Activity of Ceftazidime-Avibactam against Fluoroquinolone-Resistant Enterobacteriaceae and Pseudomonas aeruginosa

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Ceftazidime-avibactam and comparator antibiotics were tested by the broth microdilution method against 200 Enterobacteriaceae and 25 Pseudomonas aeruginosa strains resistant to fluoroquinolones (including strains with the extended-spectrum β-lactamase [ESBL] phenotype and ceftazidime-resistant strains) collected from our institution. The MICs and mechanisms of resistance to fluoroquinolone were also studied. Ninety-nine percent of fluoroquinolone-resistant Enterobacteriaceae strains were inhibited at a ceftazidime-avibactam MIC of ≤4 mg/liter (using the susceptible CLSI breakpoint for ceftazidime alone as a reference). Ceftazidime-avibactam was very active against ESBL Escherichia coli (MIC<sub>90</sub> of 0.25 mg/liter), ESBL Klebsiella pneumoniae (MIC<sub>90</sub> of 0.5 mg/liter), ceftazidime-resistant AmpC-producing species (MIC<sub>90</sub> of 1 mg/liter), non-ESBL E. coli (MIC<sub>90</sub> of ≤0.125 mg/liter), non-ESBL K. pneumoniae (MIC<sub>90</sub> of 0.25 mg/liter), and ceftazidime-nonresistant AmpC-producing species (MIC<sub>90</sub> of ≤0.5 mg/liter). Ninety-six percent of fluoroquinolone-resistant P. aeruginosa strains were inhibited at a ceftazidime-avibactam MIC of ≤8 mg/liter (using the susceptible CLSI breakpoint for ceftazidime alone as a reference), with a MIC<sub>90</sub> of 8 mg/liter. Additionally, fluoroquinolone-resistant mutants from each species tested were obtained in vitro from two strains, one susceptible to ceftazidime and the other a β-lactamase producer with a high MIC against ceftazidime but susceptible to ceftazidime-avibactam. Thereby, the impact of fluoroquinolone resistance on the activity of ceftazidime-avibactam could be assessed. The MIC<sub>90</sub> values of ceftazidime-avibactam for the fluoroquinolone-resistant mutant strains of Enterobacteriaceae and P. aeruginosa were ≤4 mg/liter and ≤8 mg/liter, respectively. We conclude that the presence of fluoroquinolone resistance does not affect Enterobacteriaceae and P. aeruginosa susceptibility to ceftazidime-avibactam; that is, there is no cross-resistance.

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A vibactam is a broad-spectrum non-β-lactam β-lactamase inhibitor with activity against clinically relevant enzymes belonging to Ambler classes A, C, and some D (e.g., extended-spectrum β-lactamase [ESBL], Klebsiella pneumoniae carbapenemase [KPC], AmpC, and OXA-48) but not to class B β-lactamases (1–3). Strains that harbor such β-lactamases are increasing in prevalence worldwide, are among the most important and frequently isolated nosocomial pathogens, and are often additionally resistant to many classes of antibiotics, such as the fluoroquinolones (4). It is known, mainly in Pseudomonas aeruginosa but also in Enterobacteriaceae, that the overexpression of some efflux pumps that confer resistance to fluoroquinolones, often associated with other mechanisms, such as mutations in genes encoding DNA gyrase and topoisomerase IV or acquisition of some plasmid-mediated quinolone-resistance genes, may increase the MIC of β-lactam antibiotics, such as ceftazidime (5). The aim of this study was to evaluate the in vitro activity of the combination ceftazidime-avibactam at a fixed avibactam concentration of 4 mg/liter (19) compared with other β-lactam antibiotics, such as cefaroline, which is the active compound of ceftaroline fosamil, ceftazidime, piperacillin, piperacillin-tazobactam, aztreonam, imipemem, and meropenem, against fluoroquinolone-resistant Enterobacteriaceae and P. aeruginosa clinical isolates and against laboratory-generated fluoroquinolone-resistant mutants of the aforementioned microorganisms with a well-defined mechanism of resistance to quinolones.

MATERIALS AND METHODS

Bacterial strains. A series of 200 Enterobacteriaceae and 25 P. aeruginosa strains resistant to fluoroquinolones (mainly from urinary tract infections and bacteremia occurring in different patients) were collected as consecutive clinical isolates in our institution (Hospital Clinic, Barcelona, Spain). Enterobacteriaceae and P. aeruginosa isolates were considered resistant to fluoroquinolones according to EUCAST breakpoints for ciprofloxacin. Some Enterobacteriaceae isolates showing a MIC above the epidemiological cutoff but considered to be susceptible according EUCAST rules (0.064 to ≤0.5 mg/liter) and with any mechanism of resistance to fluoroquinolones were also studied. Species identification was performed using matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Bremen, Germany). An ESBL screen-positive phenotype was defined according to CLSI guidelines (6). Enterobacteriaceae and P. aeruginosa were considered resistant to ceftazidime using the CLSI breakpoints for ceftazidime (>16 mg/liter and >32 mg/liter, respectively). The collection included Escherichia coli (n = 60; 50% ESBL), K. pneumoniae (n = 40; 50% ESBL), Enterobacter cloacae (n = 25; 20% ceftazidime resistant), Citrobacter freundii (n = 25; 68% ceftazidime resistant), Serratia marcescens (n = 25; 20% ceftazidime resistant)
### TABLE 1 Activity of ceftazidime-avibactam and comparators against fluoroquinolone-resistant Enterobacteriaceae and *P. aeruginosa* isolates

<table>
<thead>
<tr>
<th>Microorganism (no. of isolates tested)</th>
<th>Meropenem (MIC&lt;sub&gt;90&lt;/sub&gt; Range)</th>
<th>Imipenem (MIC&lt;sub&gt;90&lt;/sub&gt; Range)</th>
<th>Piperacillin (MIC&lt;sub&gt;90&lt;/sub&gt; Range)</th>
<th>Piperacillin-tazobactam&lt;sup&gt;b&lt;/sup&gt; (MIC&lt;sub&gt;90&lt;/sub&gt; Range)</th>
<th>Ceftazidime (MIC&lt;sub&gt;90&lt;/sub&gt; Range)</th>
<th>Aztreonam (MIC&lt;sub&gt;90&lt;/sub&gt; Range)</th>
<th>Ceftazidime-avibactam&lt;sup&gt;c&lt;/sup&gt; (MIC&lt;sub&gt;90&lt;/sub&gt; Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacteriaceae (200)</strong></td>
<td></td>
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<tr>
<td>Non-ESBL <em>E. coli</em> (30)</td>
<td>&lt;0.06 &lt;0.06 0.125 &lt;0.06 to 0.25 &gt;128 &lt;0.125 to &gt;128 16 0.125 to &gt;128 0.5 &lt;0.125 to 1</td>
<td>0.25 &lt;0.125 to 1 0.25 &lt;0.125 to 0.5 &lt;0.125 to 0.25</td>
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</tr>
<tr>
<td>ESBL <em>E. coli</em> (30)</td>
<td>&lt;0.06 &lt;0.06 0.125 &lt;0.06 to 0.5 &gt;128 &gt;128 128 4 to &gt;128 128 4 to &gt;128 64 0.25 to &gt;128 0.25 &lt;0.125 to 0.25</td>
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<tr>
<td>Non-ESBL <em>K. pneumoniae</em> (20)</td>
<td>0.125 &lt;0.06 to 2 0.5 &lt;0.06 to 0.5 &gt;128 8 to &gt;128 64 &lt;0.125 to &gt;128 0.5 &lt;0.125 to 64 0.5 &lt;0.125 to 0.5 0.5 &lt;0.125 to 1 0.25 0.03 to 1</td>
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<tr>
<td>ESBL <em>K. pneumoniae</em> (20)</td>
<td>&lt;0.06 &lt;0.06 to 4 0.25 &lt;0.06 to 1 &gt;128 &gt;128 &gt;128 4 to &gt;128 &gt;128 32 to &gt;128 &gt;128 128 to &gt;128 &gt;128 8 to &gt;128 &gt;128 8 to &gt;128 64 0.25 to &gt;128 0.25 &lt;0.125 to 0.25</td>
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<tr>
<td>Other CAZ-S <em>Enterobacteriaceae</em>&lt;sup&gt;d&lt;/sup&gt; (66)</td>
<td>&lt;0.06 &lt;0.06 to 1 4 &lt;0.06 to 8 &gt;128 0.25 to &gt;128 128 &lt;0.125 to &gt;128 &lt;0.125 to &gt;128 4 &lt;0.125 to &gt;128 2 &lt;0.125 to 4 0.5 &lt;0.015 to 1</td>
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<tr>
<td>Other CAZ-R <em>Enterobacteriaceae</em>&lt;sup&gt;d&lt;/sup&gt; (34)</td>
<td>1 &lt;0.06 to 2 4 0.125 to &gt;128 &gt;128 8 to &gt;128 &gt;128 0.25 to &gt;128 &gt;128 8 to &gt;128 &gt;128 &lt;0.125 to &gt;128 &gt;128 2 to &gt;128 &gt;128 1 &lt;0.125 to 128&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td><strong>P. aeruginosa</strong> (25)</td>
<td>16 0.125 to 64 32 0.5 to 64 &gt;128 2 to &gt;128 128 1 to &gt;128 &gt;128 2 to &gt;128 64 0.25 to 128 64 0.25 to 128 8 0.25 to 16</td>
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<sup>a</sup>Tazobactam at 4 mg/liter.
<sup>b</sup>Avibactam at 4 mg/liter.
<sup>c</sup>CAZ-S, ceftazidime-susceptible Enterobacteriaceae isolates: *P. mirabilis*, *E. cloacae*, *C. freundii*, and *S. marcescens*.
<sup>d</sup>CAZ-R, ceftazidime-resistant isolates: *P. mirabilis*, *E. cloacae*, *C. freundii*, and *S. marcescens* due to AmpC overproduction (*n* = 23), plasmid-mediated AmpC (*n* = 7), or ESBL-producing strains (*n* = 4).
<sup>e</sup>MIC of 128 mg/liter for a single AmpC-overproducing *S. marcescens* isolate with a MIC of 0.25 mg/liter versus meropenem. Otherwise, the range is <0.125 to 2 mg/liter.
sistant), Proteus mirabilis (n = 25; 28% ceftazidime resistant), and P. aeruginosa (n = 25; 24% ceftazidime resistant). For each species, additional quinolone-resistant mutants were generated in vitro from two different clinical isolates, one from an isolate with a low MIC against ceftazidime and one from a β-lactamase producer with a high MIC for ceftazidime but susceptible to ceftazidime-avibactam.

**In vitro susceptibility test methods.** The MIC values of imipenem, piperacillin, aztreonam, piperacillin-tazobactam, ciprofloxacin, norfloxacin, levofloxacin, nalidixic acid (Sigma-Aldrich Co., St. Louis, MO, USA), meropenem, cefotaroline, ceftazidime, and ceftazidime-avibactam (AstraZeneca) (avibactam was used at a fixed concentration of 4 mg/liter in combination with ceftazidime) were determined in Mueller-Hinton broth by the microdilution method according to CLSI guidelines (Oxoid Ltd., Basingstoke, United Kingdom) (6). The EUCAST breakpoints for ciprofloxacin, norfloxacin, and nalidixic acid MIC measurement were performed using Etest strips (AB bioMérieux, Solna, Sweden) in Mueller-Hinton broth by the multiple-step selection method, an inoculum (10⁹ CFU/ml) from an overnight broth culture was spread on Mueller-Hinton agar (Becton Dickinson, Sparks, MD, USA), an efflux pump inhibitor.

Detection of β-lactamas. Isolates with ESBL phenotypes were characterized by PCR and sequencing, as described before (7). Ceftazidime-resistant species showing an AmpC-overproduction phenotype or a plasmid-mediated AmpC phenotype were confirmed using a ceftazidime or cefotaxime-boronic acid synergy test with 30 µg of cephaloridine or cephalaxin discs (Becton Dickinson, Sparks, MD, USA) together with 400 µg phenylboronic acid (Sigma-Aldrich Co., St. Louis, MO, USA) (8).

Detection of the mechanisms of resistance to quinolones. Detection of mutations in the DNA gyrase and topoisomerase IV genes were studied by amplifying and sequencing the quinolone resistance-determining regions (QRDRs) of the gyrA, gyrB, parC, and parE genes by PCR, using primers described before (9–13). Investigation of plasmid-mediated quinolone resistance (PMQR) genes was performed via screening by PCR of gyrA, gyrB, qnrS, aac(3)Ib-cr, and qepA genes. The aac(3)Ib-cr gene was sequenced in all isolates. Overexpression of efflux pumps was investigated by performing ciprofloxacin, norfloxacin, and nalidixic acid MIC measurements using Etest strips (AB bioMérieux, Solna, Sweden) in Mueller-Hinton agar (Becton Dickinson, Sparks, MD, USA) in the absence and presence of 20 mg/liter phenylalanine-arginine-β-naphthylamide (PAβN; Becton Dickinson, Sparks, MD, USA), an efflux pump inhibitor.

**Selection of mutants.** Mutants were selected by following either a single- or multiple-step selection method. To perform a single-step selection method, an inoculum (10⁸ CFU/ml) from an overnight broth culture was spread on Mueller-Hinton agar (Becton Dickinson, Sparks, MD, USA) supplemented with ciprofloxacin at 2 to 4 × the MICs previously found. After overnight incubation, mutants with MICs that were ≥2-fold the MIC of ciprofloxacin were retained.

In the multiple-step selection method, several passages were performed. An inoculum (10⁶ CFU) was added to 10-ml aliquots of nutrient broth containing ciprofloxacin at the MICs found previously and incubated for up to 48 h. This was repeated daily, each time doubling the ciprofloxacin concentration. Daily subculturing was performed until mutants with MICs that were ≥2-fold the MIC of ciprofloxacin were streaked to single colonies and retained.

**RESULTS**

Using the CLSI breakpoints for ceftazidime (≤4 mg/liter for susceptibility), ceftazidime-avibactam was among the most active agents tested against the panel of fluoroquinolone-resistant Enterobacteriaceae (ciprofloxacin MIC of ≥0.5 mg/liter) studied (Table 1), with 99.7% susceptibility. Similarly, 96% of fluoroquinolone-resistant P. aeruginosa strains were inhibited by ≤8 mg/liter of ceftazidime-avibactam (using the CLSI susceptibility breakpoint for ceftazidime alone as a reference).

All fluoroquinolone-resistant E. coli isolates were inhibited by
ceftazidime-avibactam below the ceftazidime breakpoint (MIC$_{90}$ of ≤0.25 mg/liter), including ESBL-producing isolates (highest MIC detected, 0.5 mg/liter). The ESBLs carried by the E. coli isolates were mainly CTX-M-14, CTX-M-15, CTX-M-9, and SHV-12 (Table 2).

When tested against fluoroquinolone-resistant ESBL-producing (mainly CTX-M-15, CTX-M-1, and SHV-12) (Table 2) and non-ESBL-producing K. pneumoniae isolates, ceftazidime-avibactam inhibited all isolates below the ceftazidime breakpoint (MIC$_{90}$ of 0.25 mg/liter), and the highest MIC was 1 mg/liter.

Of the 25 fluoroquinolone-resistant C. freundii isolates, 17 were ceftazidime resistant; 4 of these were carrying ESBL enzymes, and 13 showed AmpC overproduction. All C. freundii isolates had ceftazidime-avibactam MIC values below the susceptibility breakpoint of ceftazidime alone. All ceftazidime-susceptible strains were inhibited by ≤0.125 mg/ml ceftazidime-avibactam, and ceftazidime-avibactam was active against all ceftazidime-resistant strains (MIC$_{90}$ of 1 mg/liter).

Ceftazidime-avibactam was active against 25 fluoroquinolone-resistant E. cloacae strains (MIC$_{90}$ of 0.5 mg/liter), including 5 ceftazidime-resistant strains that showed AmpC overproduction; the highest MIC detected was 1 mg/liter. In addition, ceftazidime-avibactam inhibited all strains of fluoroquinolone-resistant P. mirabilis (MIC$_{90}$ of 0.5 mg/liter), including seven ceftazidime-resistant strains showing a plasmid-AmpC production phenotype. The highest MIC observed in fluoroquinolone-resistant isolates was, again, 1 mg/liter.

Twenty-five fluoroquinolone-resistant S. marcescens isolates, including 5 with ceftazidime resistance, were tested. All strains but one were inhibited by ≤4 mg/liter ceftazidime-avibactam (MIC$_{90}$ of 1 mg/liter). One ceftazidime-resistant strain that showed an AmpC overproduction phenotype was not inhibited by ceftazidime-avibactam (MIC of 128 mg/liter).

Finally, MIC$_{90}$ values of ceftazidime-avibactam for 25 fluoroquinolone-resistant P. aeruginosa clinical isolates are also shown in Table 1. Ninety-six percent of isolates were inhibited by ≤8 mg/liter ceftazidime-avibactam (MIC$_{90}$ of 8 mg/liter). For the six isolates that were ceftazidime resistant, avibactam reversed ceftazidime resistance in 5 instances, while the remaining isolate was inhibited by 16 mg/liter ceftazidime-avibactam. Remarkably, ceftazidime-avibactam showed very good activity against meropenem-nonsusceptible P. aeruginosa (16 isolates), with 90% inhibited by ≤8 mg/liter ceftazidime-avibactam. This may be due to a loss of porins, mainly OprD, that affect carbapenems but not ceftazidime; however, further investigation is necessary to confirm this hypothesis.

The activity of quinolones against fluoroquinolone-resistant Enterobacteriaceae is presented in Table 3. Mechanisms of fluoroquinolone resistance detected and the associated ceftazidime-avibactam MIC ranges are shown in Table 4. Most of the fluoroquinolone-resistant strains studied (n = 200; 88.9%) showed mutations in gyrA and/or parC, gyrB, or parE QRDR regions. Twenty-five percent of the isolates did not have mutations in QRDR regions. PMQR genes were detected in 20 strains (K. pneumoniae, n = 9; E. cloacae, n = 8; C. freundii, n = 3); PMQR genes and overexpression of an efflux pump were observed in 3 strains (S. marcescens, n = 2; K. pneumoniae, n = 1), and 2 K. pneumoniae strains showed only an efflux pump overexpression. The ceftazidime-avibactam MIC ranges were not noticeably affected by the detected fluoroquinolone-resistance mechanisms, except in one S. marcescens strain that showed mutations in the QRDR regions.

The ceftazidime mechanisms of resistance in Enterobacteriaceae and associated ceftazidime MIC ranges are shown in Table 2. No changes in the ranges of the ceftazidime-avibactam MIC and ceftazidime resistance mechanisms were detected, except in one S. marcescens strain that showed AmpC overproduction.

When mutant strains resistant to fluoroquinolones were generated by selection in vitro, all Enterobacteriaceae and P. aeruginosa strains tested were inhibited by ≤4 and ≤8 mg/liter of ceftazidime-avibactam, respectively (Table 5). For the large majority of the strains, no significant increases in the ceftazidime-avibactam MICs were observed. Among 13 fluoroquinolone-resistant mutant strains, one 4-fold ceftazidime-avibactam MIC increase (0.25 mg/liter to 1 mg/liter) was observed in the strain S. marcescens 243 and its mutant strain, S. marcescens 272, which was inhibited by 8 mg/liter of ceftazidime due to AmpC overproduction. In this strain, the fluoroquinolone resistance mechanism detected was efflux pump overexpression.

**DISCUSSION**

The purpose of this study was to examine the activity of ceftazidime-avibactam against fluoroquinolone-resistant clinical iso-
CAZ-AVI, ceftazidime-avibactam; avibactam at 4 mg/liter.

Mechanisms of resistance

TABLE 4

<table>
<thead>
<tr>
<th>Organism (no. of strains)</th>
<th>No. (%) of strains resistant to fluoroquinolones detected with associated CAZ-AVI MIC ranges</th>
<th>CAZ-AVI MIC ranges</th>
<th>EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. aeruginosa (25)</td>
<td>20 (80)</td>
<td>0.25 to 165 mg/liter</td>
<td>0.125 to 128 mg/liter</td>
</tr>
<tr>
<td>S. marcescens (25)</td>
<td>20 (80)</td>
<td>0.25 to 165 mg/liter</td>
<td>0.125 to 128 mg/liter</td>
</tr>
<tr>
<td>P. mirabilis (30)</td>
<td>26 (86.7)</td>
<td>0.25 to 165 mg/liter</td>
<td>0.125 to 128 mg/liter</td>
</tr>
<tr>
<td>C. freundii (25)</td>
<td>20 (80)</td>
<td>0.25 to 165 mg/liter</td>
<td>0.125 to 128 mg/liter</td>
</tr>
<tr>
<td>K. pneumoniae (30)</td>
<td>26 (86.7)</td>
<td>0.25 to 165 mg/liter</td>
<td>0.125 to 128 mg/liter</td>
</tr>
</tbody>
</table>

No. (%) of strains resistant to fluoroquinolones detected with associated CAZ-AVI MIC ranges:

- P. aeruginosa: 20 (80) strains
- S. marcescens: 20 (80) strains
- P. mirabilis: 26 (86.7) strains
- C. freundii: 20 (80) strains
- K. pneumoniae: 26 (86.7) strains

CAZ-AVI: ceftazidime-avibactam.
TABLE 5 Activity of ceftazidime-avibactam against fluoroquinolone-resistant mutant strains obtained in vitro

<table>
<thead>
<tr>
<th>Strain (mutation type)a</th>
<th>Mechanism</th>
<th>MIC (mg/liter)b,c,d,e</th>
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<tbody>
<tr>
<td>E. coli 1 (parent)</td>
<td>gyrA (Ser83Leu)</td>
<td>CIP 0.047, CAZ 0.125, CAZAVI &lt;0.125</td>
</tr>
<tr>
<td>E. coli 2 (MUT-SP)</td>
<td>gyrA (Ser83Leu); parC (Ser80Arg); acrAB-tolC++</td>
<td>CIP 0.25, CAZ 0.125, CAZAVI 0.25</td>
</tr>
</tbody>
</table>

E. coli 242 (parent) | ND | CIP 0.047, CAZ 16, CAZAVI <0.125 |
E. coli 271 (MUT-SP) | Efflux pump | CIP 0.25, CAZ 16, CAZAVI <0.125 |
K. pneumoniae 229 (parent) | ND | CIP 0.023, CAZ AVI <0.125, CAZAVI <0.125 |
K. pneumoniae 255 (MUT-SS) | gyrA (Ser83Le) | CIP 0.25, CAZ 0.125, CAZAVI <0.125 |
K. pneumoniae 146 (parent) | qnrB | CIP 0.25, CAZAVI >128, CAZAVI <0.125 |
K. pneumoniae 251 (MUT-SS) | qnrB + efflux pump | CIP 16, CAZAVI >128, CAZAVI <0.125 |
P. mirabilis 127 (parent) | ND | CIP 0.032, CAZ AVI <0.125, CAZAVI <0.015 |
P. mirabilis 267 (MUT-SP) | Efflux pump | CIP 0.38, CAZ 0.125, CAZAVI <0.125 |
E. cloacae 131 (parent) | ND | CIP 0.032, CAZ 32, CAZAVI 0.25 |
E. cloacae 264 (MUT-SP) | Efflux pump | CIP 0.5, CAZAVI >128, CAZAVI 0.5 |
E. cloacae 123 (parent) | ND | CIP 0.016, CAZ 0.125, CAZAVI 0.125 |
E. cloacae 263 (MUT-SP) | Efflux pump | CIP 0.19, CAZ 0.25, CAZAVI 0.125 |
S. marcescens 147 (parent) | ND | CIP 0.064, CAZ AVI <0.125, CAZAVI <0.125 |
S. marcescens 261 (MUT-SS) | Efflux pump | CIP 0.75, CAZAVI <0.125, CAZAVI <0.125 |
S. marcescens 243 (parent) | ND | CIP 0.38, CAZ 8, CAZAVI 0.25 |
S. marcescens 272 (MUT-SP) | Efflux pump | CIP 8, CAZ 8, CAZAVI 1 |
C. freundii 145 (parent) | qnrB | CIP 0.125, CAZAVI >128, CAZAVI 0.25 |
C. freundii 253 (MUT-SS) | qnrB + gyrA (Ser83Le) | CIP 2, CAZAVI >128, CAZAVI <0.125 |
C. freundii 137 (parent) | ND | CIP 0.047, CAZ 0.125, CAZAVI 0.125 |
C. freundii 266 (MUT-SP) | Efflux pump | CIP 0.5, CAZ 0.5, CAZAVI 0.25 |
P. aeruginosa 51 (parent) | ND | CIP 0.25, CAZ 64, CAZAVI 8 |
P. aeruginosa 260 (MUT-SS) | Efflux pump | CIP 2, CAZ 64, CAZAVI 8 |
P. aeruginosa 124 (parent) | ND | CIP 0.125, CAZ 1, CAZAVI 1 |
P. aeruginosa 262 (MUT-SS) | Efflux pump | CIP 0.5, CAZ 1, CAZAVI 1 |

a MUT-SS, mutant strain obtained by a single step; MUT-SP, mutant strain obtained by serial passage.
b CIP, ciprofloxacin; CAZ, ceftazidime; CAZAVI, ceftazidime-avibactam.
c EUCAST susceptibility breakpoint for ciprofloxacin against Enterobacteriaceae and P. aeruginosa: ciprofloxacin MIC of ≤0.5 mg/liter determined by Etest.
d ND, not detected.
e ++, overexpression of acrAB-tolC.

Acknowledgments

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W.W.N. is an employee of AstraZeneca. T.A.K. is a former employee of AstraZeneca.

References


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