Unbound Ceftolozane and Tazobactam in Critically Ill Patients without Renal Dysfunction

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ABSTRACT
Evaluation of dosing regimens for critically ill patients requires pharmacokinetic data in this population. This prospective observational study aimed to describe the population pharmacokinetics of unbound ceftolozane and tazobactam in critically ill patients without renal impairment and to assess the adequacy of recommended dosing regimens for treatment of systemic infections. Patients received 1.5 or 3.0 g ceftolozane-tazobactam according to clinician recommendation. Unbound ceftolozane and tazobactam plasma concentrations were assayed, and data were analyzed with Pmetrics with subsequent Monte Carlo simulations. A two-compartment model adequately described the data from twelve patients. Urinary creatinine clearance (CLcr) and body weight described between-patient variability in clearance and central volume of distribution (V), respectively. Mean ± standard deviation (SD) parameter estimates for unbound ceftolozane and tazobactam, respectively, were CL of 7.2 ± 3.2 and 25.4 ± 9.4 liters/h, V of 20.4 ± 3.7 and 32.4 ± 10 liters, rate constant for distribution of unbound ceftolozane or tazobactam from central to peripheral compartment (Kcp) of 0.46 ± 0.74 and 2.96 ± 8.6 h⁻¹, and rate constant for distribution of unbound ceftolozane or tazobactam from peripheral to central compartment (Kpc) of 0.39 ± 0.37 and 26.5 ± 8.4 h⁻¹. With dosing at 1.5 g and 3.0 g every 8 h (q8h), the fractional target attainment (FTA) against Pseudomonas aeruginosa was ≥85% for directed therapy (MIC ≤ 4 mg/liter). However, for empirical coverage (MIC up to 64 mg/liter), the FTA was 84% with the 1.5-g q8h regimen when creatinine clearance is 180 ml/min/1.73 m², whereas the 3.0-g q8h regimen consistently achieved an FTA of ≥85%. For a target of 40% of time the free drug concentration is above the MIC (40% fT > MIC), 3g q8h by intermittent infusion is suggested unless a highly susceptible pathogen is present, in which case 1.5-g dosing could be used. If a higher target of 100% fT > MIC is required, a 1.5-g loading dose plus a 4.5-g continuous infusion may be adequate.

KEYWORDS ceftolozane, critically ill, dosing, intensive care unit, population pharmacokinetics, tazobactam

Ceftolozane-tazobactam is the most active beta-lactam antibiotic against Pseudomonas aeruginosa that is currently available in the market (1). Susceptibility surveillance programs report that the majority of P. aeruginosa clinical isolates (97.5%) remain susceptible (2). The current approved indications are treatment of complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI) (3), and, more recently, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. Since approval in 2014, its use has not be restricted to these indications, with some documented off-label uses against multidrug-resistant (MDR) Pseudomonas in-
Infections, including septicemia/bacteremia (4–6) and possibly extending to other relatively rare infections, including meningitis/ventriculitis. Indeed, some expert opinion has suggested that the place in therapy could encompass all infections susceptible to this agent that are caused by MDR *Pseudomonas* and other extended-spectrum-beta-lactamase-producing Gram-negative bacilli, where it could be considered as a carbapenem-sparing alternative (7). Although most of the off-label use case reports demonstrate successful ceftolozane-tazobactam therapy against multidrug-resistant strains of *P. aeruginosa*, including those with carbapenem resistance, unfortunately, some of the reports also highlight a potential risk of emergence of resistance during treatment. For example, in the treatment of MDR *P. aeruginosa* pneumonia, Katchanov et al. (4) reported the emergence of very high resistance to ceftolozane-tazobactam during the course of therapy. Escolà-Vergé et al. (6) also reported development of resistance during therapy with both the low-dose (1.5 g every 8 h [q8h] for urinary tract and soft tissue infections) and high-dose (3.0 g every 8 h for respiratory infections) regimens, with an increase in MIC ranging from 8-fold to $>$85-fold.

The development of resistance during treatment is likely to be multifactorial. In intensive care unit (ICU) patients, subtherapeutic exposure from standard doses of antibiotics is one of the major contributing factors to emergence of resistance (8). Numerous clinical studies have reported subtherapeutic antibiotic concentrations in ICU patients across different antibiotic classes while using standard dosing regimens (9, 10). This is related to marked changes in the pharmacokinetics (PK) of antibiotics in the critically ill arising from disease-related physiological changes, primarily due to an intense systemic inflammatory response syndrome (SIRS) that is triggered by infectious or noninfectious insults such as sepsis, septic shock, burns, and trauma (10–12). During the progression of SIRS, numerous endogenous inflammatory mediators can cause a hyperdynamic state characterized by high cardiac output, increased renal blood flow, and glomerular hyperfiltration, which ultimately increase clearance (CL) of renally cleared antibiotics (13). In addition, SIRS can cause a capillary leak syndrome and consequent fluid shift into interstitial space, which in turn increases the volume of distribution of hydrophilic antibiotics and thereby decrease plasma/tissue concentrations (14). In patients with hypalbuminemia, reduced plasma-oncotic pressure further augments fluid shifts, leading to increases in volume of distribution for some drugs. Hypoalbuminemia also results in a substantial increase in the unbound plasma concentration, particularly for highly protein-bound antibiotics, which means that more drug distributes into the interstitial space, with the increased fluid shift thereby accelerating the expansion in volume of distribution (15). However, although the influence of hypoalbuminemia has been described for highly protein-bound drugs, it is less frequently reported with drugs that are protein bound at low levels. Nevertheless, regardless of their protein binding, the PK of hydrophilic antibiotics, such as the beta-lactams, that normally distribute into the extracellular water and undergo predominantly renal elimination often change because of critical illness (11).

The clinical formulation of ceftolozane-tazobactam (Zerbaxa) comprises the combination of ceftolozane sulfate (molecular weight of 764.77) and tazobactam sodium (molecular weight of 322.28) in a 2:1 ratio, both of which are freely soluble in water (16). Owing to these physicochemical properties, the distribution of ceftolozane and tazobactam is generally limited to extracellular water, and their elimination is predominantly via renal excretion (17). These properties make ceftolozane-tazobactam vulnerable to disease-related PK alterations in the critically ill (11). It is now well established that designs of dosing regimens for use in the critically ill population that are based on dose finding/PK studies in healthy volunteers and/or noncritically ill patient populations do not always result in optimal regimens for use in ICU patients (10). It is therefore very important to assess dose recommendations for new agents like ceftolozane-tazobactam based on clinical PK data in this specific patient population.

The aim of this study was, therefore, to describe the population PK of unbound ceftolozane and tazobactam in critically ill patients without renal impairment and to assess the adequacy of recommended dosing regimens.
**RESULTS**

Patient demographics and clinical data are summarized in Table 1. From twelve critically ill patients, 133 unbound concentration-time data points were available for population pharmacokinetic analysis. A two-compartment structural model with linear elimination resulted in the lowest objective function values and best goodness-of-fit plots (log-likelihood ratio [LLR] of 723) compared to those of a one-compartment structural model (LLR of 795). Covariate analysis showed that ceftolozane and tazobactam clearance linearly increased with an increase in urinary creatinine clearance (CL\text{CR}). The final covariate model for clearance of both ceftolozane and tazobactam was expressed as CL = intercept + slope · CL\text{CR}, where CL\text{CR} is measured urinary creatinine clearance. Total body weight (WT) was related to volume of distribution of the central compartment (V\text{c,1}) for both ceftolozane (V\text{c,1} = V · WT/80) and tazobactam (V\text{c,1} = V · WT/80^{0.75}) where V is the typical value of the central volume of distribution. The introduction these covariates into the structural model substantially reduced the LLR to 711. Parameter estimates for the final models

| TABLE 1 Characteristics of study participantsa |
|-----------------------------------------------|
| **Characteristic**                           | **n (%) or median (IQR)** |
| Age (yr)                                      | 56 (52–61)                |
| Sex                                           |                           |
| Male                                         | 4 (33)                    |
| Female                                        | 8 (67)                    |
| Body mass index (kg/m²)                      | 28.5 (22.1–32.9)          |
| Wt (kg)                                      | 79.5 (64–99)              |
| Serum creatinine (µmol/liter)                | 46 (39–77)                |
| Urinary creatinine clearance (ml/min/1.73 m²) | 107 (74–145)              |
| Albumin (g/liter)                            | 25 (19–28)                |
| Alanine transaminase (IU/ml)                 | 35 (23–45)                |
| Aspartate transaminase (IU/ml)               | 37 (30–67)                |
| Alkaline phosphatase (IU/ml)                 | 102 (75–222)              |
| Total bilirubin (µmol/liter)                 | 12 (7–26)                 |
| APACHE II score (on admission)               | 19.5 (16–26)              |
| SOFA score                                   | 6 (3–8)                   |
| Site/source of infection                     |                           |
| Blood                                        | 2 (17)                    |
| CNS abscess                                  | 3 (23)                    |
| Intra-abdominal                              | 3 (27)                    |
| Lung                                         | 9 (75)                    |
| Urinary tract                                | 1 (8)                     |
| Vascular access                              | 1 (8)                     |
| Patients with positive culture               | 12 (100)                  |
| Organism isolated                            |                           |
| *Acinetobacter baumannii* complex            | 1 (8)                     |
| *Aspergillus flavus* complex                 | 1 (8)                     |
| *Candida albicans*                           | 3 (27)                    |
| *Candida glabrata* complex                   | 1 (8)                     |
| *Citrobacter koseri*                        | 1 (8)                     |
| *Enterobacter cloacae*                       | 2 (17)                    |
| *Enterococcus faecium*                       | 1 (8)                     |
| *Escherichia coli*                           | 3 (27)                    |
| *Haemophilus influenzae*                     | 1 (8)                     |
| *Klebsiella pneumoniae*                      | 1 (8)                     |
| *Proteus mirabilis*                          | 1 (8)                     |
| *Pseudomonas aeruginosa*                     | 2 (17)                    |
| Staphylococci                                | 1 (8)                     |
| *Staphylococcus epidermis*                   | 1 (8)                     |
| *Streptococcus salivarius*                   | 1 (8)                     |

aAbbreviations: IQR, interquartile range; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; CNS, central nervous system.
are given in Table 2. The individual and population predicted versus observed unbound concentration plots for ceftolozane and tazobactam are given in Fig. 1. A visual predictive check plot based on 1,000 simulations with the final model is given in Fig. 2. 

The probability of target attainment (PTA) for ceftolozane, considering the median urinary creatinine clearance (108 ml/min/1.73 m²) and body weight (80 kg) of the study population, for different dosing regimens during the first 24 h and at steady state from 48 to 72 h is given in Table 3 by MIC for different targets (40, 60, and 100% \( f_{T}/H_{MIC} \)). Generally, intermittent dosing regimens of ceftolozane-tazobactam (1.5 g q8h and 3.0 q8h) were adequate to achieve 100% PTA, well above the highest anticipated clinical breakpoint of susceptibility (4 mg/liter for \( P. aeruginosa \)), for 40% and 60% \( f_{T}/H_{MIC} \) targets. For the 100% \( f_{T}/H_{MIC} \) target, the 1.5-g q8h intermittent regimens achieved a 90% PTA for an MIC of 2 mg/liter and the 3.0-g q8h regimens achieved a 90% PTA up to the \( P. aeruginosa \) clinical breakpoint (MIC ≤ 4 mg/liter). Loading dose (LD) plus continuous infusion (CI) regimens (1.5-g LD plus 4.5-g CI and 3.0-g LD plus 9-g CI) were able to provide optimal exposure (≥90% PTA) up to MICs of 8 mg/liter and 16 mg/liter, respectively. The regimen of a 3.0-g LD plus 9.0-g CI in particular achieved high steady-state ceftolozane concentrations of 22.4 (±6.7) and 38 (±11) mg/liter for augmented (180 ml/min/1.73-m²) and normal (100 ml/min/1.73-m²) creatinine clearance values, respectively. On the other hand, for tazobactam, all simulated dosing regimens had a 100% probability of achieving the recommended target of 20% \( f_{T}/H_{MIC} \). Table 4 present the FTA for ceftolozane against the \( P. aeruginosa \) EUCAST MIC distribution, considering steady-state exposure, for increasing values of urinary creatinine clearance. For directed therapy, i.e., for isolates with MICs within the susceptibility range, the 1.5-g q8h intermittent regimen achieved the optimal FTA (>85%) even in patients with urinary creatinine clearance as high as 180 ml/min/1.73 m², except when targeting a 100% \( f_{T}/H_{MIC} \) whereas the 3.0-g q8h dosing regimen achieve the optimal FTA for all targets and high creatinine clearance values for directed therapy. On the other hand, for empirical coverage against the entire MIC distribution, the 1.5-g q8h regimen appears to be suboptimal in patients with high creatinine clearance (>140 ml/min/1.73 m²) when considering the standard target of 40% \( f_{T}/H_{MIC} \) and even in patients with creatinine clearance as low as 100 ml/min/1.73 m² if high PK/pharmacodynamic (PD) targets (>60% \( f_{T}/H_{MIC} \)) are required. Both low- and higher-dose continuous infusion regimens (Table 4) achieved 100% FTA for both empirical and directed therapy against the \( P. aeruginosa \) MIC distribution.

### Table 2: Pharmacokinetic parameter estimates for the final covariate model

| Drug and parameter | Mean  | SD   | CV (%) |
|--------------------|-------|------|--------|
| **Ceftolozane**    |       |      |        |
| Intercept          | 0.86  | 0.69 | 80     |
| Slope              | 6     | 3.3  | 54     |
| V (liters)         | 20.4  | 3.7  | 18     |
| Kcp (h⁻¹)          | 0.46  | 0.74 | 159    |
| Kpc (h⁻¹)          | 0.39  | 0.37 | 94     |
| CL (liters/h)      | 7.2   | 3.2  | 45     |
| **Tazobactam**     |       |      |        |
| Intercept          | 6.9   | 5.6  | 81     |
| Slope              | 17.5  | 6.9  | 40     |
| V (liters)         | 32.4  | 10   | 31     |
| Kcp (h⁻¹)          | 2.96  | 8.69 | 293    |
| Kpc (h⁻¹)          | 26.5  | 8.4  | 32     |
| CL (liters/h)      | 25.4  | 9.4  | 37     |

**Abbreviations**: CV, coefficient of variance; V, typical volume of distribution of the central compartment; Kcp, rate constant for distribution of unbound ceftolozane or tazobactam from central to peripheral compartment; Kpc, rate constant for distribution of unbound ceftolozane or tazobactam from peripheral to central compartment; CL, clearance. 

**Value calculated for the study population.**
DISCUSSION

In this study, we have described the population pharmacokinetics of ceftolozane and tazobactam based on measured unbound concentrations to enable a more robust assessment of the adequacy of recommended dosing regimens for critically ill patients. Given that the free concentration of antibiotics is responsible for the clinical effect, assessment based on direct measurement of unbound concentrations avoids a significant confounding factor when based on total concentration corrected for protein binding. This is because, first, correction for protein binding is often done using a single reported binding ratio uniformly for all patients, disregarding significant between-patient and within-patient variability observed for many drugs (18). Second, there have been discrepancies in the reported binding ratios for ceftolozane in humans (negligible [19, 20], 6.3% [21], and 16 to 21% [17]) and in preclinical studies (5.3% [22] and <5% [23]). Third, binding ratios reported for less sick patients or healthy individuals may not reflect those for critically ill patients because of the high variability in plasma protein concentration and altered binding properties in the critically ill (24, 25). Therefore, the use of unbound pharmacokinetics in this study enables a more reliable prediction of optimal ceftolozane-tazobactam dosing.

FIG 1 Observed versus predicted goodness-of-fit plots for unbound ceftolozane and tazobactam concentrations. Top panel, population predicted concentrations; bottom panel, individual predicted concentrations.
The dosing regimen for the approved indication of ceftolozane-tazobactam in cUTI and IAI, a 1.5-g q8h intermittent infusion, achieved high and optimal PTA when considering 40% and 60% $f_{T_{\text{MIC}}}$ against MICs as high as 8 mg/liter (Table 3). This is well above the EUCAST Enterobacterales (1-mg/liter) and P. aeruginosa (4-mg/liter) clinical breakpoints. For the 40% and 60% $f_{T_{\text{MIC}}}$ targets, the 1.5-g q8h regimen also achieves optimal exposure in patients with high creatinine clearance for directed therapy against susceptible P. aeruginosa (Table 4). These results are concordant with previous assessments of the approved dose considering a 32.2% $f_{T_{\text{MIC}}}$ target (26, 27). Data from animal model studies show that $30\text{ to }40\% f_{T_{\text{MIC}}}$ exposure is adequate to achieve a 1- to 2-log kill at 24 h (23, 28), and therefore, a 1.5-g dose is generally appropriate for most patients with susceptible infections. However, in critically ill patients it may be prudent to target a more aggressive exposure of 100% $f_{T_{\text{MIC}}}$ (10). Considering this target, the 1.5-g q8h regimen achieved optimal PTA only against MICs of $\leq 2 \text{ mg/liter}$ (for susceptible P. aeruginosa) (Table 4). In other words, this dosage is likely to result in suboptimal exposure in most critically ill patients with augmented renal clearance, even against susceptible P. aeruginosa (13). For empirical coverage against the entire P. aeruginosa MIC distribution, exposures are highly likely to be suboptimal even in patients with average creatinine clearance (e.g., 100 ml/min/1.7 m$^2$) (Table 4) if a 100% $f_{T_{\text{MIC}}}$ is the desired target.

On the other hand, the 3.0-g q8h intermittent regimen currently licensed for nosocomial pneumonia achieved very high PTA (≥90%) up to an MIC of 8 mg/liter even when considering the aggressive dosing target recommended for the critically ill (100% $f_{T_{\text{MIC}}}$) (Table 3). It also achieved the optimal FTA for susceptible pathogens even in patients with augmented renal clearance (Table 4). Therefore, our data strongly suggest that the 3.0-g q8h intermittent infusion regimen is preferable for the treatment of susceptible infections in the critically ill. This is in agreement with Xiao et al., who similarly observed consistently high exposure with a 3.0-g q8h intermittent regimen in their in silico simulation study (29). However, for empirical coverage of a suspected P. aeruginosa infection, the 3.0-g q8h regimen achieves a relatively low FTA in patients with severe augmented renal clearance (FTA of 80% for creatinine clearance of 180 ml/min/1.73 m$^2$) when targeting 100% $f_{T_{\text{MIC}}}$ (Table 4). This may be particularly problematic when using ceftolozane-tazobactam in the management of MDR Pseudomonas infections, where the strains may be less susceptible to ceftolozane-tazobactam (30, 31).

To ensure adequate empirical coverage of 100% $f_{T_{\text{MIC}}}$ while susceptibility data are pending, the use of continuous-infusion regimens may be highly advantageous. In this study, a 1.5-g loading dose followed by a 4.5-g continuous infusion was adequate to achieve an FTA of ≥85% even in patients with high creatinine clearance (Table 4). For this continuous-infusion regimen, the mean (± standard deviation [SD]) of simulated...
### TABLE 3  Probability of target attainment for ceftolozane from different ceftolozane-tazobactam dosing regimens<sup>a</sup>

| PK/PD target | Dose          | PTA (%) by MIC (mg/liter): | At steady state (48–72 h) |
|--------------|---------------|-----------------------------|---------------------------|
|              |               | During the first 24 h       |                           |
|              |               | 0.032 0.064 0.125 0.25 0.5 1 | 0.032 0.064 0.125 0.25 0.5 1 |
| 40% $f_{T>MIC}$ | 1.5 g q8h    | 100 100 100 100 100 100 100 93 41 | 100 100 100 100 100 100 100 97 59 |
|              | 1.5 g 4-h EI q8h | 100 100 100 100 100 100 100 100 52 | 100 100 100 100 100 100 100 100 72 |
|              | 1.5 g LD + 4.5 g CI | 100 100 100 100 100 100 100 100 70 | 100 100 100 100 100 100 100 100 68 |
|              | 3 g q8h       | 100 100 100 100 100 100 100 100 93 | 100 100 100 100 100 100 100 100 97 |
|              | 3 g 4-h EI q8h | 100 100 100 100 100 100 100 100 100 | 100 100 100 100 100 100 100 100 100 |
|              | 3 g LD + 9 g CI | 100 100 100 100 100 100 100 100 100 | 100 100 100 100 100 100 100 100 100 |
| 60% $f_{T>MIC}$ | 1.5 g q8h    | 100 100 100 100 100 100 100 73 3 | 100 100 100 100 100 100 100 78 31 |
|              | 1.5 g 4-h EI q8h | 100 100 100 100 100 100 100 100 82 17 | 100 100 100 100 100 100 100 94 55 |
|              | 1.5 g LD + 4.5 g CI | 100 100 100 100 100 100 100 100 68 | 100 100 100 100 100 100 100 100 67 |
|              | 3 g q8h       | 100 100 100 100 100 100 100 100 73 | 100 100 100 100 100 100 100 78 10 |
|              | 3 g 4-h EI q8h | 100 100 100 100 100 100 100 100 82 | 100 100 100 100 100 100 100 100 93 |
|              | 3 g LD + 9 g CI | 100 100 100 100 100 100 100 100 100 | 100 100 100 100 100 100 100 100 100 |
| 100% $f_{T>MIC}$ | 1.5 g q8h    | 100 100 100 100 100 100 100 99 69 | 100 100 100 100 100 100 100 81 55 |
|              | 1.5 g 4-h EI q8h | 100 100 100 100 100 100 100 100 69 0 | 100 100 100 100 100 100 100 96 69 |
|              | 1.5 g LD + 4.5 g CI | 100 100 100 100 100 100 100 100 98 3 | 100 100 100 100 100 100 100 96 10 |
|              | 3 g q8h       | 100 100 100 100 100 100 100 100 99 69 | 100 100 100 100 100 100 100 81 55 |
|              | 3 g 4-h EI q8h | 100 100 100 100 100 100 100 100 72 0 | 100 100 100 100 100 100 100 97 69 |
|              | 3 g LD + 9 g CI | 100 100 100 100 100 100 100 100 99 | 100 100 100 100 100 100 100 100 100 |

<sup>a</sup>Abbreviations: PK, pharmacokinetic; PD, pharmacodynamic; % $f_{T>MIC}$, percentage of time free drug concentration is above the MIC; q8h, every-8-h intermittent infusion (1 h); EI, extended infusion; LD, loading dose; CI, continuous infusion.
steady-state unbound ceftolozane concentrations from 48 to 72 h were 11.2 (±3.4) mg/liter and 19 (±5.5) mg/liter for creatinine clearance values of 180 and 100 ml/min/1.73 m², respectively. These values are about three to five times the P. aeruginosa clinical breakpoint (4 mg/liter). Previous studies have shown maximal antibacterial effects for beta-lactam antibiotics when trough concentrations are kept above 4 to 5 times the MIC (32–34). Therefore, a 4.5-g continuous infusion is likely to be highly effective and is supported by clinical case reports demonstrating success against MDR Pseudomonas infection susceptible to ceftolozane-tazobactam (35).

Higher doses of a 9.0-g continuous infusion with a 3.0-g initial loading dose result in relatively high average steady-state unbound concentrations of 22.4 (±6.7) and 38 (±11) mg/liter for creatinine clearance values of 180 and 100 ml/min/1.73 m², respectively. Thus, continuous infusion with high-dose regimens is highly likely to consistently achieve high exposure (100% $f_{T>MIC}$) even in patients with augmented renal clearance. This observation is concordant with the recent clinical findings by Pilmis et al. (36) that a 3.0-g (2/1-g) ceftolozane-tazobactam continuous infusion attains 100% $f_{T>MIC}$ in patients infected with P. aeruginosa up to an MIC of 8 mg/liter. Of note, although there is no clear-cut value for maximum concentration to target, current therapeutic drug monitoring (TDM) practice generally aims to keep a steady-state trough concentration of not more than ten times the MIC as the upper threshold (37). Our results show that continuous infusion with 3.0 g ceftolozane-tazobactam achieves a steady-state unbound concentration of about ten times the MIC clinical breakpoint for P. aeruginosa in patients with average creatinine clearance (about 100 ml/min/1.73 m²) or less. For more susceptible isolates with MICS of ≤2 mg/liter, this will be more than twenty times the MIC, clearly above the arbitrary upper threshold common in TDM interventions (37). However, higher-dose continuous infusion may be beneficial in the empirical management of MDR P. aeruginosa infection given that underexposure is likely to trigger resistance in vivo during treatment, resulting in reduced susceptibility (30). Such dosing can potentially avoid the treatment failure due to less susceptible strains that is experienced with low-dose intermittent regimen during off-label use (31).

An important limitation in this study is that we have assessed dosing adequacy based on plasma concentrations. While this covers the target site of action for bacteremia, the distribution of ceftolozane in to other sites such as epithelial lining fluid (ELF)
in pneumonia could be variable. However, a study (38) recently reported ELF penetration of 97% for ceftolozane, although data in that study were pooled from patients with various levels of renal function to estimate the penetration ratio (the interquartile range of creatinine clearance was 38 to 238 ml/min) and therefore are not likely to reflect a population value extrapolatable to all patients. In a more homogeneous healthy volunteer cohort, a penetration ratio of 0.48 was estimated (39). In either case, given the high PTA up to an MIC of 8 mg/liter (Table 3), adequate exposure will be attained at the ELF up to the \( P. aeruginosa \) breakpoint of 4 mg/liter. Another important limitation of this study is the small sample size, which offers a limited spread of covariates, limiting broad extrapolation of the study findings.

In conclusion, intermittent infusion of 1.5 g ceftolozane-tazobactam q8h achieves adequate unbound plasma exposure against susceptible pathogens. For empirical treatment initiation, intermittent infusion of 3.0 g ceftolozane-tazobactam q8h will be more appropriate and ensures adequate exposure in the lungs given reported penetration ratios of about 0.5 to 1. A loading dose of 1.5 g followed by continuous infusion of 4.5 g is adequate for empirical coverage of a more aggressive dosing target of 100% \( f_{T-MIC} \) including in patients with augmented renal clearance.

MATERIALS AND METHODS

Studies design and setting. This prospective observational pharmacokinetic study was conducted at a quaternary referral intensive care unit (ICU) of the Royal Brisbane and Women’s Hospital (RBWH), Australia. The human research ethics committees of RBWH (HREC/16/QRBW/211) and the University of Queensland (no. 2016001368) granted ethical clearance.

Patients. ICU patients, aged \( \geq 18 \) years, were enrolled if diagnosed with a systemic infection known or suspected to be caused by a bacterium susceptible to ceftolozane-tazobactam. Patients were excluded if they had renal dysfunction that necessitated the use of renal replacement therapy, had a known or suspected allergy to cephalosporins, had received piperacillin-tazobactam in the preceding 7 days, or were pregnant. Informed consent was obtained from each patient or their legally authorized representative.

Ceftolozane-tazobactam administration. At the discretion of the treating physician, the study participants received either 1.5 g or 3.0 g ceftolozane-tazobactam (2:1 ratio) administered every 8 h via intravenous infusion over 1 h. The attending clinicians determined the duration of therapy based on the patients’ clinical scenario.

Sample collection. Blood samples (3 ml each) were collected in heparinized Vacutainers from an established arterial line. The sampling times were as follows: first sample just prior to administration of the dose; second and third samples at 15 and 45 min, respectively, after commencement of drug infusion; fourth sample at the end of line flushing (15 to 20 min) following the 1-h drug infusion; samples at 2, 3, 4, 5, 6, and 7 h after the start of infusion; and a final sample just before the second dose. The actual time of collection for individual samples was recorded and used for analysis. Blood samples were spun (3,000 rpm for 10 min) immediately after collection to separate plasma, an aliquot of which was stored in a \( -80 \)°C freezer until assayed by a validated chromatographic method.

Clinical data. An electronic case report form developed in the REDCap web platform was used to collect clinical data, including the following: patient demographics; physical examination, including vital signs; ICU and hospital admission and discharge dates and times; Acute Physiology and Chronic Health Evaluation II (APACHE II) score; Sequential Organ Failure Assessment (SOFA) score at ICU admission; presence of shock on days of sampling; presence of mechanical ventilation; renal function markers (serum creatinine concentration and urinary creatinine clearance); liver laboratory test results (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, international normalized ratio, and bilirubin); medication list on days of sampling; antibiotic data, including type, dose, dosing interval, duration of infusion, and other antibiotics administered on day of sampling; and infection data (organisms isolated and sample type, MIC if available).

Ceftolozane-tazobactam assay. Unbound concentrations of ceftolozane and tazobactam in plasma were measured by an ultra-high-performance liquid chromatography-tandem mass spectrometry (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). The sample (10 \( \mu \)l) was spiked with phosphate-buffered saline (pH 7.4), an internal standard (sulbactam and \( L \)-cefazolin), and acetonitrile. The stationary phase was a C\textsubscript{18} Ultra IBD column (100 by 2.1 mm, 3 \( \mu \)m) (Restek, USA) operated at room temperature. Mobile phase A was 0.1% (vol/vol) formic acid in 10 mM ammonium formate, and mobile phase B was 100% acetonitrile with 0.1% (vol/vol) formic acid. The mobile phase was delivered with gradient from 15% to 50% B at a flow rate of 0.3 ml/min for a 5-min run time and produced a back pressure of approximately 2,800 lb/in\(^2\). Ceftolozane was monitored by positive-mode electrospray at MRM\(_{299.20-232.20}\), the stationary phase was a C\textsubscript{18} Ultra IBD column (100 by 2.1 mm, 3 \( \mu \)m) (Restek, USA) operated at room temperature. Mobile phase A was 0.1% (vol/vol) formic acid in 10 mM ammonium formate, and mobile phase B was 100% acetonitrile with 0.1% (vol/vol) formic acid. The mobile phase was delivered with gradient from 15% to 50% B at a flow rate of 0.3 ml/min for a 5-min run time and produced a back pressure of approximately 2,800 lb/in\(^2\). Ceftolozane was monitored by positive-mode electrospray at MRM\(_{299.20-232.20}\), 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/liter, 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 (40).

Population PK modeling. A population pharmacokinetic (PK) model was developed in R using Pmetrics version 1.5.2. Unbound ceftolozane and tazobactam concentration-time data were modelled using nonparametric adaptive grid (NPAG) analysis in Pmetrics. Initially, one- and two-compartment structural base models were tested considering first-order elimination from the central compartment and intercompartmental distribution. With each structural base model, either a multiplicative or additive error model was tested. The additive error mode was given by the equation Error = SD · γ, where SD represents the standard deviation of observations and A and γ represent process noise. In addition, assay error was modelled as a linear function of observations (obs) as Error = C0 + C1 · obs, where the coefficients C0 and C1 were optimized interactively.

Covariate models were tested following the standard forward-addition and backward-deletion approach. Initially, covariates were selected based on biological plausibility as well as a preliminary regression analysis of each plausible covariate against primary model parameters using built-in tools within Pmetrics. Covariates selected for investigation include serum creatinine, urinary creatinine clearance, body weight, body mass index, albumin concentration, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and Sequential Organ Failure Assessment (SOFA) score. Model evaluation and selection were based on assessment of diagnostic plots and statistics. Diagnostic plots included observed versus population or individual predicted concentrations and normalized prediction distribution errors (NPDEs) versus time of observation errors. Statistics included regression coefficient of observed versus predicted concentrations, bias (defined as the mean weighted error of predicted minus observed concentrations, i.e., (predicted − observed)/standard deviation)/N, imprecision (defined as the bias-adjusted, mean weighted squared error of predicted minus observed concentration, i.e., (predicted − observed)²/standard deviation))²/N, where N is the number of observations/predictions), and objective functions, including log-likelihood ratio (LLR) chi-square test for the nested models, Akaike information criterion (AIC), and Bayesian information criterion (BIC). The LLR chi-square test was used for statistical comparison of nested models (a P value of <0.05 was considered significant).

Dosing simulations. Using the final covariate model, Monte Carlo dosing simulations (n = 1,000) were performed to determine the probability of target attainment (PTA) during the first 24 h and at steady state from 48 to 72 h after commencement of treatment. Simulated dosing regimens of ceftolozane-tazobactam (2:1 ratio) included a 1.5-g intermittent infusion (over 1 h) every 8 h (q8h), a 1.5-g loading dose over 1 h plus a 4.5-g continuous infusion over 24 h, a 3-g intermittent infusion (over 1 h) q8h, a 3-g extended infusion (over 4 h) q8h, and a 9-g continuous infusion over 24 h.

The primary pharmacokinetic (PK)/pharmacodynamic (PD) dosing target used for determination of PTA for ceftolozane was 40% FTA on MIC. This is based on preclinical studies that showed that a 32.2% FTA on MIC exposure achieves a 1-log kill (23) and that a 40% to 50% FTA on MIC is likely to achieve a 1- to 2-log kill (28). In addition, we determined the PTA for a higher exposure of 60% FTA on MIC, which is generally considered optimal for cephalosporins (41), and a more aggressive exposure of 100% FTA on MIC, which is advocated as a prudent target for severely ill patient populations (10). For tazobactam, we used a 20% FTA on MIC (20% of the time above the minimum effective concentration of 1 mg/liter) as a target for assessment of dosing adequacy as previously suggested based on data from preclinical studies (26, 27, 42).

The cumulative fractional response or fractional target attainment (FTA) for ceftolozane was estimated for the Pseudomonas aeruginosa EUCAST MIC distribution for both empirical and directed therapy using the equation $F_TA = \sum_{i=0.125}^{n} PTA_i \times F_i$, where i is the MIC category ranging from 0.125 to n, n is 64 mg/liter for empirical therapy and the EUCAST clinical breakpoint of 4 mg/liter for directed therapy, PTA, is the PTA for MIC category i, and F_i is the fraction of the bacterial population at each MIC category.

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