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***Background.*** DTR organisms are defined as nonsusceptible to all high-efficacy, low-toxicity antibiotics (penicillins, cephalosporins, carbapenems, and quinolones), leaving physicians with limited first-line treatment options. Analyses of electronic health records have shown that patients with DTR Gram-negative bacterial infections are more likely to receive inappropriate antibiotic therapy, have longer hospital stay and increased risk of mortality. CFDC is a novel parenteral siderophore cephalosporin with potent activity against aerobic Gram-negative pathogens, including carbapenem-resistant strains. We evaluated the *in vitro* activity of CFDC and comparators against DTR pathogens collected by the SIDERO-WT surveillance study.

***Methods.*** A total of 30,459 clinical isolates of Gram-negative bacilli were systematically collected from United States, Canada, and 11 EU countries during 2014–2017. MICs were determined by broth microdilution for a panel of 7 antibiotics, including CFDC, ceftazidime–avibactam (CZA), ceftolozane–tazobactam (C/T), colistin (CST), cefepime (FEP), meropenem (MEM), and ciprofloxacin (CIP) according to CLSI guidelines. All antibiotics were tested in cation-adjusted Mueller–Hinton broth (CAMHB) except CFDC, for which iron-depleted CAMHB was used. Susceptibility was determined according to CLSI interpretive breakpoints except CST, where EUCAST breakpoints were used. DTR pathogens were defined as being nonsusceptible to FEP, MEM, and CIP according to CLSI breakpoints.

***Results.*** Among 30,459 Gram-negative isolates collected between 2014 and 2017, 9.3% were nonsusceptible to FEP, MEM, and CIP and could be defined as DTR. DTR was most frequently observed in *Acinetobacter* spp. (55.5%), followed by *Burkholderia* spp. (19%), *Pseudomonas aeruginosa* (9.5%), and Enterobacterales (2.7%). Of the 1,173 *Stenotrophomonas maltophilia* tested, 97% had MEM MIC of ≥8 mg/L; however, only 2.9% could be defined as DTR. Cefiderocol was the most active antibiotic tested against DTR isolates with 94.5% DTR-*Acinetobacter* spp., 98.3% DTR-*P. aeruginosa*, and 99.8% DTR-Enterobacterales susceptible (Table 1).

***Conclusion.*** CFDC demonstrated potent activity against DTR Gram-negative pathogens with limited first-line treatment options.

**Table 1.**

| *Acinetobacter* spp. (n, 1794) | Breakpoints (S, R) | $MIC_{50}$ | $MIC_{90}$ | % S | % I | % R |
|---|---|---|---|---|---|---|
| Cefiderocol | ≤4, ≥16 | 0.25 | 2 | 94.5 | 2.5 | 3 |
| Colistin† | ≤2, ≥4 | 1 | 8 | 85 | – | 15 |
| Ceftazidime-avibactam* | N/A | 32 | >64 | – | – | – |
| Ceftolozane-tazobactam* | N/A | 32 | >64 | – | – | – |
| *P. aeruginosa* (n, 470) | Breakpoints (S, R) | $MIC_{50}$ | $MIC_{90}$ | % S | % I | % R |
| Cefiderocol | ≤4, ≥16 | 0.25 | 1 | 99.8 | 0.2 | 0 |
| Colistin† | ≤2, ≥4 | 1 | 2 | 98.3 | – | 1.7 |
| Ceftazidime-avibactam | ≤8/4, ≥16/4 | 16 | >64 | 49.5 | – | 50.5 |
| Ceftolozane-tazobactam | ≤4/4, ≥16/4 | 8 | >64 | 48.8 | 5.7 | 45.5 |
| Enterobacterales (n, 573) | Breakpoints (S, R) | $MIC_{50}$ | $MIC_{90}$ | % S | % I | % R |
| Cefiderocol | ≤4, ≥16 | 1 | 4 | 98.3 | 1.5 | 0.2 |
| Colistin† | ≤2, ≥4 | 1 | >8 | 68.2 | – | 31.8 |
| Ceftazidime-avibactam | ≤8/4, ≥16/4 | 1 | >64 | 78.2 | – | 21.8 |
| Ceftolozane-tazobactam | ≤2/4, ≥8/4 | >64 | >64 | 2.05 | 1.65 | 96.3 |

*No Breakpoint available; †EUCAST Breakpoint

***Disclosures.*** **All authors:** No reported disclosures.

**680. *In vitro* Activity of Ceftazidime–Avibactam and Comparator Agents Against *Pseudomonas aeruginosa* from ICU and Non-ICU Wards Collected in Latin America and Globally as Part of the ATLAS Surveillance Program 2016–2017**

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***Background.*** Ceftazidime–avibactam (CAZ-AVI) is a β-lactam/non-β-lactam β-lactamase inhibitor combination that can inhibit class A, C and some class D β-lactamases but not class B metallo-β-lactamases (MBLs). Antimicrobial resistance due to these β-lactamases and other mechanisms is increasing and is especially high in ICUs. This study evaluated the *in vitro* activity of CAZ-AVI and comparators against *Pseudomonas aeruginosa* isolates from patients in ICU and non-ICU wards.

***Methods.*** Nonduplicate clinical isolates were collected in 2016–2017 in Asia/Pacific, Europe, Latin America, and Middle East/Africa. Susceptibility testing was performed using CLSI broth microdilution and interpreted using CLSI 2019 breakpoints. PCR and sequencing were used to determine the β-lactamase genes present in all isolates with meropenem (MEM) MIC >2 µg/mL.

***Results.*** The activity of CAZ-AVI and comparators is shown in the table. Susceptibility rates among global *P. aeruginosa* were generally lower for isolates from patients in ICU than non-ICU wards, but this difference was small for CAZ-AVI (89% and 92% susceptible, respectively) and for amikacin and colistin. Among MEM-nonsusceptible (NS) isolates, CAZ-AVI was active against 72% and 70% of isolates, respectively, of which 18.4% and 18.7% were MBL-positive. CAZ AVI inhibited >83% of MEM-NS MBL-negative isolates globally. In Latin America (LA), CAZ-AVI was active against 87% of isolates from both ward types. Susceptibility rates were generally lower than the global average, especially among MEM-NS isolates and isolates from non-ICU wards. The proportion of MBL-positive isolates in the MEM-NS subset was only slightly higher in LA than globally (19.2% and 19.5% in ICU and non-ICU wards, respectively), suggesting the presence of additional resistance mechanisms. Only colistin exceeded the activity of CAZ-AVI against isolates collected globally and in LA.

***Conclusion.*** CAZ-AVI showed potent antimicrobial activity, second only to that of colistin, against *P. aeruginosa* isolates from both ICU and non-ICU wards, with >88% of isolates collected globally testing as susceptible. Activity was in part compromised by MBLs, although additional resistance mechanisms may also be responsible.

| | | Drug (% Susceptible) | | | | |
|---|---|---|---|---|---|---|
| Region/phenotype | Ward type (n) | CAZ-AVI | CAZ | MEM | AMK | CST |
| **Global** | | | | | | |
| All *P. aeruginosa* | ICU (2024) | 88.8 | 69.7 | 63.8 | 88.4 | 99.7 |
| | Non-ICU (4856) | 92.3 | 78.8 | 76.5 | 91.3 | 99.8 |
| MEM-NS | ICU (733) | 71.6 | 39.3 | 0.0 | 72.4 | 99.5 |
| | Non-ICU (1142) | 69.5 | 40.9 | 0.0 | 67.4 | 99.6 |
| MEM-NS MBL-negative | ICU (598) | 87.3 | 47.8 | 0.0 | 84.3 | 99.3 |
| | Non-ICU (929) | 83.7 | 49.8 | 0.0 | 79.0 | 99.5 |
| **Latin America** | | | | | | |
| All *P. aeruginosa* | ICU (434) | 86.6 | 67.5 | 61.5 | 80.9 | 99.5 |
| | Non-ICU (731) | 86.9 | 69.8 | 66.4 | 81.8 | 99.6 |
| MEM-NS | ICU (167) | 67.1 | 35.3 | 0.0 | 60.5 | 100 |
| | Non-ICU (246) | 61.0 | 32.1 | 0.0 | 51.6 | 99.2 |
| MEM-NS MBL-negative | ICU (135) | 82.2 | 43.0 | 0.0 | 73.3 | 100 |
| | Non-ICU (198) | 74.2 | 39.4 | 0.0 | 60.6 | 99.0 |

[a]Includes isolates from Asia/Pacific, Europe, Latin America, and Middle East/Africa
CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; MEM, meropenem; AMK, amikacin; CST, colistin; NS, nonsusceptible; MBL, metallo-β-lactamase

***Disclosures.*** **All authors:** No reported disclosures.

**681. *In vitro* Activity of the β-Lactamase Inhibitor QPX7728 in Combination with Several β-Lactams Against *Acinetobacter baumannii* (AB) and *Pseudomonas aeruginosa* (PSA)**

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***Background.*** QPX7728 (QPX) is a novel broad-spectrum boron-containing inhibitor of serine- and metallo-β-lactamases (MBLs). We evaluated the *in vitro* activity of QPX combined with several β-lactams against carbapenem-resistant AB (CRAB) and PSA clinical isolates with varying β-lactam resistance mechanisms.

***Methods.*** A total of 503 CRAB (meropenem [MEM] MIC ≥8 µg/mL) and 762 PSA clinical isolates were tested by the reference broth microdilution method against β-lactams alone and combined with QPX (4 µg/mL and 8 µg/mL). PSA isolates were selected to represent the normal distribution of MEM, ceftazidime–avibactam (CAZ-AVI), and ceftolozane-tazobactam (TOL-TAZ) resistance according to 2017 surveillance data (representative panel). Additionally, 262 PSA isolates that were either nonsusceptible (NS) to MEM (MIC, ≥4 µg/mL) or to TOL-TAZ (MIC, ≥8 µg/mL), or resistant (R) to CAZ-AVI (MIC, ≥16 µg/mL) (challenge panel) were also tested. Within this 262 strain challenge set, 56 strains carried MBLs and the majority also had nonfunctional OprD.

***Results.*** Against CRAB, QPX at 4 and 8 µg/mL increased the potency of all β-lactams tested. MEM-QPX was the most potent combination (table) displaying $MIC_{50}$/$MIC_{90}$ at 1/8 and 0.5/4 µg/mL with QPX at fixed 4 and 8 µg/mL, respectively. Susceptibility (S) to MEM was restored in >95% of strains. Against the 500 PSA from the representative panel, S for all QPX combinations was >90%. For the challenge panel, TOL-QPX and piperacillin (PIP)-QPX were the most potent combinations, restoring S in 76–77% of strains. TOL-QPX and MEM-QPX or cefepime (FEP)-QPX restored the MIC values to S rates when applying the CLSI breakpoint for the compound alone (comparison purposes only) in ~90% and ~75% of non-MBL-producing strains, respectively, vs. 60–70% for TOL-TAZ and CAZ-AVI. PIP-QPX reduce the MIC values to S values for PIP-TAZ in ~60% of MBL-producing strains vs. 20–30% and 3–7% for other QPX combinations and non-QPX tested combinations, respectively.

***Conclusion.*** Combinations of QPX with various β-lactam antibiotics displayed potent activity against CRAB and resistant PSA isolates and warrant further investigation.

| | $MIC_{50}$/$MIC_{90}$ (µg/ml) (% inhibited at the β-lactam alone breakpoint for CLSI [for comparison only]) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | MEM | MEM-QPX | TOL-TAZ | TOL-QPX | FEP | FEP-QPX | PIP-TAZ | PIP-QPX | CAZ-AVI |
| CRAB (503) | >32/>32 (1.0) | 0.5/4 (99.8) | 32/>32 (2.0) | 8/32 (40.2) | >32/>32 (0.6) | 16/32 (41.2) | ND | ND | ND |
| PSA (500), representative panel | 0.5/16 (84.8) | 0.25/8 (91.6) | 0.5/4 (91.8) | 0.5/1 (97.6) | 4/32 (74.4) | 2/8 (90.2) | 8/128 (71.6) | ND | 2/8 (92.2) |
| PSA (262), challenge panel | 16/>64 (41.6) | 4/>64 (66.0) | 8/>64 (48.9) | 1/>64 (77.1) | 32/>64 (19.8) | 8/>64 (64.9) | 128/>256 (16.8) | 16/32 (76.0) | 16/>64 (48.0) |
| PA (no MBL) (206) | 8/64 (51.0) | 4/16 (75.7) | 4/>64 (60.7) | 1/4 (91.7) | 32/>64 (24.3) | 8/16 (76.2) | 128/>256 (19.4) | 8/32 (80.1) | 8/64 (61.2) |
| PA (MBL) (56) | >64/>64 (7.1) | 64/>64 (30.4) | >64/>64 (5.4) | >64/>64 (23.2) | >64/>64 (3.6) | 64/>64 (23.2) | 128/>256 (7.1) | 16/64 (60.7) | >64/>64 (3.6) |

QPX at fixed 8 µg/ml. AVI and TAZ at fixed 4 µg/ml. Breakpoints: MEM ≤ 8 µg/ml; TOL ≤ 4 µg/ml; FEP ≤ 8 µg/ml; CAZ ≤ 8 µg/ml, PIP ≤ 16 µg/ml.
ND, not done.

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