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Activity of Cefiderocol Against Carbapenem-Nonsusceptible Gram-Negative Isolates from Skin and Soft Tissue Infections in US and European Medical Centers Collected as Part of the SENTRY Antimicrobial Surveillance Program (2020–2024)

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INTRODUCTION

- Gram-negative pathogens are frequently isolated from certain skin and soft tissue infections (SSTIs) in patients with burns, diabetic foot infections, chronic wounds, and patients with compromised immune systems.[1]
- Multidrug-resistant (MDR) organisms, including those with carbapenem resistance, are often isolated from patients with prolonged hospital stays and exposure to first-line antibiotics, which may limit treatment options.[2]
- Cefiderocol is a siderophore-conjugated cephalosporin with activity against aerobic Gram-negative organisms, including MDR isolates.

OBJECTIVES

- To compare the activities of cefiderocol and comparator antibiotics among carbapenem-nonsusceptible Gram-negative isolates collected from patients with SSTIs at 44 sites in the USA and 42 sites in Europe, Israel, Turkey, and the UK from 2020 to 2024 as part of the SENTRY Antimicrobial Surveillance Program.

METHODS

- Minimum inhibitory concentration (MIC) values were determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines using the broth microdilution method with iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB) for cefiderocol and CAMHB for other antibiotics.
- Susceptibility to cefiderocol and comparator agents was determined by CLSI, US Food and Drug Administration (FDA), and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints.
- Carbapenem nonsusceptibility was defined as intermediate or resistant to imipenem and/or meropenem based on CLSI 2026 breakpoints. Only the meropenem MIC was used for organisms from the Morganellaceae family.
- Extensive drug resistance (XDR) was defined as nonsusceptibility to antibiotics of all but one or two classes tested.
- Difficult-to-treat resistance (DTR) was defined as nonsusceptibility to aztreonam, cefepime, ceftazidime, ciprofloxacin, levofloxacin, imipenem, meropenem, and piperacillin-tazobactam.

References

1. Moffarah AS, et al. Microbiol Spectr. 2016;4(4). doi: 10.1128/microbiolspec.dmih2-0014-2015.
2. Jabbour JF, et al. Curr Opin Infect Dis. 2020;33(2):146–154. doi: 10.1097/QCO.0000000000000635.

Disclosures
SS, BLMDJ, STN, TL, CL, HY, YY are employees of the Shionogi Group. JMM and REM are employees of Element Iowa City, which received compensation from Shionogi & Co., Ltd. for conducting the experiments associated with this study.

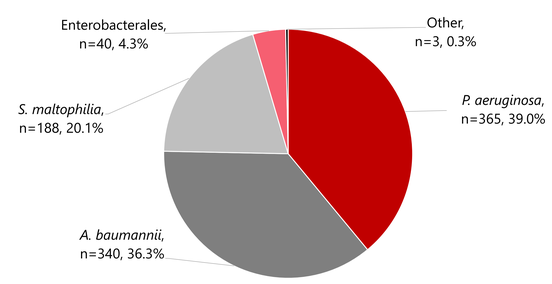
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RESULTS

- Among 4785 isolates collected from SSTIs, carbapenem nonsusceptibility was found in 936 isolates (19.6%) and included isolates primarily from wound/drainage cultures (**Figure 1**, **Figure 2**).
- Carbapenem nonsusceptibility rates were highest for *Acinetobacter baumannii-calcoaceticus* complex (38.9%) and *Pseudomonas aeruginosa* (19.1%), but low for Enterobacterales (2.6%).
- The most frequently identified carbapenem-nonsusceptible pathogen was *P. aeruginosa*, followed by *A. baumannii-calcoaceticus* complex and *Stenotrophomonas maltophilia* (**Figure 1**).
- Cefiderocol was highly active against carbapenem-nonsusceptible isolates, with >87.4% of all isolates susceptible using FDA breakpoints and >94.7% susceptible using CLSI breakpoints (**Table 1**).
- Cefiderocol was also highly active against XDR *A. baumannii-calcoaceticus* complex and DTR *P. aeruginosa* isolates, including those with resistance to ceftolozane-tazobactam (**Table 2**).

Figure 1. Carbapenem-nonsusceptible organisms isolated (n=936)



Other: *Acinetobacter radioresistens* (1), *A. ursingii* (2).

Figure 2. Culture sources of carbapenem-nonsusceptible isolates (n=936)

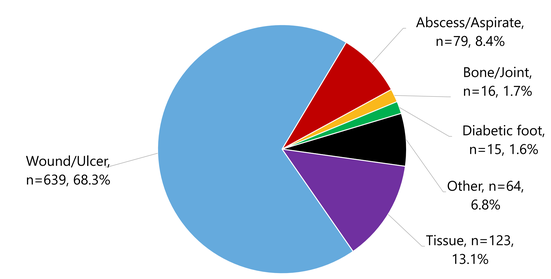


Table 1. Activity of cefiderocol and comparator agents against carbapenem-nonsusceptible Gram-negative isolates from SSTIs collected as part of the SENTRY surveillance program (2020–2024)

Isolate set (number tested)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	CLSI[a] %S	FDA[a] %S	EUCAST[a] %S
Carbapenem-nonsusceptible *P. aeruginosa* (n=365)[b]						
Cefiderocol	0.12	0.5	≤0.004 to 16	99.2	95.9	98.9
Imipenem-relebactam	1	4	0.06 to >8	87.7	87.7	87.7
Ceftazidime-avibactam	4	16	0.5 to >32	83.3	83.3	83.3
Ceftolozane-tazobactam	1	8	0.25 to >16	86.8	86.8	86.8
Meropenem-vaborbactam	8	>8	0.25 to >8	–	–	62.5
Cefepime	8	32	0.25 to >32	59.5	59.5	59.5
Piperacillin-tazobactam	32	>128	0.25 to >128	47.1	47.1	47.1
Ciprofloxacin	1	>4	0.015 to >4	47.4	47.4	47.4
Colistin	1	1	0.12 to 4	–	–	100
Carbapenem-nonsusceptible Enterobacterales (n=40)[b]						
Cefiderocol	0.5	4	0.015 to 8	97.5	97.5	80.0
Imipenem-relebactam	0.5	>8	0.06 to >8	70.0	70.0	75.0
Meropenem-vaborbactam	0.5	32	≤0.015 to >32	72.5	72.5	77.5
Ceftazidime-avibactam	1	>32	0.06 to >32	80.0	80.0	80.0
Aztreonam-avibactam	0.25	0.5	≤0.03 to 2	100	100	100
Colistin	0.25	>8	0.12 to >8	–	–	62.5
Carbapenem-nonsusceptible *A. baumannii-calcoaceticus* complex (n=340)[b]						
Cefiderocol	0.25	2	0.03 to >64	94.7	87.4	–
Sulbactam-durlobactam (n=162)[c]	2	4	≤0.25 to >32	95.7	95.7	–
Minocycline	8	16	0.12 to 32	25.6	25.6	–
Ampicillin-sulbactam	64	>64	2 to >64	8.8	8.8	–
Colistin	0.5	2	0.12 to >8	–	–	91.7
***S. maltophilia* (n=188)**						
Cefiderocol	0.06	0.25	0.015 to 8	98.4	98.4	–
Aztreonam-avibactam	2	4	0.5 to >16	–	–	–
Levofloxacin	1	4	0.12 to >32	83.0	–	–
Trimethoprim-sulfamethoxazole	≤0.12	0.5	≤0.12 to >4	97.9	–	–
Minocycline	0.25	1	0.12 to 16	90.9	–	–

[a]Criteria as published by CLSI (2026), EUCAST (2026), and US FDA (2026).
[b]Intermediate/resistant to meropenem and/or imipenem based on CLSI breakpoints.
[c]Only isolates collected in 2023 and 2024 were tested.

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit growth of ≥50%/90% of isolates; n, number; %S, percentage susceptible; SSTI, skin and soft tissue infection.

Table 2. Activity of cefiderocol and comparator agents against XDR *A. baumannii* and DTR *P. aeruginosa* isolates from SSTIs collected as part of the SENTRY surveillance program (2020–2024)

Isolate set (number tested)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	CLSI[a] %S	FDA[a] %S	EUCAST[a] %S
DTR *P. aeruginosa* (n=71)[b]						
Cefiderocol	0.12	2	≤0.004 to 2	100	87.3	100
Imipenem-relebactam	2	>8	0.25 to >8	63.4	63.4	63.4
Ceftazidime-avibactam	16	>32	2 to >32	47.9	47.9	47.9
Ceftolozane-tazobactam	4	>16	1 to >16	62.0	62.0	62.0
Colistin	1	1	0.25 to 2	–	–	100
***P. aeruginosa* nonsusceptible to ceftolozane-tazobactam (n=53)**						
Cefiderocol	0.25	2	0.015 to 16	96.2	79.2	96.2
Imipenem-relebactam	4	>8	0.25 to >8	49.1	49.1	49.1
Ceftazidime-avibactam	16	>32	2 to >32	28.3	28.3	28.3
Colistin	0.5	1	0.5 to 1	–	–	100
XDR *A. baumannii-calcoaceticus* complex (n=285)[c]						
Cefiderocol	0.25	2	0.03 to >64	93.7	86.3	90.5
Sulbactam-durlobactam (n=137)[d]	2	4	0.5 to >32	94.9	94.9	–
Minocycline	8	16	0.12 to 32	12.6	12.6	–
Ampicillin-sulbactam	64	>64	4 to >64	3.2	3.2	–
Colistin	0.5	2	0.12 to >8	–	–	90.8

[a]Criteria as published by CLSI (2026), EUCAST (2026), and US FDA (2026).
[b]Nonsusceptible to aztreonam, cefepime, ceftazidime, ciprofloxacin, imipenem, levofloxacin, meropenem, and piperacillin-tazobactam.
[c]Nonsusceptible to antibiotics of all but one or two classes tested.
[d]Only isolates collected in 2023 and 2024 were tested.

CLSI, Clinical and Laboratory Standards Institute; DTR, difficult-to-treat resistance; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, US Food and Drug Administration; MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit growth of ≥50%/90% of isolates; n, number; %S, percentage susceptible; SSTI, skin and soft tissue infection; XDR, extensive drug resistance.

CONCLUSIONS

- Cefiderocol maintained potent activity against highly resistant Gram-negative isolates collected from SSTIs, including carbapenem-nonsusceptible and XDR *A. baumannii-calcoaceticus* complex, carbapenem-nonsusceptible, DTR, and ceftolozane-tazobactam-nonsusceptible *P. aeruginosa*, carbapenem-nonsusceptible Enterobacterales, and *S. maltophilia*, and may be an important consideration for patients exhibiting SSTI with pathogens for which there are limited treatment options.