Evaluation the efficacy of optimized two-step-administration therapy with ceftazidime/avibactam for treating Extensively drug-resistance (XDR) *Pseudomonas aeruginosa* pulmonary infections: a Pharmacokinetic/pharmacodynamic analysis

Yixin Kang  
Chinese People's Liberation Army General Hospital

Junchang Cui  
(✉ guoyoumeng@163.com)  
Chinese People's Liberation Army General Hospital

Research Article

**Keywords:** extensively drug resistance *Pseudomonas aeruginosa*, ceftazidime-avibactam, optimized two-step-administration therapy, Monte Carlo simulations

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**Background**: The objective of this pharmacokinetic (PK)/pharmacodynamic (PD) analysis was to evaluate the efficacy of different dosing regimens of ceftazidime-avibactam (CZA) for the treatment of extensively drug-resistance (XDR) *Pseudomonas aeruginosa* pulmonary infections by using optimized two-step-administration therapy (OTAT) and traditional infusion (TI).

**Methods**: We used Monte Carlo simulations (MCS) to integrate PK parameters with PD parameters to assess the adequacy of ceftazidime-avibactam dosing for XDR *P. aeruginosa* pulmonary infections. We obtained pharmacokinetic parameters from a previously published study and pharmacodynamic parameters from the international network for optimal resistance monitoring (INORM). Dosing models were as follows: 2.5 g q8h, 2.5 g q6h, 4 g q8h, 4g q6h, 1.25 g q8h, 1.25 g q6h, and 0.94 g q12h.

**Results**: MCS showed that the cumulative fraction of response (CFR) of all dosing regimens of OTAT was higher than 90%. Similarly, the probability of target attainments (PTAs) of all dosing regimens of OTAT at MICs of 16-32 mg/L was higher than those of TI. Based on the models, PK/PD goals were met with OTAT regimens even with high MICs (>16 mg/L) compared with traditional infusion intervals.

**Conclusion**: Our work indicated that OTAT with sufficient pharmacokinetic exposures could improve the efficacy of CZA for XDR *P. aeruginosa* pulmonary infections.

**Materials And Methods**

**2.1. MIC distributions**

We obtained MIC distributions of CZA against 689 XDR *P. aeruginosa* isolates from the international network for optimal resistance monitoring (INORM) program, as listed in Table I [8]. The database was selected because it included a total of 7452 *P. aeruginosa* strains, most of which were isolated from patients with pulmonary infections (50.5%) [8].

**2.2. Dosing regimens**

We adjusted various dosing models of CZA against XDR *P. aeruginosa* according to the simulated patient's degree of renal dysfunction. All simulated dosing regimens were listed in Table II. For patients with normal renal function (CLCR > 51 ml/min), the standard regimen was 2.5g q8h (2h infusion). The previously published clinical studies confirm the poor efficacy of CZA against MDR *P. aeruginosa*. We simulated dosing regimens of increasing the dose of CZA (4g q8h), shortening the dosing interval (2.5g q6h) and applying both of these methods together (4g q6h). For OTAT, the dosing regimen was: a rapid infusion of 1.25g (0.5h infusion) in the first step and a continuation of the remaining 1.25g (2h infusion) in the second step. Simulated patients received the above anti-infective treatment every 8 hours. Similarly, OTAT dosing regimens for normal renal function patients were 1.25g (0.5h infusion) + 1.25g (2h infusion) q6h, 2g (0.5h infusion) + 2g (2h infusion) q8h, and 2g (0.5h infusion) + 2g (2h infusion) q6h. For patients with 30 ml/min < CLCR ≤ 50 ml/min, dosing regimens for TI were 1.25g q8h and 1.25g q6h, for OTAT were 0.625g (0.5h infusion) + 0.625g (2h infusion) q6h and 0.625g (0.5h infusion) + 0.625g (2h infusion)
Discussion
daily if administered via TI and CFR was 99.62% for CZA 0.47g (0.5h) + 0.47g (2h) twice daily if administered via OTAT. 75.73% for CZA 1.25g (2h) four times daily if administered via TI. For patients with CL
creatinine clearance (CL\(_C\)r) > 51 ml/min, dosing regimens for TI were 1.25g q6h and 99.29% for CZA 0.625g (0.5h) + 0.625g (2h) four times daily if administered via OTAT. CFRs were 72.81% for CZA 1.25g (2h) three times daily and four times daily if administered via OTAT. For patients with CL\(_C\)r ≤ 30 ml/min, the PTA of OTAT were 0%. For patients with CL
function (CL\(_C\)r) > 16 ml/min, CFR was for 93.23% CZA 0.94g (2h) twice daily and 99.29% for CZA 1.25g (0.5h) + 1.25g (2h) three times daily and 93.49% for CZA 1.25g (0.5h) + 1.25g (2h) four times daily if administered via OTAT. For patients with CL
function (CL\(_C\)r) < 16 ml/min, the PTA of TI were 0%. For patients with mild renal insucien
ty (CL\(_C\)r) > 16 to ≤ 30 ml/min, CFRs were 93.23% for CZA 0.94g (2h) twice daily and 99.49% for CZA 1.25g (0.5h) + 1.25g (2h) three times daily and 93.49% for CZA 1.25g (2h) four times daily if administered via OTAT. CFRs were 72.81% for CZA 1.25g (2h) three times daily and 75.73% for CZA 1.25g (2h) four times daily if administered via TI. For patients with CL\(_C\)r ≥ 30 ml/min, CFR was for 45.38% CZA 0.94g (2h) twice daily if administered via TI and CFR was 99.62% for CZA 0.47g (0.5h) + 0.47g (2h) twice daily if administered via OTAT.

2.3. PK/PD modeling
We obtained PK parameters of CZA from a previous publication by Stein et al. (2018) [2]. This study included ten critically ill patients with lower respiratory tract infections. The mean clearance and \( V_d \) for ceftazidime were 6.1 ± 3.8 L/h, 35 ± 10.5 L. For avibactam, above mentioned parameters were 11.1 ± 6.8 L/h, 50.8 ± 14.3 L. We used following equation to calculate the total body clearance \( CLT = CL_S \times CL_G + CL_I \) [2]. \( CL_S \) and \( CL_I \) stand for clearance slope and intercept terms, respectively. We considered that 50% \( T > 5 \times MIC \) and (\( %T > CT (1 mg/L) \)) were the best targets to predict the microbiological outcomes of ceftazidime and avibactam for pulmonary infections, respectively [10]. CT means a minimum free avibactam concentration (threshold concentration). We applied the following equation to calculate \( %T > 5 \times MIC \) [6].

\[ T > 5 \times MIC = \frac{R_{02}}{LN(1 - \frac{R_{01}}{R_{02}}) exp(\frac{R_{01} - R_{02}}{5 \times CL \times MIC})} - \frac{5 \times CL \times MIC}{5 \times CL \times MIC} \]

\[ T_1 \] is the administration time of the rst step of infusion. \( T_2 \) is the infusion time of the second step of infusion. \( R_{01} = \) first-dose/\( T_1 \) (mg/h). \( R_{02} = \) first-dose/\( T_2 \) (mg/h). exp represents exponent. And \( %T > 5 \times MIC = (T > 5 \times MIC) \times \frac{100}{D_1} \). \( D_1 \) represents the dosing interval (h). Furthermore, the \( %T > 5 \times MIC \) in TI was calculated using a previously published one-compartment infusion equation [11].

2.4. Monte Carlo simulations
Oracle Crystal Ball v.11.1.24 was used to conduct 10000 patients' Monte Carlo simulations. A log-normal distribution followed PK parameters. For each dosing regimen, the probability of target attainment (PTA) was deined as the probability of reaching the PK/PD target at each MIC. The following equation was used to calculate the cumulative fraction of response (CFR) of various dosing regimens: CFR = \( \sum_{i=1}^{n} PTA(MICi) \times p(MICi) \). MIC stands for each MIC value, and \( p(MICi) \) represents a percentage of strains with this MIC. When a CFR value ≥ 90%, we considered that this dosing regimen has a favorable microbiology outcome.

Results
3.1. Probability target attainment
The probability of target attainment (PTA) for achieving 50% \( T > 5 \times MIC \) for different CZA dosing models was shown in Fig. 1. For patients with normal renal function (CL\(_C\)r > 51 ml/min), CZA (2.5 g q8h) achieved 100% target attainment when the MIC was below 8 mg/L. The probability declined to 12.21% at MICs of 16 mg/L. For the attainment of 50% \( T > 5 \times MIC \) the dosage regimens of 2.5 g q6h, 4g q6h, and 4 g q6h would be sufficient for the treatment of XDR P\(_\text{aeruginosa}\) with MICs ≤ 16 mg/L if administered via 2h TI. If patients administered via OTAT, dosage regimens of 4g [e.g., 2 g (0.5h) + 2 g (2h)] q6h and 4g [e.g., 2 g (0.5h) + 2 g (2h)] q8h for the isolates with MICs of 64 mg/L, 2.5 g [e.g., 1.25 g (0.5h) + 1.25 g (2h)] q6h for the isolates with MICs of 32 mg/L, 2.5g [e.g., 1.25 g (0.5h) + 1.25 g (2h)] q8h for the isolates with MICs of 32 mg/L produced suficient pharmacokinetic exposures when 50% \( T > 5 \times MIC \) was used as the PD target.

For patients with mild renal insucien
ty (CL\(_C\)r > 30 to ≤ 50 ml/min), CZA 1.25 g [e.g., 0.675 g (0.5h) + 0.675 g (2h)] q8h and 1.25 g [e.g., 0.675 g (0.5h) + 0.675 g (2h)] q6h achieved a PTA of 100% when the MIC was 16 mg/L. The PTA of above OTAT dosing regimens were 100% and 95% at an MIC of 32 mg/L, respectively. At an MIC of 64mg/L, PTA of OTAT were 0%. For patients with CL\(_C\)r > 16 to ≤ 30 ml/min, the PTA of CZA 0.94 g [e.g., 0.47 g (0.5h) + 0.47 g (2h)] q12h were greater than 90% with MIC values of between 0.25 and 64 mg/L. However, only strains with MIC ≤ 4 can be covered by 0.94 g q12h if CZA administered via 2h TI.

We have the following fiindings to summarize the PTA of CZA against XDR P\(_\text{aeruginosa}\). In simulations of various renal functions across XDR P\(_\text{aeruginosa}\) pulmonary infections with MICs of 16 to 64 mg/L, OTAT had a higher PTA than TI.

3.2. Cumulative fraction of response
Cumulative fraction of responses (CFRs) of CZA various dosing models for XDR-Pa pulmonary infections were shown in Table III. For patients with creatinine clearance (CL\(_C\)r) > 51 ml/min, CFRRs were 92.72% for CZA 1.25g (0.5h) + 1.25g (2h) three times daily and 93.49% for CZA 1.25g (0.5h) + 1.25g (2h) four times daily if administered via OTAT. For patients with CL\(_C\)r > 30 to ≤ 50 ml/min, CFRRs were 93.23% for CZA 0.625g (0.5h) + 0.625g (2h) three times daily and 99.29% for CZA 0.625g (0.5h) + 0.625g (2h) four times daily if administered via OTAT. CFRRs were 72.81% for CZA 1.25g (2h) three times daily and 75.73% for CZA 1.25g (2h) four times daily if administered via TI. For patients with CL\(_C\)r ≥ 30 ml/min, CFR was for 45.38% CZA 0.94g (2h) twice daily if administered via TI and CFR was 99.62% for CZA 0.47g (0.5h) + 0.47g (2h) twice daily if administered via OTAT.
XDR *P. aeruginosa* has now spread worldwide and has become a severe challenge to clinical work, especially the treatment of immunocompromised patients with severe infections [12]. Furthermore, CDC (Centers for Disease Control and Prevention) classified MDR/XDR *P. aeruginosa* as a serious antibiotic resistance threat [1]. Several studies demonstrated that clinical and microbiology responses of CZA against MDR/XDR *P. aeruginosa* pulmonary infections were inferior to other gram-negative bacteria [4, 5]. However, most of these researches were case series or retrospective studies and confined to small sample sizes. The main resistance mechanisms of *P. aeruginosa* are intrinsic resistome, mutational resistome, and horizontally acquired resistome [13]. Furthermore, CZA is a novel β-lactam/β-lactamase inhibitors (BL/BLIs) and has been regarded as a new treatment option for XDR *P. aeruginosa* [14]. By the way, in vitro studies showed that the susceptibility rate of CZA to XDR *P. aeruginosa* ranged from 73.7–76.2% [8, 15, 16].

Based on the above research background, our team conducted a PK/PD analysis. In our study, we used OTAT and TI to evaluate the efficacy of different CZA dosing models to treat XDR *P. aeruginosa* pulmonary infections. MCSs have been performed to study CZA dosing models and define the optimal dosing regimen of CZA therapy for XDR *P. aeruginosa* pneumonia, testing various renal function statuses and doses.

And we found that all OTAT dosing regimens (ie: 2.5 g [e.g., 1.25 g (0.5h) + 1.25 g (2h)] q6h, 2.5 g [e.g., 1.25 g (0.5h) + 1.25 g (2h)] q8h, 4g [e.g., 2 g (0.5h) + 2 g (2h)] q6h, 4g [e.g., 2 g (0.5h) + 2 g (2h)] q8h for normal renal function patients. 1.25 g [e.g., 0.675 g (0.5h) + 0.675 g (2h)] q6h, 1.25 g [e.g., 0.675 g (0.5h) + 0.675 g (2h)] q8h for patients with ClCR range 30 to 50 ml/min. 0.94 g [e.g., 0.47 g (0.5h) + 0.47 g (2h)] q12h for patients with ClCR > 16 to ≤ 30 ml/min.) with adequate PK exposures (CZA concentration decreased to 5 × MIC after the second step infusion) can obtain favorable response. Compared with TI, we considered that OTAT can be an ideal strategy for XDR *P. aeruginosa* with MICs of 16 to 32 mg/L.

Eguchi et al. (2010) [6] conducted a PK/PD analysis, and they found that OTAT can significantly improve the initial killing rate of meropenem. Another study demonstrated that meropenem monotherapy is competent for meropenem-nonsusceptible bacterial infections if administered rational OTAT [11]. These were similar to the results of our study. As with other time depended antibiotics (i.e., meropenem, ceftazidime), administration by OTAT is a potential treatment option for improving the probability of attaining the PK/PD target.

In clinical setting, drug-resistant *P. aeruginosa* in the respiratory tract is often found in patients with chronic lung disease states such as cystic fibrosis, immunosuppression, and so on. Considering that patient population can affect treatment decision and has varying PK/PD parameters, I suggest that the application of OTAT regimens should be considered the variation of PK parameters.

From the pharmacoeconomic perspective, our study has great significance for some developing countries with poor healthcare situations. At the same dosing model (i.e., same medical expenses), OTATs with sufficient PK exposures were more effective than TI. CZA is a novel antibiotic with high prices. In case of poor efficacy of CZA therapy for XDR *P. aeruginosa* pneumonia, doctors can use an OTAT rather than increasing the dose or frequency blindly. This can significantly reduce the burden on patients.

From the perspective of safety of CZA, our study helps to reduce toxic reactions caused by overdose. At the standard dose of CZA (2.5 g q8h), the TI does not provide good bactericidal effect for XDR *P. aeruginosa* pulmonary infections, but the OTAT provides good bactericidal effect for XDR *P. aeruginosa* pneumonia. There are limits to the effectiveness of attempts to increase doses to achieve therapeutic goals, and the risk of overdose should be taken into account.

Our work had several limitations, as follows. Firstly, PK parameters of ceftazidime and avibactam were obtained from critically ill patients’ serum samples and confined to its small sample size. Nevertheless, our study aimed to evaluate the efficacy of CZA for the treatment of XDR *P. aeruginosa* pneumonia. Epithelial lining fluid (ELF) samples of patients with pneumonia would be the best [17].

Secondly, local surveillance and epidemiology should always be considered when deciding a therapy for drug-resistant organisms. Knowing resistance patterns is a key to control antimicrobial resistance as well as to avoid any antibiotic misuse or overuse. Therefore, applicability of Mic from a different country should be considered with caution as the strategies against multi-drug organisms (MDRO) may differ country by country, state by state, and even city by city. XDR *P. aeruginosa* was isolated from the United States from 2012 to 2015. XDR *P. aeruginosa* were collected in recent years would be better, but MIC distributions of these strains were unavailable.

Alternative regimens included longer dosage interval, prolonged infusions of the full dose for both drugs and OTAT. In addition, those regimens could reduce dosing errors, drug cost and nurse labor. Clinical investigation of those alternative dosage regimens would be required before implementation.

The treatment of XDR *P. aeruginosa* pulmonary infections is a massive challenge in our future work. In this study, we conducted Monte Carlo simulations to evaluate the efficacy of CZA for the treatment of XDR *P. aeruginosa* pulmonary infections. We found that OTAT dosing regimens can vastly improve the PTA at MIC ≥ 16mg/L. Moreover, all OTAT dosing regimens can obtain favorable CFR values.

**Conclusion**

In conclusion, OTAT with sufficient pharmacokinetic exposures can improve the efficacy of CZA for the treatment of XDR *P. aeruginosa* pulmonary infections.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.
Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The manuscript was written by Yixin Kang and revised by Junchang Cui.

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All methods were performed in accordance with the relevant guidelines and regulations

References


Tables

Table I. MIC distribution of ceftazidime-avibactam (CZA) monotherapy for extensively drug-resistant (XDR) P. aeruginosa isolates from four years (2012 to 2015) of the International Network for Optimal Resistance Monitoring Program in the United States.

<table>
<thead>
<tr>
<th>Number of isolates at MIC (mg/liter)</th>
<th>≤0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
</tr>
</thead>
<tbody>
<tr>
<td>XDR P. aeruginosa</td>
<td>1</td>
<td>4</td>
<td>28</td>
<td>109</td>
<td>179</td>
<td>208</td>
<td>88</td>
<td>36</td>
<td>45</td>
</tr>
</tbody>
</table>

Table II. Simulated dosing models of ceftazidime-avibactam (CZA).

<table>
<thead>
<tr>
<th>Renal status</th>
<th>Dosing models</th>
<th>Simulated dosing regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL\textsubscript{CR} &gt; 51 ml/min</td>
<td>2.5g q8h</td>
<td>2.5g (2h)</td>
</tr>
<tr>
<td></td>
<td>2.5g q6h</td>
<td>2.5g (2h)</td>
</tr>
<tr>
<td></td>
<td>4g q8h</td>
<td>4g (2h)</td>
</tr>
<tr>
<td></td>
<td>4g q6h</td>
<td>4g (2h)</td>
</tr>
<tr>
<td>30 ml/min &lt; CL\textsubscript{CR} ≤ 50 ml/min</td>
<td>1.25g q8h</td>
<td>1.25g (2h)</td>
</tr>
<tr>
<td></td>
<td>1.25g q6h</td>
<td>1.25g (2h)</td>
</tr>
<tr>
<td>16 ml/min &lt; CL\textsubscript{CR} ≤ 30 ml/min</td>
<td>0.94g q12h</td>
<td>0.94g (2h)</td>
</tr>
</tbody>
</table>

TI: traditional infusion, OTAT: optimized two-step-administration therapy.

Table III. Cumulative fraction of responses (CFRs) for various dosing regimens of ceftazidime-avibactam (CZA) against XDR P. aeruginosa.

<table>
<thead>
<tr>
<th>Dosing models</th>
<th>Simulated dosing regimens</th>
<th>CFRs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5g q8h</td>
<td>2.5g (2h)</td>
<td>77.27</td>
</tr>
<tr>
<td>2.5g q6h</td>
<td>2.5g (2h)</td>
<td>88.34</td>
</tr>
<tr>
<td>4g q8h</td>
<td>4g (2h)</td>
<td>89.11</td>
</tr>
<tr>
<td>4g q6h</td>
<td>4g (2h)</td>
<td>88.34</td>
</tr>
<tr>
<td>1.25g q8h</td>
<td>1.25g (2h)</td>
<td>72.81</td>
</tr>
<tr>
<td>1.25g q6h</td>
<td>1.25g (2h)</td>
<td>93.29</td>
</tr>
<tr>
<td>2g (0.5h) +2g (2h)</td>
<td>99.29</td>
<td></td>
</tr>
<tr>
<td>0.94g q12h</td>
<td>0.94g (2h)</td>
<td>45.38</td>
</tr>
</tbody>
</table>

Figures
Figure 1

The probability of target attainment for achieving 50% $T>5\times$MIC for different ceftazidime-avibactam dosing regimens.

a. $CL_{CR} > 51$ ml/min, b. $30$ ml/min < $CL_{CR} \leq 50$ ml/min, c. $16$ ml/min < $CL_{CR} \leq 30$ ml/min.