Activity of Cefiderocol and Comparators against Isolates from Cancer Patients

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Abstract

Cefiderocol inhibited 97.5% of 478 Gram-negative isolates from cancer patients at ≤ 4 mg/L. It had potent activity against ESBL positive Enterobacteriaceae, carbapenem resistant Enterobacteriaceae, and non-fermenting Gram-negative bacilli including Pseudomonas aeruginosa, Stenotrophomonas maltophilia, and Acinetobacter spp. Amikacin, ceftazidime/avibactam and meropenem had appreciable activity against non-CRE Enterobacteriaceae. No comparators were active against MDR P. aeruginosa. Only trimethoprim/sulfamethoxazole had appreciable activity against S. maltophilia. Overall, cefiderocol was associated with the lowest level of resistance.

Gram-negative organisms (GNO) are the predominant bacterial pathogens at many cancer centers and many have developed resistance to commonly used antimicrobial agents. (1–4) Cefiderocol (CFDC) is a new siderophore cephalosporin which has been reported to be more stable than other beta-lactams against beta-lactamases including NDM-1 and KPC-3 carbapenemases.(5-6) Its vitro activity has been evaluated against GNOs from various sources, but data against organisms from cancer patients are rare. (7) We evaluated its activity against GNOs isolated exclusively from cancer patients. All organisms tested were clinical isolates (2014 to 2017) with > 90% being from blood cultures. Minimal inhibitory concentrations (MICs) were determined using a broth microdilution method.(8) When available CLSI or FDA breakpoints for susceptibility and resistance were used. Ten comparator agents were tested (Table 1). Trimethoprim/sulfamethoxazole was tested instead of aztreonam against Stenotrophomonas maltophilia only. Whole genome sequencing was done on the 12 isolates that...
were non-susceptible to CFDC (1 each of *E. coli*, *P. aeruginosa*, and *Citrobacter* spp., 2 *Klebsiella pneumoniae*, 3 Acinetobacter spp., and 4 *Enterobacter* spp.). (9)

Overall, 466 of the 478 isolates (97.5%) were susceptible to CFDC. Selected susceptibility test results are shown in Table 1. Against 52 ESBL positive *E. coli* isolates CFDC had an MIC\(_{90}\) value of 2.0 mg/L (range of < 0.03 to 4.0 mg/L). Comparator agents active against these isolates included amikacin, ceftazidime/avibactam, ceftolozane/tazobactam, meropenem, and tigecycline. Against 37 ESBL positive *Klebsiella pneumoniae* isolates, CFDC had MIC\(_{90}\) value of 2.0 mg/L. Overall, 36 of 37 isolates (97%) were susceptible to CFDC with a lone isolate having an MIC of >64.0 mg/L. Among comparator agents amikacin, ceftazidime/avibactam and meropenem had appreciable activity against these isolates.

**Activity against carbapenem-resistant Enterobacteriaceae**

Forty carbapenem-resistant *Enterobacteriaceae* were tested (23 *K. pneumonia*, 10 *E. coli*, and 7 *E. cloacae*). MIC\(_{90}\) value of CFDC against these isolates was 4.0 mg/L with 37 of the 40 isolates (92.5%) having CFDC MICs ≤ 4.0 mg/L. Three isolates (7.5%) had CFDC MICs of >4mg/L including 2 *Klebsiella* and one *Enterobacter* isolate. Among comparator agents only tigecycline had activity against these organisms with an MIC\(_{90}\) value of 4.0 mg/L.

**Activity against other Enterobacteriaceae**

Cefiderocol had good activity against ESBL negative *E. coli* and *Klebsiella* spp. and against *Citrobacter* spp. and Serratia spp. (data not shown). Among comparator agents amikacin, ceftazidime/avibactam, ceftolozane/tazobactam, meropenem and tigecycline were active against these isolates. Most agents were less active against *E. cloacae* than they were against *Citrobacter*
spp. Whilst CFDC inhibited 34 of 38 Enterobacter spp. isolates (89%) at ≤ 4.0 mg/L, 2 isolates had a MIC of 8.0 mg/L and 2 had MICs of > 64.0 mg/L. All agents except colistin had good activity against Serratia spp.

**Activity against Non-fermenting Gram Negative Bacilli (NFGNB)**

CFDC was the most active agent tested against *Stenotrophomonas maltophilia* with an MIC$_{90}$ of 0.25 mg/L, and a range of <0.03 to 4.0 mg/L. Among comparators only trimethoprim/sulfamethoxazole was active against *S. maltophilia*. CFDC was active against *Acinetobacter* spp., (MIC$_{90}$ of 4.0 mg/L). Two of 20 isolates tested were resistant to CFDC with MICs of 16.0 and >64.0 mg/L respectively. Among comparator agents amikacin, colistin, and tigecycline inhibited ≥ 90% of isolates. The MIC$_{90}$ of CFDC against 15 isolates of *Achromobacter* spp., was 0.125 mg/L. Among comparator agents imipenem had the best activity.

CFDC inhibited all 38 *P. aeruginosa* isolates that did not exhibit multi drug resistance at ≤ 1.0 mg/L. Comparator agents with activity against these isolates included ceftolozane/tazobactam, ceftazidime/avibactam, amikacin, colistin, and ceftazidime. Against 32 multi drug resistant *P. aeruginosa* isolates, CFDC was the most active agent tested with an MIC$_{90}$ of 1.0 mg/L. Only one isolate was resistant to CFDC with an MIC of >64.0 mg/L. The activity of comparator agents against these isolates was uniformly poor.

**Activity against uncommon organisms**

Cefiderocol inhibited all 7 *Burkholderia cepacia* isolates at ≤ 0.25 mg/L, all 7 *Pantoea* spp. isolates at ≤ 1.0 mg/L, all 7 *Sphingomonas paucimobilis* isolates at ≤ 0.5 mg/L, and all 3...
*Elizabethkingia meningoseptica* isolates at ≤ 4.0 mg/L. One of 8 *Rhizobacterium radiobacter* isolates was non-susceptible to CFDC (MIC – 8.0 mg/L).

**Non-susceptible isolates**

CFDC was associated with the lowest level of non-susceptibility (Table 1) The highest level of non-susceptibility to CFDC was seen amongst non-CRE *Enterobacter* spp. with 2 of 38 isolates (5.3%) being non-susceptible. Many comparators had non-susceptibility percentages of less than 2%. Of note, MDR *P. aeruginosa* non-susceptibility to CFDC was 3.1% whereas the non-susceptible range for comparator agents was 25 to 91%. The MIC distributions for individual organisms and antimicrobial agents are presented in Table 2. Distributions for CFDC showed lower MICs for non-susceptible organisms including CRE, MDR *P. aeruginosa* and *S. maltophilia* than all other agents tested.

Illumina MiSeq short-read whole-genome sequencing was performed for the cefiderocol resistant isolates followed by a focused analysis looking at presence of β-lactamase encoding genes and the composition of major porins known to contribute to β-lactam resistance. (9) *Klebsiella* spp. demonstrated OmpK36, K37 and K35 disruption and the presence of various β-lactamases. The *Enterobacter* spp. had alterations in OmpC and F and the presence of AmpC and ESBLs. Finally, the *Acinetobacter* spp. had the presence of carbapenemases and various β-lactamases. No clear mechanisms for cefiderocol resistance were found.

The standard of care for the treatment of febrile episodes in cancer patients is the prompt administration of empiric antibiotic therapy. (10) GNOs are now the predominant bacterial pathogens in this setting and resistance among many GNOs is increasing. CFDC has potent *in vitro* activity against a variety of GNOs isolated from patients with cancer, including...
carbapenem-resistant organisms and multidrug-resistant non-lactose fermenting organisms, including *S. maltophilia*. Based on these *in vitro* findings and the general exclusion of patients with cancer from registration studies, we believe future study of the clinical utility of CFDC in patients with cancer is warranted.

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Table 1. In vitro activity of cefiderocol and comparator agents against select clinical isolates.

| Isolate type                  | Antimicrobial Agent   | MIC 90 (mg/L) | Range of MICs (mg/L) | % Susceptible |
|-------------------------------|-----------------------|---------------|----------------------|---------------|
| *Escherichia coli* (ESBL Positive) n=52 | Cefiderocol           | 2             | <0.03 to 4           | 100           |
|                               | Ceftolozane/tazobactam | 32            | 0.125 to >64         | 82            |
|                               | Meropenem             | 0.06          | <0.03 to 0.25        | 100           |
|                               | Ceftazidime           | >64           | 1 to >64             | 15            |
|                               | Ceftazidime/avibactam | 1             | <0.03 to 4           | 100           |
|                               | Colistin              | 1             | 1 to 4               | N/A           |
|                               | Aztreonam             | >32           | <0.5 to >32          | 10            |
|                               | Amikacin              | 16            | <4 to 32             | 98            |
|                               | Ciprofloxacin         | >4            | <0.25 to >4          | 8             |
|                               | Cefepime              | >16           | <0.5 to >16          | 10            |
|                               | Tigecycline           | 0.5           | <0.25 to 2           | 100           |

| *Klebsiella pneumoniae* (ESBL Positive) n=37 | Cefiderocol           | 2             | 0.125 to >64         | 97            |
|                                              | Ceftolozane/tazobactam | 32            | 0.25 to >64         | 62            |
|                                              | Meropenem             | 0.125         | <0.03 to 4          | 97            |
|                                              | Ceftazidime           | >64           | 4 to >64            | 0             |
|                                              | Ceftazidime/avibactam | 0.5           | <0.03 to >64        | 97            |
|                                              | Colistin              | >8            | 1 to >8             | N/A           |
|                                              | Aztreonam             | >32           | 8 to >32            | 0             |
|                                              | Amikacin              | 16            | <4 to >64           | 92            |
|                                              | Ciprofloxacin         | >4            | <0.25 to >4         | 11            |
|                                              | Cefepime              | >16           | 1 to >16            | 11            |
| Antibiotic          | CRE (E. coli=10, E. cloacae =7 and K. pneumoniae =23). n=40 | Citrobacter spp. n=20 | E. cloacae n=38 | Serratia spp. n=20 |
|---------------------|------------------------------------------------------------|------------------------|----------------|------------------|
|                    | Tigecycline >4 <0.25 to >4 54                             |                        |                |                  |
| Cefiderocol         | 4 0.06 to >64 95                                          |                       |                |                  |
| Ceftriaxone/tazobactam | >64 0.5 to >64 18                                      |                       |                |                  |
| Meropenem           | >64 <0.03 to >64 18                                       |                       |                |                  |
| Ceftazidime         | >64 16 to >64 0                                          |                       |                |                  |
| Ceftazidime/avibactam | >64 0.06 to >64 78                                    |                       |                |                  |
| Colistin            | >8 <0.5 to >8 N/A                                        |                       |                |                  |
| Aztreonam           | >32 16 to >32 0                                          |                       |                |                  |
| Amikacin            | 64 <4 to >64 73                                           |                       |                |                  |
| Ciprofloxacin       | >4 <0.25 to >4 15                                         |                       |                |                  |
| Cefepime            | >16 <0.5 to >16 68                                        |                       |                |                  |
| Tigecycline         | 4 <0.25 to >4 65                                          |                       |                |                  |
| Citrobacter spp. n=20 | Cefiderocol 1 <0.03 to 8 95    |                       |                |                  |
| Ceftriaxone/tazobactam | 64 0.06 to >64 70                                      |                       |                |                  |
| Meropenem           | 0.25 <0.03 to 8 95                                        |                       |                |                  |
| Ceftazidime         | >64 0.25 to >64 60                                        |                       |                |                  |
| Ceftazidime/avibactam | 1 0.06 to 8 100                                         |                       |                |                  |
| Colistin            | 2 1 to >8 N/A                                             |                       |                |                  |
| Aztreonam           | >32 <0.5 to >32 55                                        |                       |                |                  |
| Amikacin            | <4 <4 100                                                 |                       |                |                  |
| Ciprofloxacin       | >4 <0.25 to >4 70                                         |                       |                |                  |
| Cefepime            | 16 <0.5 to >16 80                                         |                       |                |                  |
| Tigecycline         | 2 <0.25 to >4 95                                          |                       |                |                  |
| E. cloacae n=38 | Cefiderocol 4 <0.03 to >64 90                        |                       |                |                  |
| Ceftriaxone/tazobactam | >64 0.06 to >64 55                                       |                       |                |                  |
| Meropenem           | 1 <0.03 to 64 90                                          |                       |                |                  |
| Ceftazidime         | >64 0.125 to >64 95                                       |                       |                |                  |
| Ceftazidime/avibactam | 4 0.125 to 16 95                                         |                       |                |                  |
| Colistin            | >8 1 to >8 N/A                                             |                       |                |                  |
| Aztreonam           | >32 <0.5 to >32 45                                        |                       |                |                  |
| Amikacin            | <4 <4 100                                                 |                       |                |                  |
| Ciprofloxacin       | >4 <0.25 to >4 63                                         |                       |                |                  |
| Cefepime            | >16 <0.5 to >16 66                                        |                       |                |                  |
| Tigecycline         | 2 <0.25 to >4 90                                          |                       |                |                  |
| Serratia spp. n=20 | Cefiderocol 0.5 <0.03 to 0.5 100                      |                       |                |                  |
| Ceftriaxone/tazobactam | 0.5 0.25 to 1 100                                        |                       |                |                  |
| Meropenem           | 0.125 <0.03 to 0.125 100                                   |                       |                |                  |
| Ceftazidime         | 0.5 0.25 to 0.5 100                                        |                       |                |                  |
| Ceftazidime/avibactam | 0.5 0.06 to 0.5 100                                       |                       |                |                  |
| Colistin            | >8 >8 N/A                                                  |                       |                |                  |
| Aztreonam           | <0.5 <0.5 100                                              |                       |                |                  |
| Antibiotic                  | Acinetobacter spp. n=20 | P. aeruginosa (MDR) n=32 | S. maltophilia n=50 |
|-----------------------------|--------------------------|--------------------------|---------------------|
| Amikacin               | 8                        | >64                      | >64                 |
| Ciprofloxacin            | <0.25                    | 0.5 to >64               | 0.25 to >0.5        |
| Cefepime                | <0.5                     | 1 to >64                 | 1 to >64            |
| Tigecycline             | 2                        | 1 to 2                   | 2                   |
| Cefiderocol             | 4                        | <0.03 to >64             | 0.25 to >4          |
| Ceftolozane/tazobactam | >64                      | 0.5 to >64               | 0.5 to >64          |
| Meropenem               | >64                      | 1 to >64                 | 1 to >64            |
| Ceftazidime             | >64                      | 2 to >64                 | 2 to >64            |
| Ceftazidime/avibactam  | 32                       | 0.06 to >64              | 0.06 to >0.03       |
| Colistin                | 2                        | 1 to 2                   | 1                   |
| Aztreonam               | 32                       | 8 to 32                  | 2                   |
| Amikacin                | 16                       | <4 to >64                | <0.5 to >4          |
| Ciprofloxacin           | >4                       | 0.25 to >4               | 2 to >16            |
| Cefepime                | >16                      | <0.5 to >16              | 1                   |
| Tigecycline             | 2                        | <0.25 to 4               | 2                   |
| Cefiderocol             | 1                        | <0.03 to >64             | 1                   |
| Ceftolozane/tazobactam | >64                      | 0.5 to >64               | 0.5 to >64          |
| Meropenem               | >64                      | 1 to >64                 | 1 to >64            |
| Ceftazidime             | >64                      | 2 to >64                 | 2 to >64            |
| Ceftazidime/avibactam  | >64                      | 1 to >64                 | 1 to >64            |
| Colistin                | 8                        | 1 to >8                  | 1 to >8             |
| Aztreonam               | 32                       | 2 to >32                 | 2                   |
| Amikacin                | 64                       | <4 to >64                | <0.5 to >4          |
| Ciprofloxacin           | >4                       | 0.25 to >4               | 2                   |
| Cefepime                | >16                      | <0.5 to >16              | 1                   |
| Tigecycline             | 4                        | <0.25 to >4              | 1                   |
| Ceftazidime/avibactam  | >64                      | 1 to >64                 | 1 to >64            |
| Colistin                | >8                       | <0.5 to >8               | 1 to >8             |
| Trimethoprim/          | 0.5/9.5                  | <0.03/0.57 to 2/38       | 0.5/9.5             |
| Sulfamethoxazole       |                          |                          |                     |
| Amikacin                | >64                      | <4 to >64                | N/A                 |
| Ciprofloxacin           | >4                       | 0.5 to >4                | N/A                 |
| Cefepime                | >16                      | 8 to >16                 | N/A                 |
| Tigecycline             | >4                       | <0.25 to >4              | N/A                 |
Table 2. Distribution Table: In vitro activity of cefiderocol and comparator agents against commonly resistant bacterial isolates from cancer patients using MIC (mg/L) distribution data

|                  | <0.03 | 0.03 | 0.06 | 0.12 | 0.25 | 0.50 | 1 | 2 | 4 | 8 | 16 | 32 | 64 | >64 | Other |
|------------------|-------|------|------|------|------|------|---|---|---|---|----|----|----|-----|-------|
| **E. coli**      |       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| **ESBL positive**|       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| (n=52)           |       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| Cefiderocol      | 2     | 2    | 7    | 3    | 14   | 13   | 8 | 3 |   |   |    |    |    |     | 1    |
| Meropenem        | 32    | 2    | 14   | 3    | 1    |      |   |   |   |   |    |    |    |     |      |
| Cefotolozane/tazobactam | 6   | 15   | 14   | 3    | 3    | 1    | 1 | 1 | 3 | 2 |    |    |    |     |      |
| Cefazidime       | 3     | 1    | 4    | 7    | 12   | 7    | 8 | 10|    |   |    |    |    |     |      |
| Cefazidime/avibactam | 3 | 5   | 18   | 15   | 3    | 4    | 2 | 2 |    |   |    |    |    |     |      |
| Cefepime         | 2     | 2    | 4    | 8    | 11   | 5    | 8 | 1 |    |   |    |    |    |     |      |
| Aztreonam        | 1     | 3    | 11   | 10   | 19   |      |   |   |    |   |    |    |    |     |      |
| Amikacin         | 14    | 7    | 1    |      |      |      |   |   |    |   |    |    |    |     |      |
| Colistin         | 48    | 3    | 1    |      |      |      |   |   |    |   |    |    |    |     |      |
| Ciprofloxacin    | 2     | 1    |      |      |      |      |   |   |    |   |    |    |    |     |      |
|                  | 2 (<0.25); 47 (>4) |      |      |      |      |      |   |   |    |   |    |    |    |     |      |
| **K. pneumoniae**|       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| **ESBL positive**|       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| (n=37)           |       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| Cefiderocol      | 8     | 16   | 8    | 4    | 1    |      |   |   |    |   |    |    |    |     |      |
| Meropenem        | 5     | 14   | 14   | 1    | 1    |      |   |   |    |   |    |    |    |     |      |
| Cefotolozane/tazobactam | 2   | 7    | 4    | 10   | 8    | 1    | 2 | 3 |    |   |    |    |    |     |      |
| Cefazidime       | 1     | 1    | 3    | 8    | 16   |      |   |   |    |   |    |    |    |     |      |
| Cefazidime/avibactam | 1 | 1    | 3    | 15   | 13   | 3    |    |   |    |   |    |    |    |     |      |
| Cefepime         | 1     | 3    | 4    | 5    |      | 24   | (>16) |   |    |    |   |    |    |    |     |      |
| Aztreonam        | 1     | 6    | 22   |      | 8    | (>32) |   |   |    |   |    |    |    |     |      |
| Amikacin         | 6     | 4    | 2    | 25   | (<4) |      |   |   |    |   |    |    |    |     |      |
| Colistin         | 23    | 8    | 1    |      | 5    | (>8) |   |   |    |   |    |    |    |     |      |
| Ciprofloxacin    | 1     | 5    | 2    |      | 4    | (<0.25); 25 (>4) |   |   |    |   |    |    |    |     |      |
| Tigecycline      | 4     | 3    | 6    | 7    |    | 10 (<0.25); 7 (>4) |   |   |    |   |    |    |    |     |      |
| **E. cloacae**   |       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| (n=38)           |       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| Cefiderocol      | 1     | 1    | 1    | 3    | 9    | 8    | 8 | 3 | 2 |    |   |    |    |     |      |
| Meropenem        | 10    | 8    | 6    | 6    | 4    | 0    | 1 | 1 | 1 | 1 |    |    |    |     |      |
| Cefotolozane/tazobactam | 1   | 6    | 7    | 3    | 1    | 3    | 1 | 5 | 2 | 1 | 6 |    |    |     |      |
| Cefazidime       | 9     | 4    | 1    |      | 1    | 3    | 3 | 19|    |   |    |    |    |     |      |
| Cefazidime/avibactam | 4 | 12   | 6    | 8    | 3    | 3    | 16|    |    |   |    |    |    |     |      |
| Cefepime         | 1     | 2    | 2    | 1    | 2    | 22   | (<0.5); 8 (>6) |   |    |    |   |    |    |    |     |      |
| Aztreonam        | 3     | 1    | 3    | 2    | 9    | 10   | (<0.5); 10 (>32) |   |    |    |   |    |    |    |     |      |
| Amikacin         | 3     | 3    |      |      | 32   | (<4) |    |   |    |   |    |    |    |     |      |
| Colistin         | 18    | 4    | 1    | 1    |      | 14   | (>8) |   |    |    |   |    |    |    |     |      |
| Ciprofloxacin    | 2     | 4    |      |      | 24   | (<0.5); 8 (>4) |   |   |    |   |    |    |    |     |      |
| Tigecycline      | 6     | 4    | 3    | 2    |      | 21   | (<0.5); 2 (>4) |   |   |    |   |    |    |    |     |      |
| **CRE (n=40)**   |       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| **CRE E. coli**  |       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| (n=10)           |       |      |      |      |      |      |   |   |   |   |    |    |    |     |       |
| Cefiderocol      | 2     | 2    | 3    | 2    | 1    |      |   |   |    |   |    |    |    |     |      |
| Meropenem        | 1     | 2    | 4    | 1    | 1    |      |   |   |    |   |    |    |    |     |      |
| Cefotolozane/tazobactam | 1 | 1    | 1    | 1    | 1    | 1 | 1 | 4 |    |   |    |    |    |     |      |
| Cefazidime       | 2     | 2    | 6    |      |      |      |   |   |    |   |    |    |    |     |      |
| Drug                        | CRE K. pneumoniae (n=23) | CRE E. cloacae (n=7) | P. aeruginosa MDR (n=32) | Acinetobacter spp. (n=20) |
|-----------------------------|--------------------------|----------------------|--------------------------|--------------------------|
| Ceftazidime/avibactam      | 1 1 3 1 2 2             |                      |                          |                          |
| Cefepime                    | 1                         | 9 (>16)              |                          |                          |
| Aztreonam                  | 2 8                       |                      |                          |                          |
| Amikacin                   | 2 1 1 2 4 (<4)            |                      |                          |                          |
| Colistin                   | 7 1                       | 2 (<0.5)             |                          |                          |
| Ciprofloxacin              | 10 (>4)                   |                      |                          |                          |
| Tigecycline                | 1 2 1 2 4 (<0.25)         |                      |                          |                          |
| **CRE K. pneumoniae (n=23)** |                          |                      |                          |                          |
| Ceftazidime/avibactam      | 1 2 3 5 2 2 1 1 4        |                      |                          |                          |
| Cefepime                   | 23 (>16)                  |                      |                          |                          |
| Aztreonam                  | 18 (13 >32)               |                      |                          |                          |
| Amikacin                   | 6 1 4 1 2 9 (<4)          |                      |                          |                          |
| Colistin                   | 16 1 2 4 (>8)             |                      |                          |                          |
| Ciprofloxacin              | 1                         | 22 (>4)              |                          |                          |
| Tigecycline                | 1 5 5 8 3 (<0.25); 1 (>4) |                      |                          |                          |
| **CRE E. cloacae (n=7)**   |                          |                      |                          |                          |
| Ceftazidime/avibactam      | 1 4                       | 2                    |                          |                          |
| Cefepime                   | 1 1 1 1 1 1 3 (<0.5)      | 2                    |                          |                          |
| Aztreonam                  | 2 2                       | 3 (>32)              |                          |                          |
| Amikacin                   | 6 (<4)                    |                      |                          |                          |
| Colistin                   | 3 1                       | 3 (>8)               |                          |                          |
| Ciprofloxacin              | 6 (<0.25); 1 (>4)         |                      |                          |                          |
| Tigecycline                | 1 3 1 2 (<0.25)           |                      |                          |                          |
| **P. aeruginosa MDR (n=32)** |                          |                      |                          |                          |
| Ceftazidime/avibactam      | 6 9 6 6 4 1              | 12 (>16)             |                          |                          |
| Cefepime                   | 1 1 3 9 9 5 4            | 2 (>8)               |                          |                          |
| Aztreonam                  | 1 2                       | 12 (>16)             |                          |                          |
| Amikacin                   | 7 3 2 6 2 12 (<4)         | 3 (>0.25)            |                          |                          |
| Colistin                   | 3 21 4 2                 | 2 (>8)               |                          |                          |
| Ciprofloxacin              | 1 2 6 3                  | 3 (<0.25); 17 (>4)   |                          |                          |
| Tigecycline                | 1 1                      | 30 (>4)              |                          |                          |
| **Acinetobacter spp. (n=20)** |                          |                      |                          |                          |
| Ceftazidime/avibactam      | 8 4 1 2 1 1 1 1          | 1                    |                          |                          |
| Cefepime                   | 1 1 2 8 3                | 1                    | 1 1 3 1                  | 3                        |
| Aztreonam                  | 2 2                       | 3 (<0.25); 17 (>4)   |                          |                          |
| Amikacin                   | 7 3 2 6 2 12 (<4)         | 3 (>0.25)            |                          |                          |
| Colistin                   | 3 21 4 2                 | 2 (>8)               |                          |                          |
| Ciprofloxacin              | 1 2 6 3                  | 3 (<0.25); 17 (>4)   |                          |                          |
| Tigecycline                | 1 1                      | 30 (>4)              |                          |                          |
| Antibiotic          | MIC (μg/mL) |
|---------------------|-------------|
| Ceftazidime         | 4 3 2 3 3 2 3 |
| Ceftazidime/avibactam | 1 1  1 2 3 4 3 2 1  2 |
| Cefepime            | 7 3 1 2 1 2 (<0.5); 4 (>16) |
| Aztreonam           | 1 10 9 |
| Amikacin            | 1 2 1 16 (<4) |
| Colistin            | 9 11 |
| Ciprofloxacin       | 1 13 (<0.5); 6 (>4) |
| Tigecycline         | 1 4 5 1 9 (<0.25) |
References

1. Montassier E, Batard E, Gastinne T, Potel G, de La Cochetière MF. 2013. Recent changes in bacteremia in patients with cancer: a systematic review of epidemiology and antibiotic resistance. Eur J Clin Microbiol Infect Dis 32:841–850.

2. Kenneth V.I. Rolston, A. Freifeld, A. Zimmer, J. Baddley, Z. El Boghdadly, E. Maziarz, J. Montoya, S. Shoham, L. Strasfeld, J. Young, Y. Zhang JM. 2018. ESCMID: ESCMID eLibrary, p. P0673. In Bloodstream infection survey in high-risk oncology patients (BISHOP) with fever and neutropenia (FN): microbiology data. Madrid, Spain.

3. Rapoport B, Klastersky J, Raftopoulos H, Freifeld A, Aoun M, Zinner SH, Rolston KVI. 2016. The emerging problem of bacterial resistance in cancer patients; proceedings of a workshop held by MASCC “Neutropenia, Infection and Myelosuppression” Study Group during the MASCC annual meeting held in Berlin on 27–29 June 2013. Support Care Cancer 24:2819–26.

4. Patel G, Bonomo RA. 2013. “Stormy waters ahead”: global emergence of carbapenemases. Front Microbiol 4:48.

5. Kohira N, West J, Ito A, Ito-Horiyama T, Nakamura R, Sato T, Rittenhouse S, Tsuji M, Yamano Y. 2016. In Vitro Antimicrobial Activity of a Siderophore Cephalosporin, S-649266, against Enterobacteriaceae Clinical Isolates, Including Carbapenem-Resistant Strains. Antimicrob Agents Chemother 60:729–734.

6. Ito-Horiyama T, Ishii Y, Ito A, Sato T, Nakamura R, Fukuhara N, Tsuji M, Yamano Y, Yamaguchi K, Tateda K. Stability of Novel Siderophore Cephalosporin S-649266 against Clinically Relevant Carbapenemases. Antimicrob Agents Chemother. 2016 Jun 20;60(7):4384-6.

7. Ito A, Kohira N, Bouchillon SK, West J, Rittenhouse S, Sader HS, Rhomberg PR, Jones RN, Yoshizawa H, Nakamura R, Tsuji M, Yamano Y. 2016. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. J Antimicrob Chemother 71:670–677.

8. CLSI. Clinical and Laboratory Standards Institute. 2019. Performance Standards for Antimicrobial Susceptibility Testing An informational supplement for global application developed through the Clinical and Laboratory Standards Institute consensus process. 29th Edition.

9. Castanheira M, Doyle TB, Mendes RE, Sader HS. Comparative Activities of Ceftazidime-Avibactam and Ceftolozane-Tazobactam against Enterobacteriaceae Isolates Producing Extended-Spectrum β-Lactamases from U.S. Hospitals. Antimicrob Agents Chemother. 2019 Jun 24;63(7). pii: e00160-19.

10. Freifeld AG, Bow EJ, Sepkowitz KA, Boeckh MJ, Ito II, Mullen CA, Raad II, Rolston K V, Young JA, Wingard JR, America IDS of. 2011. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis 52:e56-93.