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Activity of Cefiderocol and Comparator Agents Against Uncommon Gram-negative Isolates Collected During 2020–2022 as Part of the SENTRY Antimicrobial Surveillance Program

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BACKGROUND

The majority of hospital-acquired infections involving Gram-negative bacteria are caused by four pathogens: *Escherichia coli*, *Klebsiella* spp., *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* complex. Cefiderocol is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria.[1]

OBJECTIVE

In this study, the activity of cefiderocol and comparator agents was determined against less commonly represented genera collected during the period 2020–2022 in Europe and the USA as part of the SENTRY antimicrobial surveillance program.

METHODS

- A total of 35,837 Gram-negative isolates were collected from clinical labs in Europe (n=18,409) and USA (n=17,428) during 2020–2022 as part of the SENTRY surveillance programme.
- Uncommon pathogens were defined as isolates from genera representing <5% of the total Gram-negative bacteria.
- Minimum inhibitory concentrations (MICs) were determined according to CLSI guidelines against 6,461 isolates using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparator agents and iron-depleted CAMHB for cefiderocol.
- Comparator agents included β-lactam/β-lactamase inhibitor combinations ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam, aztreonam-avibactam, and piperacillin-tazobactam, as well as meropenem, imipenem, ceftazidime, colistin, levofloxacin, amikacin, trimethoprim-sulfamethoxazole, and minocycline.
- For Enterobacterales, susceptibility was interpreted by both EUCAST (i.e., ≤2 µg/mL) and CLSI (i.e., ≤4 µg/mL) breakpoints. For glucose non-fermenters, activity was interpreted against EUCAST non-species related PK/PD breakpoints (i.e., ≤2 µg/mL).

RESULTS

- A total of 6,461 isolates were analysed of which 4,893 were Enterobacterales (20 genera) and 1,568 were glucose-non-fermenters (4 genera).
- As shown in Figure 1 and Figure 2, the most common Enterobacterales were *Proteus* spp. (32%), *Serratia* spp. (28%) and *Citrobacter* spp. (22%), with *Stenotrophomonas maltophilia* representing >75% of non-enterics.
- Enterobacterales remained susceptible to most antibiotics tested (Table 1) including cefiderocol (99.8% susceptible).
  - The exception was colistin with only 27.7 % susceptibility due to high numbers of *Proteus* spp., *Serratia* spp., *Morganella* spp., *Providencia* spp. and *Hafnia* spp. which are intrinsically resistant.
  - Among glucose non-fermenters, resistance was >50% for most antibiotics tested. Cefiderocol retained highest susceptibility (98.7%), while aztreonam-avibactam was active against *S. maltophilia* but had 16% resistance in *Burkholderia* spp. and no activity against *Achromobacter* spp. or *Chryseobacterium* spp.

Figure 1: Relative frequency of uncommon (<5% total) Gram-negative pathogens collected during 2020–2022 as part of the SENTRY Antimicrobial Surveillance Program A. Enterobacterales (N=4,893) and B. Glucose non-fermenters (N=1,568)

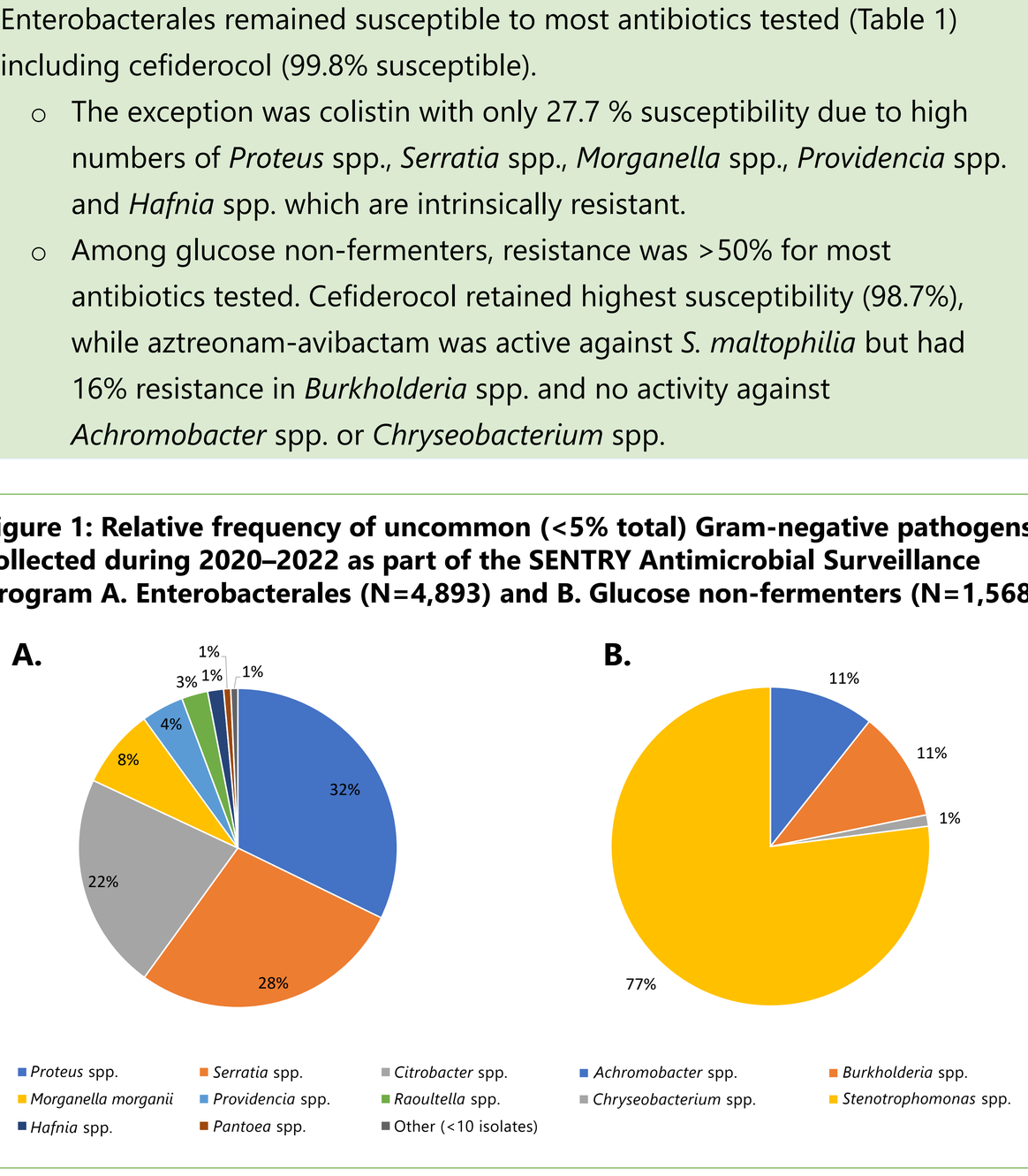
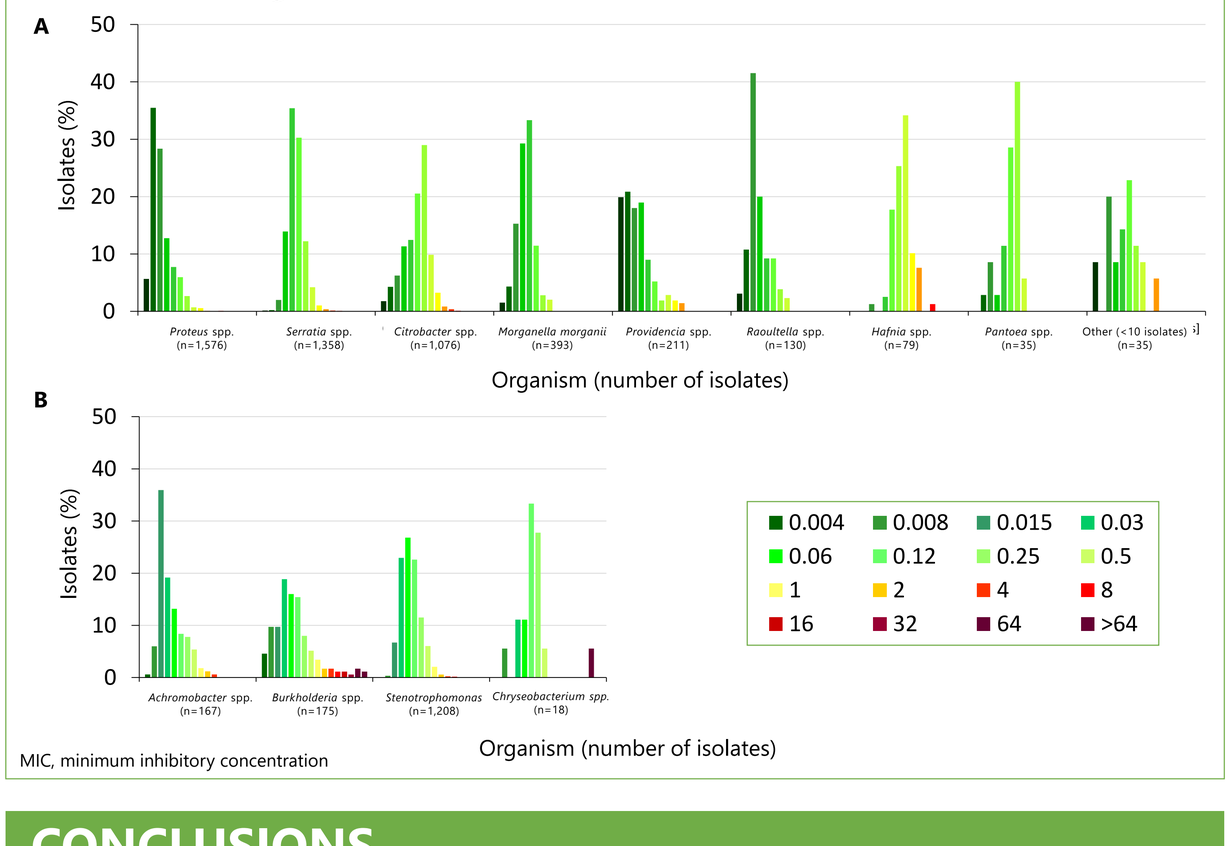


Table 1: Susceptibility of cefiderocol and comparator agents against uncommon (<5% total) Gram-negative pathogens collected during 2020–2022 as part of the SENTRY Antimicrobial Surveillance Program

Organism group / Agent	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC range (µg/mL)	EUCAST %S	EUCAST %R	CLSI %S	CLSI %I	CLSI %R
Uncommon Enterobacterales (N=4,893)[a]								
Cefiderocol	0.06	0.25	0.04–8	99.8	0.2	99.9	0.1	0
Imipenem-relebactam	0.5	2	0.03–>8	95.2	4.8	75.5	19.7	4.8
Meropenem-vaborbactam	0.06	0.12	0.015–>8	99.9	0.1	99.9	0	0.1
Ceftazidime-avibactam	0.12	0.25	0.015–>32	99.7	0.3	99.7	0	0.3
Ceftolozane-tazobactam	0.5	1	0.12–>16	95	5	95	1	4
Aztreonam-avibactam[b]	≤0.03	0.12	0.03–8	99.8	0.02	99.9	0.1	0
Ceftazidime	0.12	2	0.015–>32	88.1	9.5	91.7	1	7.3
Piperacillin-tazobactam	1	8	0.06–>128	90.6	9.4	90.6	3.2	6.2
Meropenem	0.06	0.12	0.015–>32	99.5	0.5	99.4	0.1	0.5
Imipenem	1	2	0.12–>8	94.1	0.8	70.1	24	5.9
Levofloxacin	0.06	2	0.015–>32	84.8	11	84.8	4.1	11.1
Amikacin	2	4	0.25–>32	(98.3)	1.7	93.2	5.1	1.7
Trimethoprim-sulfamethoxazole	≤0.12	>4	0.12–>4	86.3	13	86.3	–	13.7
Minocycline	4	16	0.06–>32	N/A	N/A	61.8	12.1	26.1
Colistin	>8	>8	0.06–>8	(27.7)	72.3	–	27.7	72.3
Organism group / Agent	**MIC_{50} (µg/mL)**	**MIC_{90} (µg/mL)**	**MIC range (µg/mL)**	**EUCAST[c] %S**	**EUCAST[c] %R**			
Uncommon glucose-non-fermenters (N=1,568)[d]								
Cefiderocol	0.06	0.5	0.004–>64	98.7	1.3			
Imipenem-relebactam	>8	>8	0.03–>8	21.1	78.9			
Meropenem-vaborbactam	>8	>8	0.015–>8	23.2	76.8			
Ceftazidime-avibactam	16	>32	0.03–>32	45.1	54.9			
Ceftolozane-tazobactam	>16	>16	0.12–>16	25.1	74.9			
Aztreonam-avibactam[b]	4	>16	0.03–>16	79.9	14.4			
Ceftazidime	32	>32	0.06–>32	24.9	66.2			
Piperacillin-tazobactam	>128	>128	0.06–>128	16.5	81			
Meropenem	>32	>32	0.015–>32	14.9	77.9			
Imipenem	>8	>8	0.12–>8	9.9	86.5			
Levofloxacin	1	8	0.015–>32	23.4	44.4			
Amikacin	>32	>32	0.25–>32	0.3	99.7			
Trimethoprim-sulfamethoxazole	≤0.12	1	0.12–>4	N/A	N/A			
Minocycline	0.5	2	0.06–>32	N/A	N/A			
Colistin	8	>8	0.06–>8	N/A	N/A			

[a]Organisms included: *Citrobacter amalonaticus / farmeri* (30), *C. braakii* (2), *C. freundii* (19), *C. freundii* species complex (512), *C. koseri* (503), *C. sedlakii* (1), *C. youngae* (1), *Cronobacter sakazakii* (4), *Hafnia alvei* (77), *H. alvei/ Hafnia paralvei* (2), *Kluyvera ascorbata* (4), *K. cryocrescens* (1), *K. georgiana* (1), *Kosakonia cowanii* (1), *Leclercia adecarboxylata* (2), *Lelliottia amnigena* (2), *Morganella morganii* (393), *Pantoea agglomerans* (21), *P. ananatis* (2), *P. anthophila* (1), *P. calida* (1), *P. dispersa* (2), *P. piersonii* (1), *Phytobacter diazotrophicus* (3), *Pluralibacter gergoviae* (8), *Proteus hauseri* (6), *P. mirabilis* (1,377), *P. penneri* (27), *P. vulgaris* (97), *P. vulgaris* group (69), *Providencia alcalifaciens* (1), *P. rettgeri* (103), *P. stuartii* (102), *Pseudocitrobacter faecalis* (1), *Rahnella aquatilis* (3), *Raoultella ornithinolytica* (64), *R. planticola* (13), *Serratia fonticola* (5), *S. liquefaciens* (34), *S. liquefaciens* complex (11), *S. marcescens* (1,299), *S. odorifera* (5), *S. rubidaea* (4), unspeciated *Citrobacter* (8), unspeciated *Erwinia* (1), unspeciated *Pantoea* (7), unspeciated *Providencia* (5), unspeciated *Raoultella* (53), Unspeciated *Yersinia* (not *Yersinia pestis*) (1), *Yersinia enterocolitica* (2), *Yokenella regensburger* (1); [b]Aztreonam breakpoint was used in the absence of approved breakpoint for aztreonam-avibactam; [c]Susceptibility was interpreted according to EUCAST PK/PD non-species related breakpoints only; [d]Organisms included: *Achromobacter denitrificans* (1), *A. insolitus* (3), *A. marplatensis* (1), *A. xylosoxidans* (30), *Burkholderia cepacia* species complex (162), *B. gladioli* (10), *B. multivorans* (3), *Chryseobacterium arthrosphaerae* (3), *C. gleum* (1), *C. indologenes* (12), *Stenotrophomonas maltophilia* (1,208), unspeciated *Achromobacter* (132), unspeciated *Chryseobacterium* (2); N/A, not applicable; S, susceptible; I, intermediate; MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit the growth of 50%/90% of organisms; R, resistant.

Figure 2: MIC distributions of cefiderocol against uncommon Gram-negative bacteria collected during 2022–2022 as part of the SENTRY Antimicrobial Surveillance Program A) Enterobacterales and B) Glucose non-fermenters



CONCLUSIONS

- Cefiderocol showed potent activity against a set of 6,461 contemporary uncommon Gram-negative clinical isolates. These *in vitro* data suggest that cefiderocol could be an important treatment option for infections caused by these infrequently isolated pathogens.

References

1. Shortridge D, et al. Microbiol Spectr. 2022;10(2):e0271221.

Acknowledgments

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