In vitro activity of cefiderocol against difficult-to-treat resistance European Gram-negative bacterial pathogens from the multi-national sentinel surveillance study, SENTRY in 2020 and 2021

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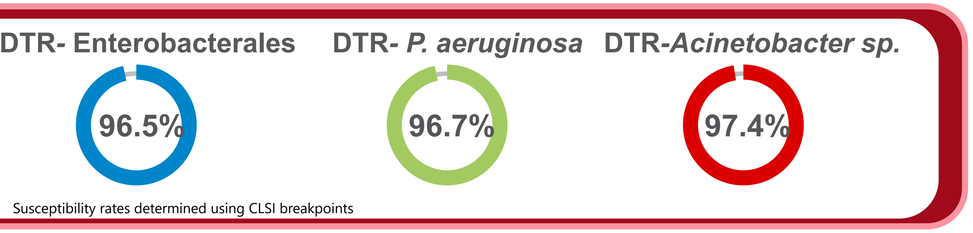
QUESTION What is the activity of cefiderocol and comparators against European isolates of difficult-to-treat resistance (DTR) Gram-negative pathogens?

CONCLUSION Cefiderocol was shown to have *in vitro* activity against a high proportion of DTR Gram-negative pathogens with limited first-line treatment options

RESULT



Susceptibility rates determined using CLSI breakpoints

BACKGROUND

DTR organisms are defined as non-susceptible to all first-line high-efficacy, low-toxicity antibiotics (penicillins, cephalosporins, carbapenems and quinolones), leaving physicians with limited treatment options[1]

Analyses of electronic health records have shown that patients with DTR Gram-negative bacterial infections have increased risk of mortality compared with patients with infections caused by Gram-negative bacteria with less-resistant phenotypes[2]

Cefiderocol is a novel parenteral siderophore cephalosporin with potent *in vitro* activity against aerobic Gram-negative pathogens, including carbapenem-resistant strains[3]

AIM

To evaluate the *in vitro* activity of cefiderocol and comparators against DTR clinical isolates collected during the SENTRY (2020-21) surveillance studies

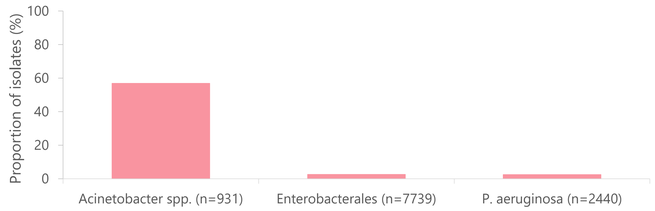
METHODS

[a] Antibiotics were tested centrally by JMI (North Liberty, Iowa, US), according to CLSI guidelines, in cation-adjusted Mueller-Hinton broth (CAMHB) except for cefiderocol, for which iron-depleted CAMHB was used.

RESULTS

Among 11434 Gram-negative isolates collected in the SENTRY (2020-21) study in Europe, Israel and Turkey, 792 (7.0%) were defined as DTR as being resistant to all 1st line therapy.

FIGURE 1. Proportion of isolates defined as DTR



Susceptibility of DTR isolates to cefiderocol and comparators according to CLSI and EUCAST breakpoints is shown in **Table 1.**

TABLE 1. *In vitro* susceptibility of DTR pathogens to cefiderocol and comparator agents

	MIC_{50}, mg/L	MIC_{90}, mg/L	EUCAST susceptibility BP, mg/L	% Susceptible by EUCAST	CLSI susceptibility BP, mg/L	% Susceptible by CLSI
DTR-*Acinetobacter* spp. (n=530)						
Cefiderocol	0.25	2	≤2[a]	94.5	≤4	97.4
Ampicillin/sulbactam	64	>64	≤8[b,c]	0.6	≤8	0.6
Minocycline	8	16	NA	NA	≤4	31.5
DTR-*P. aeruginosa* (n=61)						
Cefiderocol	0.25	2	≤2	93.4	≤4	96.7
Amikacin	>32	>32	≤16	27.9	≤16	27.9
Aztreonam/avibactam	16	>16	≤16	59.0	≤8	34.4
Ceftazidime/avibactam	32	>32	≤8	21.3	≤8	21.3
Ceftolozane/tazobactam	>16	>16	≤4	18.0	≤4	18.0
Imipenem/relebactam	>8	>8	≤2	27.9	≤2	27.9
DTR-Enterobacterales (n=201)						
Cefiderocol	1	4	≤2	83.1	≤4	96.5
Ampicillin/sulbactam	>64	>64	≤8	0	≤8	0
Aztreonam/avibactam[b]	0.25	0.5	≤4	99.5	≤4	99.5
Ceftazidime/avibactam	2	>32	≤8	78.1	≤8	78.1
Ceftolozane/tazobactam	0.5	>8	≤2	0	≤2	0
Imipenem/relebactam	2	>64	≤2	63.7	≤1	59.2
Meropenem/vaborbactam	2	32	≤8	63.7	≤4	58.7

Susceptibility >80%; Susceptibility >50% to ≤80%; Susceptibility ≤50%.

BP, breakpoint; CLSI, Clinical & Laboratory Standards Institute; DTR, difficult-to-treat resistance; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC_n, minimum inhibitory concentration required to inhibit growth of n% of organisms. NA:Non-Applicable

[a]EUCAST PK/PD breakpoint; [b] Based on aztreonam breakpoint for increased exposure; [c]Susceptibility for increased exposure

DISCUSSION

Based on susceptibility by EUCAST and CLSI breakpoints, rates of susceptibility were highest for cefiderocol, compared with the other agents tested, against DTR-Acinetobacter spp. (94.5% and 97.4%, respectively) and DTR-P. aeruginosa (93.4% and 96.7%, respectively). For DTR-Enterobacterales (83.1% and 96.5%, respectively) the difference in breakpoints influenced the susceptibility to cefiderocol indicating a large number of isolates with a MIC at 4 mg/L.

Aztreonam/avibactam was very potent against DTR-Enterobacterales but was less active against DTR- *P. aeruginosa*.

Ampicillin/sulbactam was active in less than 1% of the DTR-Acinetobacter spp isolates.

None of the drugs recommended by the IDSA for the treatment of resistant Gram-negative infections were as potent as cefiderocol (**Table 1**).

The higher susceptibility rates of cefiderocol against DTR isolates compared with the β-lactam/β-lactamase inhibitor combinations ceftazidime/avibactam and ceftolozane/tazobactam is likely to be due to its stability against both serine- and metallo-β-lactamases[6], and its novel mode of uptake through iron transporters, which makes its activity less affected by porin loss or increased efflux[7]

CONCLUSION

Cefiderocol was the only treatment option with demonstrated in vitro activity against more than 80% of all the tested DTR Gram-negative pathogens with limited treatment options.

References

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Disclosure

ASH is a contractor for Shionogi BV; CL is an employee of Shionogi BV; MT and YY are employees of Shionogi; DS and JMS are employees of JMI labs.