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Elevated MICs of Susceptible Antipseudomonal Cephalosporins in Non-Carbapenemase-Producing, Carbapenem-Resistant *Pseudomonas aeruginosa*: Implications for Dose Optimization

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The present study evaluated the in vitro potency of ceftazidime and cefepime among carbapenem-resistant *Pseudomonas aeruginosa* isolates collected as part of a global surveillance program and assessed the pharmacodynamic implications using previously published population pharmacokinetics. When susceptible, MICs resulted at the high end of distribution for both ceftazidime and cefepime, thus 6 g/day was required to achieve optimal pharmacodynamic profiles. These findings should be considered in the clinic and for the application of CLSI susceptibility breakpoints.

**KEYWORDS** *Pseudomonas aeruginosa*, carbapenem resistance, cefepime, ceftazidime, pharmacodynamics, pharmacokinetics

Ceftazidime and cefepime remain common antipseudomonal agents in clinical practice. Despite rising rates of carbapenem resistance among *Pseudomonas aeruginosa* due to porin alterations, efflux, and cephalosporinase and carbapenemase production, some carbapenem-resistant isolates remain susceptible to ceftazidime and cefepime.

**ABSTRACT** The present study evaluated the in vitro potency of ceftazidime and cefepime among carbapenem-resistant *Pseudomonas aeruginosa* isolates collected as part of a global surveillance program and assessed the pharmacodynamic implications using previously published population pharmacokinetics. When susceptible, MICs resulted at high end of distribution for both ceftazidime and cefepime, thus 6 g/day was required to achieve optimal pharmacodynamic profiles. These findings should be considered in the clinic and for the application of CLSI susceptibility breakpoints.


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CLSI previously introduced the “susceptible dose dependent” (SDD) breakpoint for Enterobacterales with cefepime MICs of 4 to 8 mg/liter that are susceptible if pharmacodynamically optimized doses of cefepime are administered (2 g intravenously [i.v.] every 8 h) (2, 3). Conversely, P. aeruginosa isolates are susceptible at MICs of ≤8 mg/liter with doses of cefepime of 2 g i.v. every 12 h or 1 g i.v. every 8 h despite a notable proportion of P. aeruginosa isolates testing within the 4 to 8 mg/liter range (3, 4).

The purpose of this study therefore was 2-fold as follows: (i) evaluate the MIC distribution of ceftazidime and cefepime in the setting of carbapenem resistance and (ii) utilize pharmacodynamic profiling techniques to evaluate the adequacy of the dosing regimens used to establish the current CLSI breakpoints (CLSI breakpoint dose) in this isolate population.

Isolates in the present study were a subset of those collected as part of the ERACE-PA Global Study Group (5). Briefly, isolates were sent from 17 centers in 12 different countries. Isolates were submitted if they were determined to be CRPA by conventional MIC methods at the submitting site. Isolates underwent phenotypic carbapenemase testing using the modified carbapenem inactivation method (mCIM). MIC testing using reference broth microdilution was conducted for ceftazidime and cefepime per CLSI standards (3).

In the present analysis, all phenotypically carbapenemase-positive isolates were excluded because of the ambiguity of using these agents in the setting of confirmed carbapenemase production despite testing susceptible (6). Among the remaining isolates, ceftazidime- and cefepime-susceptible isolates per CLSI interpretation (≤8 mg/liter) were then selected for analysis.

To evaluate the pharmacodynamic differences of ceftazidime and cefepime dosing regimens for patients with normal renal function, 5,000-patient Monte Carlo simulations (Crystal Ball) were performed using previously defined population pharmacokinetic models (mean creatinine clearance, 88 and 90 ml/min, respectively) (7, 8). The target of 70% free-time above the MIC ($f_{T>MIC}$) was used to evaluate target attainment as a more conservative estimate of the pharmacodynamic target for cephalosporin antimicrobials associated with maximal in vivo bacterial killing (50 to 70%) and supported by observational outcome data in patients (9–12). For comparison, assessments of 50% and 60% $f_{T>MIC}$ targets were conducted. Optimal probability of target attainment (PTA) was defined as >90% of simulated patients meeting 70% $f_{T>MIC}$. For ceftazidime, the CLSI breakpoint dose of 2 g i.v. every 8 h was evaluated as both a 0.5-h and 3-h infusion. For comparison, a ceftazidime dose of 1 g i.v. every 8 h was also assessed. The CLSI breakpoint doses of cefepime 1 g i.v. every 8 h and 2 g i.v. every 12 h were assessed as 0.5-h infusions. For comparison, cefepime 2 g i.v. every 8 h was assessed as both a 0.5- and 3-h infusion. Both agents’ current P. aeruginosa breakpoints are 8 mg/liter (3). Each dosing regimen was displayed with the probability of target attainment at a given MIC ranging from 0.25 to 8 mg/liter (Fig. 1) (13).

The MIC$_{50}$ and MIC$_{90}$ were evaluated to assess the MIC distribution of ceftazidime- and cefepime-susceptible isolates per CLSI in this cohort of CRPA. To evaluate the pharmacodynamic adequacy of the evaluated dosing regimens in this specific isolate population, the cumulative fraction of response (CFR) was calculated as previously described for each dosing regimen against the specific MIC distribution evaluated in the present study (13). Greater than 90% CFR was considered optimal for each dosing regimen.

Of the 807 total CRPA isolates in the program, 542 phenotypically carbapenemase-negative isolates were evaluated. Of these, 351 (65%) and 341 (62%) were susceptible to ceftazidime and cefepime, respectively. The MIC$_{50}$ and MIC$_{90}$ were 4 and 8 mg/liter for both agents, respectively. Of the ceftazidime-susceptible isolates, 39% and 17% had MICs of 4 or 8 mg/liter, respectively. Conversely, for cefepime-susceptible isolates, 26% and 34% of isolates had MICs of 4 or 8 mg/liter, respectively. Figure 1 describes the MIC distribution of ceftazidime-susceptible (Fig. 1a) and cefepime-susceptible (Fig. 1b) P. aeruginosa isolates and the corresponding probability of target attainment from the Monte Carlo simulations.
For comparison, the targets plotted against 50% and 60% $\text{fT}_{\text{MIC}}$ are presented in Fig. S1 in the supplemental material. Evaluating the CLSI breakpoint ceftazidime dose, ceftazidime 2 g i.v. every 8 h, >90% CFR was achieved as a 0.5- or 3-h infusion (Table 1). To improve to >90% PTA at the highest MICs (8 mg/liter), an extended 3-h infusion was needed. Conversely, the CLSI breakpoint cefepime doses of 2 g i.v. every 12 h and 1 g i.v. every 8 h resulted in suboptimal CFR with 85% and 89%, respectively. Maximum doses of cefepime 2 g i.v. every 8 h resulted in CFR values of 97% and 99% for 0.5- and 3-h infusions, respectively.

The present study highlights that despite testing susceptible to ceftazidime or cefepime, CRPA had MICs at the higher end of the susceptibility distribution, many of which were at the 8-mg/liter breakpoint. This is in contrast to the general MIC distribution where only 8% and 18% resided at 8 mg/liter for ceftazidime and cefepime, respectively, in all collected *P. aeruginosa* from the SENTRY database (14). For cefepime, the CLSI breakpoint doses resulted in suboptimal exposure for the higher MIC isolates, and this translated to lower CFR in this cohort of CRPA. If cefepime therapy is being used, the 6 g per day regimen is needed for optimal pharmacodynamic exposure.

### TABLE 1

Cumulative fraction of response based on the pharmacodynamic simulations in this population of ceftazidime-susceptible and cefepime-susceptible carbapenem-resistant *P. aeruginosa*

<table>
<thead>
<tr>
<th>CRPA type and dose regimen</th>
<th>Cumulative fraction of response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime-susceptible CRPA</td>
<td></td>
</tr>
<tr>
<td>1 g every 8 h, 0.5-h infusion</td>
<td>85</td>
</tr>
<tr>
<td>1 g every 8 h, 3-h infusion</td>
<td>97</td>
</tr>
<tr>
<td>2 g every 8 h, 0.5-h infusion</td>
<td>97</td>
</tr>
<tr>
<td>2 g every 8 h, 3-h infusion</td>
<td>100</td>
</tr>
<tr>
<td>Cefepime-susceptible CRPA</td>
<td></td>
</tr>
<tr>
<td>2 g every 12 h, 0.5-h infusion</td>
<td>85</td>
</tr>
<tr>
<td>1 g every 8 h, 0.5-h infusion</td>
<td>89</td>
</tr>
<tr>
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<td>97</td>
</tr>
<tr>
<td>2 g every 8 h, 3-h infusion</td>
<td>99</td>
</tr>
</tbody>
</table>
Indeed, a more conservative pharmacodynamic target for cephalosporins was used, 70% \( f_{T>\text{MIC}} \) as it has been associated with maximal efficacy in vivo against Gram-negative organisms including \( P. \text{aeruginosa} \) (9, 10). Additionally, interisolate variability of \( f_{T>\text{MIC}} \) targets associated with 1-log\(_{10} \) and 2-log\(_{10} \) bacterial kill have been described for \( \beta \)-lactams (15). Thus, targeting the higher end of the cephalosporin target range (e.g., 70% \( f_{T>\text{MIC}} \)) will capture the individual isolate with true kill targets that are lower than 70%, but the same is not true in reverse (i.e., targeting 50% \( f_{T>\text{MIC}} \)). Similarly, 60% to 74% \( f_{T>\text{MIC}} \) has been associated with improved clinical and microbiologic outcomes in observational studies of both Gram-negative infections and \( P. \text{aeruginosa} \) infections specifically (10, 11). Even higher targets have been suggested for suppression of resistance (16); however, in vivo and clinical confirmatory data are needed for this endpoint.

In conclusion, the current CLSI breakpoint dosing regimen of ceftazidime 2 g i.v. every 8 h resulted in adequate CFR in the setting of ceftazidime-susceptible carbapenem-resistant \( P. \text{aeruginosa} \), although extended infusion may provide improved exposure for isolates at the highest susceptible MIC (8 mg/liter). Pharmacodynamically enhanced doses of 2 g i.v. every 8 h improved cefepime PTA and CFR in the present analysis against cefepime-susceptible carbapenem-resistant \( P. \text{aeruginosa} \) compared with those of the current CLSI breakpoint doses. The introduction of cefepime SDD for MICs of 4 to 8 mg/liter would be a viable strategy to improve pharmacodynamic target attainment in cefepime-susceptible \( P. \text{aeruginosa} \), especially in the setting of carbapenem resistance not due to carbapenemase production.

**SUPPLEMENTAL MATERIAL**

Supplemental material is available online only.

**SUPPLEMENTAL FILE 1**

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