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In vitro activity of cefiderocol and comparators against isolates of Gram-negative bacterial pathogens from a range of infection sources: SIDERO–WT–2014–2018 studies in Spain

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ABSTRACT

Objectives: The incidence of antimicrobial resistance in Europe is rising. Cefiderocol is approved in Europe for treatment of aerobic Gram-negative bacterial (GNB) infections in adults with limited treatment options. We report the *in vitro* activity of cefiderocol versus comparators against GNB clinical isolates from Spain.

Methods: MICs were determined by broth microdilution according to International Organization for Standardization guidelines. Cefiderocol was tested using iron-depleted cation-adjusted Mueller–Hinton broth. Susceptibility rates were based on EUCAST breakpoints; if a species-specific breakpoint was unavailable, pharmacokinetic/pharmacodynamic breakpoints were used.

Results: Of 2303 isolates [1502 (65.2%) Enterobacterales and 801 (34.8%) non-fermenters], 2260 (98.1%) were susceptible to cefiderocol compared with 80.8–86.9% for comparators. By infection source, susceptibility to cefiderocol ranged from 97.3% (721/741) in isolates from patients with nosocomial pneumonia to 98.9% (349/353) in bloodstream infection isolates and was greater than susceptibility to comparators (70.7–93.6% across infection sources). Overall, 368/2303 isolates (16.0%) were meropenem-resistant. A high proportion of meropenem-resistant *Acinetobacter baumannii* [169/175 (96.6%)] and *Pseudomonas aeruginosa* [48/50 (96.0%)] were cefiderocol-susceptible, similar to colistin [169/175 (96.6%) and 47/50 (94.0%), respectively] but higher than ceftazidime/avibactam [26/175 (14.9%) and 20/50 (40.0%), respectively] and ceftolozane/tazobactam [17/175 (9.7%) and 25/50 (50.0%), respectively]. All meropenem-resistant *Stenotrophomonas maltophilia* isolates [120/120 (100%)] were cefiderocol-susceptible, including one trimethoprim/sulfamethoxazole-resistant isolate, with fewer susceptible to colistin [86/120 (71.7%)], ceftazidime/avibactam [42/120 (35.0%)] and ceftolozane/tazobactam [35/120 (29.2%)].

Conclusion: A high proportion of clinical isolates from Spain, representing a wide range of pathogens across multiple infection sources, were susceptible to cefiderocol. Cefiderocol retained activity against meropenem-resistant isolates.

1. Introduction

The incidence of antimicrobial resistance in Europe is rising. A major threat to patients is the increase in carbapenem-resistant (CR) Gram-negative bacteria (GNB) as there are few therapeutic options available [1,2].

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As in the rest of Europe, CR-GNB infections are a substantial burden on Spanish healthcare systems [2]; as a result, much research has been carried out into the epidemiology of CR-GNB infections. Cantón et al. estimated that ~3.2% (~12 090/372 346) of patients with nosocomial infections in Spain in 2017 had infection due to CR-GNB [mainly *Pseudomonas aeruginosa* (~6662], *Acinetobacter baumannii* (~4620) and *Klebsiella pneumoniae* (~809)] [3]. The CARBAR retrospective chart review of 11 040 adults admitted to hospital between April 2017 and March 2018 with confirmed GNB infection/colonisation demonstrated that 12% were infected with a CR-GNB pathogen and 63.4% (976/1539) of these were non-fermenter species [4]. Carbapenem resistance varies by pathogen, with higher levels generally observed in non-fermenter species than among Enterobacterales [3]. The prevalence of infections due to CR Enterobacterales in Spain appears to be slowly rising, with the European Centre for Disease Prevention and Control (ECDC) reporting an increase in prevalence of CR *K. pneumoniae* from 2.2% in 2015 to 3.8% in 2018 [1]. Correspondingly, a Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) analysis concluded that the prevalence of CR *K. pneumoniae* was 3.9% in 2019 [5]. SEIMC also reported in 2018 that the majority of a set of 903 isolates from multidrug-resistant (MDR) GNB infections were due to CR *P. aeruginosa* (11.4%), extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae* (9.4%) and CR *K. pneumoniae* (4.0%) [5].

A wide range of carbapenem resistance mechanisms are evident in Spanish regions. The PIRASOA surveillance programme analysed drug resistance mechanisms in 2005 MDR-GNB isolates from Andalusia from 2014–2018 [6]. A large proportion of isolates (62.0%) were carbapenemase-producers. The most common carbapenemases were found to be KPC-3 and OXA-48-like, and the prevalence of metallo-β-lactamases (MBLs) such as VIM, NDM and IMP increased dramatically from 1.5% (2/133) in 2014 to 45.5% (166/365) in 2018 [6]. In addition to the social burden of CR-GNB infections, total economic costs due to CR-GNB nosocomial infections in Spain were estimated at €472 million in 2017 [3].

There are limited treatment options available for patients with CR-GNB infections as they are often caused by MDR bacteria [7]. Although therapeutic options such as tigecycline and polymyxins are available, tigecycline outcomes are hampered by low serum concentrations of the drug and colistin is associated with considerable toxicities [8]. In addition, intrinsic resistance has been demonstrated in several species of Enterobacterales [9]. It is also important to highlight that even fewer treatment options exist for infections caused by MBL-producing GNB as current β-lactam/β-lactamase inhibitor combinations are ineffective [10].

Cefiderocol is a novel siderophore cephalosporin recently approved in Europe for the treatment of infections due to aerobic GNB organisms in adults with limited treatment options [11] and in the USA for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, and hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia caused by GNB isolates in adults with limited or no alternative treatment options [12]. The structure of cefiderocol consists of a cephalosporin core with a catechol functional group at the 3–position side chain. The mechanism of action of cefiderocol is the same as other cephalosporins, binding primarily to penicillin-binding proteins to inhibit peptidoglycan cell wall biosynthesis. The catechol moiety differentiates cefiderocol from other cephalosporins and allows cefiderocol to be actively transported into the cell as it chelates ferric (Fe-III) iron to mimic natural siderophores [13,14]. The resulting increase in periplasmic concentration bypasses non-specific resistance (e.g. due to porin loss or efflux) and increases the activity of cefiderocol relative to other cephalosporins, carbapenems and β-lactam/β-lactamase inhibitor combinations [12,15].

In the global SIDERO-WT surveillance studies, clinical isolates of GNB collected between 2014 and 2018 from hospitalised patients were tested against cefiderocol and comparators using recommended International Organization for Standardization (ISO) broth microdilution methodology [16]. Cefiderocol was tested using iron-depleted (iron concentration <0.03 mg/L) cation-adjusted Mueller–Hinton broth (CAMHB) according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [17]. Previous data published from the SIDERO-WT studies have demonstrated that cefiderocol is potent against a range of MDR-GNB, including CR isolates and those producing β-lactamases from all Ambler classes, including KPC, VIM, IMP, NDM and OXA [18–20].

In this report, we focus on the clinical isolates provided for the SIDERO-WT-2014–2018 studies by hospitals in Spain.

2. Methods

2.1. Study design

The full methodology for the SIDERO-WT studies and molecular characterisation of isolates by PCR has been published previously [21–23]. The presented data set represents pooled data from the SIDERO-WT studies for Spanish isolates only, collected between 2014 and 2018 with the exception of data for meropenem/vaborbactam and aztreonam/avibactam (2018).

2.2. Bacterial isolates

Participating sites were instructed to collect clinical GNB isolates from patients with documented intra-abdominal, urinary tract, skin and soft tissue, respiratory tract or bloodstream infections (BSI). Isolates included Enterobacterales (*Escherichia coli, K. pneumoniae, Klebsiella* spp., *Enterobacter* spp., *Serratia* spp. and *Citrobacter* spp.) and non-fermenters (*P. aeruginosa, A. baumannii, Burkholderia cepacia* and *Stenotrophomonas maltophilia*). *Proteus* spp., *Providencia* spp. and *Morganella* spp. were not initially included in the study but were collected from 2015 onwards. Only one isolate per patient infection episode was accepted; participating sites were requested to provide 100 isolates per site, per year. All isolates were from an unselected isolate population, collected independently of their antimicrobial susceptibility phenotype.

Isolates were identified by source of infection, and subgroups were created for nosocomial pneumonia (NP), cUTI, BSI and complicated intra-abdominal infection (cIAI) (see Supplementary material for more infection source detail).

2.3. Antimicrobial susceptibility testing

Isolates were tested at a central laboratory by International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA) and were identified using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Daltonics, Billerica, MA, USA). Molecular characterisation was performed only in a subset of 102 meropenem-resistant isolates by PCR and sequencing.

Minimum inhibitory concentrations (MICs) were determined for meropenem, ceftazidime/avibactam, ceftolozane/tazobactam, colistin and meropenem/vaborbactam by broth microdilution according to ISO guidelines [16] and for cefiderocol using EUCAST guidelines [17]. Aztreonam/avibactam was tested using ISO guidelines for aztreonam [16] with a fixed avibactam concentration of 4 mg/L. In addition, the activity of trimethoprim/sulfamethoxazole was tested only against *S. maltophilia*.

Susceptibilities to all antibiotics, with the exception of aztreonam/avibactam, were interpreted using EUCAST breakpoints;

Table 1
In vitro activity of cefiderocol against SIDERO-WT-2014–2018 isolates from Spain by infection source

Pathogen	Total			NP			cUTI			BSI/sepsis			cIAI		
	n	*N*	%S	*n*	*N*	%S	*n*	*N*	%S	*n*	*N*	%S	*n*	*N*	%S
Enterobacterales	1471	1502	97.9	301	316	95.3	201	207	97.1	282	286	98.6	403	406	99.3
Escherichia coli	369	373	98.9	32	32	100	47	48	97.9	98	100	98.0	137	138	99.3
Klebsiella pneumoniae	338	356	94.9	64	75	85.3	66	71	93.0	66	67	98.5	98	98	100
Other *Klebsiella* spp.	202	202	100	48	48	100	25	25	100	38	38	100	51	51	100
Enterobacter cloacae	130	135	96.3	36	39	92.3	10	10	100	19	19	100	27	28	96.4
Other *Enterobacter* spp.	30	32	93.8	4	5	80.0	1	1	100	4	5	80.0	16	16	100
Serratia marcescens	178	179	99.4	80	80	100	12	12	100	38	38	100	13	13	100
Other *Serratia* spp.	9	9	100	4	4	100	–	–	–	–	–	–	3	3	100
Citrobacter spp.	109	110	99.1	19	19	100	18	18	100	7	7	100	41	42	97.6
Proteus spp.	63	63	100	7	7	100	16	16	100	8	8	100	11	11	100
Morganella morganii	39	39	100	7	7	100	5	5	100	4	4	100	5	5	100
Providencia rettgeri	2	2	100	–	–	–	1	1	100	–	–	–	1	1	100
Raoultella spp.	2	2	100	–	–	–	–	–	–	–	–	–	–	–	–
Non-fermenters	789	801	98.5	420	425	98.8	75	76	98.7	67	67	100	60	62	96.8
Pseudomonas aeruginosa	372	375	99.2	191	193	99.0	33	33	100	34	34	100	34	35	97.1
Other *Pseudomonas* spp.	1	1	100	–	–	–	–	–	–	–	–	–	–	–	–
Acinetobacter baumannii	248	255	97.3	125	126	99.2	30	31	96.8	16	16	100	11	12	91.7
Other *Acinetobacter* spp.	16	16	100	6	6	100	3	3	100	–	–	–	–	–	–
Stenotrophomonas maltophilia	122	123	99.2	75	76	98.7	8	8	100	11	11	100	15	15	100
Burkholderia spp.	30	31	96.8	23	24	95.8	1	1	100	6	6	100	–	–	–
Total	2260	2303	98.1	721	741	97.3	276	283	97.5	349	353	98.9	463	468	98.9

BSI, bloodstream infection; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; *N*, total number of isolates tested; *n*, total number of isolates susceptible; NP, nosocomial pneumonia; %S, percent susceptible.

Table 2
Cefiderocol minimum inhibitory concentration (MIC) distribution by species for SIDERO-WT-2014–2018 isolates from Spain [a]

Species (*n*)	No. of isolates at cefiderocol MIC (mg/L) of:											
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
Enterobacterales (1502)	454	182	245	249	192	95	54	30	1	0	0	0
Escherichia coli (373)	152	44	54	55	35	21	8	4	0	0	0	0
Klebsiella spp. (558)	182	58	66	81	70	49	34	17	1	0	0	0
Klebsiella pneumoniae (356)	101	19	31	56	57	43	31	17	1	0	0	0
Enterobacter spp. (167)	12	7	22	54	36	17	12	7	0	0	0	0
Serratia spp. (188)	30	44	61	30	20	2	0	1	0	0	0	0
Citrobacter spp. (110)	25	12	23	18	25	6	0	1	0	0	0	0
Pseudomonas aeruginosa (375)	41	57	95	101	40	28	10	3	0	0	0	0
Acinetobacter baumannii (255)	27	54	73	42	23	19	10	7	0	0	0	0
Burkholderia spp. (31)	16	6	4	2	1	1	0	0	0	0	1	0
Stenotrophomonas maltophilia (123)	38	31	26	19	5	3	0	0	0	0	0	1

[a] ≥20 isolates tested.

where species-specific breakpoints were not available, pharmacokinetic/pharmacodynamic breakpoints were used (cefiderocol, ≤2 mg/L; colistin, ≤2 mg/L; ceftazidime/avibactam, ≤8 mg/L; and ceftolozane/tazobactam, ≤4 mg/L) [24]. Cefiderocol was tested using iron-depleted (iron concentration <0.03 mg/L) CAMHB [17], necessary to promote the natural production of siderophores by bacterial cells. All other antimicrobial agents were tested using standard CAMHB. Quality control testing was performed on each day of testing.

2.4. Statistical analysis

Post-hoc statistical analysis was carried out. Odds ratios with 95% confidence intervals were calculated based on the assumption that the odds ratio is normally distributed. Significance was determined by the null value (1) lying outside of the confidence interval.

3. Results

3.1. Epidemiology and cefiderocol data

3.1.1. Epidemiology

Twelve sites across Spain participated in the study (see Supplementary material for details of participating centres). In total, 2303 GNB clinical isolates were collected between 2014 and 2018; 1502 (65.2%) were Enterobacterales and 801 (34.8%) were non-fermenters. The most common Enterobacterales were *E. coli* [373/1502 (24.8%)] and *K. pneumoniae* [356/1502 (23.7%)]. The most common non-fermenters were *P. aeruginosa* [375/801 (46.8%)], *A. baumannii* [255/801 (31.8%)] and *S. maltophilia* [123/801 (15.4%)].

3.1.2. Cefiderocol results by infection source

Cefiderocol demonstrated activity against a wide range of pathogens regardless of the source of infection (Table 1). Susceptibility to cefiderocol across infection sources ranged from 97.3% in NP to 98.9% in BSI and cIAI.

3.1.3. Cefiderocol results by pathogen

A high proportion of isolates were susceptible to cefiderocol, ranging from 93.8% of *Enterobacter* spp. [with the exception of *Enterobacter cloacae* (96.3%)] to 100% of *Serratia* spp., *Proteus* spp., *Providencia* spp., *Morganella* spp. and *Acinetobacter* spp. (with the exception of *A. baumannii*) (Table 1).

Data for cefiderocol MIC distribution by species are presented in Table 2. In total, 43/2303 (1.9%) isolates were cefiderocol-resistant (MIC > 2 mg/L). Of these cefiderocol-resistant isolates, 31 were Enterobacterales (30 with MIC of 4 mg/L and 1 with MIC of 8 mg/L) including 18 *K. pneumoniae*. Moreover, 27 of the cefiderocol-resistant Enterobacterales were meropenem-susceptible, 16 were

Table 3
In vitro activity of cefiderocol and comparators against SIDERO-WT-2014–2018 isolates from Spain

Species (*n*) [a]	Antimicrobial agent	MIC (mg/L)			MIC interpretation (%S) [a]
		Range	MIC_{50}	MIC_{90}	
Enterobacterales (1502)	Cefiderocol	<0.002–8	0.12	1	97.9
	Meropenem	<0.06 to >64	<0.06	0.12	98.9
	Ceftolozane/tazobactam	<0.06 to >64	0.25	2	90.6
	Ceftazidime/avibactam	<0.03 to >64	0.12	0.5	98.7
	Colistin	<0.25 to >8	0.5	>8	78.3
	Meropenem/vaborbactam (*n* = 311)	<0.06–8	<0.06	<0.06	99.7
	Aztreonam/avibactam (*n* = 311)	<0.12–2	<0.12	0.25	NA
Escherichia coli (373)	Cefiderocol	<0.002–4	0.06	0.5	98.9
	Meropenem	<0.06 to >64	<0.06	<0.06	99.7
	Ceftolozane/tazobactam	<0.06 to >64	0.25	0.5	98.9
	Ceftazidime/avibactam	<0.03–32	0.12	0.25	99.5
	Colistin	<0.25–2	0.5	1	100
	Meropenem/vaborbactam (*n* = 76)	<0.06–0.12	<0.06	<0.06	100
	Aztreonam/avibactam (*n* = 76)	<0.12–<0.12	<0.12	<0.12	NA
Klebsiella spp. (558)	Cefiderocol	<0.002–8	0.12	1	96.8
	Meropenem	<0.06 to >64	<0.06	0.5	98.0
	Ceftolozane/tazobactam	0.12 to >64	0.25	8	85.5
	Ceftazidime/avibactam	<0.06 to >64	0.25	1	98.6
	Colistin	<0.25 to >8	0.5	1	96.4
	Meropenem/vaborbactam (*n* = 114)	<0.06–8	<0.06	<0.06	100
	Aztreonam/avibactam (*n* = 114)	<0.12–1	<0.12	0.25	NA
Klebsiella pneumoniae (356)	Cefiderocol	<0.002–8	0.25	2	94.9
	Meropenem	<0.06 to >64	<0.06	2	97.2
	Ceftolozane/tazobactam	0.12 to >64	0.25	32	80.9
	Ceftazidime/avibactam	<0.06 to >64	0.25	1	97.8
	Colistin	<0.25 to >8	0.5	2	94.7
	Meropenem/vaborbactam (*n* = 76)	<0.06–0.12	<0.06	<0.06	100
	Aztreonam/avibactam (*n* = 76	<0.12–1	<0.12	0.25	NA
Serratia spp. [b] (188)	Cefiderocol	0.008–4	0.12	0.5	99.5
	Meropenem	<0.06–64	<0.06	0.12	99.5
	Ceftolozane/tazobactam	0.12 to >64	0.5	1	96.8
	Ceftazidime/avibactam	<0.03 to >64	0.25	1	97.3
	Colistin	<0.25 to >8	>8	>8	6.4
	Meropenem/vaborbactam (*n* = 49)	<0.06–0.25	<0.06	0.12	100
	Aztreonam/avibactam (*n* = 49)	<0.12–1	<0.12	0.25	NA
Citrobacter spp. (110)	Cefiderocol	<0.002–4	0.12	0.5	99.1
	Meropenem	<0.06–1	<0.06	<0.06	100
	Ceftolozane/tazobactam	0.12–8	0.25	0.5	93.6
	Ceftazidime/avibactam	<0.06–1	0.12	0.25	100
	Colistin	<0.25–2	0.5	1	100
	Meropenem/vaborbactam (*n* = 24)	<0.06–<0.06	<0.06	<0.06	100
	Aztreonam/avibactam (*n* = 24)	<0.12–0.5	<0.12	<0.12	NA
Enterobacter spp. (167)	Cefiderocol	<0.002–4	0.25	2	95.8
	Meropenem	<0.06–64	<0.06	1	97.6
	Ceftolozane/tazobactam	0.12 to >64	0.25	32	76.0
	Ceftazidime/avibactam	<0.06 to >64	0.25	1	97.6
	Colistin	<0.25 to >8	0.5	>8	84.4
	Meropenem/vaborbactam (*n* = 33)	<0.06–2	<0.06	0.12	97.0
	Aztreonam/avibactam (*n* = 33)	<0.12–2	<0.12	1	NA
Proteus spp. [b] (63)	Cefiderocol	0.004–0.5	0.015	0.12	100
	Meropenem	<0.06–0.5	<0.06	0.12	100
	Ceftolozane/tazobactam	0.25–1	0.25	1	100
	Ceftazidime/avibactam	<0.06–0.25	<0.06	0.12	100
	Colistin	>8 to >8	>8	>8	0
	Meropenem/vaborbactam (*n* = 8)	<0.06–0.12	NA	NA	100
	Aztreonam/avibactam (*n* = 8)	<0.12	NA	NA	NA
Morganella morganii [b] (39)	Cefiderocol	0.015–0.5	0.12	0.5	100
	Meropenem	<0.06–0.12	0.12	0.12	100
	Ceftolozane/tazobactam	0.12–32	0.25	0.5	92.3
	Ceftazidime/avibactam	<0.06–0.5	<0.06	0.12	100
	Colistin	>8 to >8	>8	>8	0
	Meropenem/vaborbactam (*n* = 5)	<0.06–<0.06	NA	NA	100
	Aztreonam/avibactam (*n* = 5)	<0.12–<0.12	NA	NA	NA
Non-fermenters (801)	Cefiderocol	<0.002–64	0.12	1	98.5
	Meropenem	<0.06 to >64	8	>64	56.2
	Ceftolozane/tazobactam	<0.06 to >64	1	64	62.4
	Ceftazidime/avibactam	<0.06 to >64	4	64	64.8
	Colistin	<0.25 to >8	1	4	89.5
	Meropenem/vaborbactam (*n* = 165)	<0.06 to >64	2	64	60.6
	Aztreonam/avibactam (*n* = 165)	0.25 to >8	8	>8	NA

(*continued on next page*)

Table 3 (*continued*)

Species (n) [a]	Antimicrobial agent	MIC (mg/L)			MIC interpretation (%S) [a]
		Range	MIC_{50}	MIC_{90}	
Pseudomonas aeruginosa (375)	Cefiderocol	<0.002–4	0.12	1	99.2
	Meropenem	<0.06 to >64	0.5	16	86.7
	Ceftolozane/tazobactam	<0.06 to >64	0.5	4	92.3
	Ceftazidime/avibactam	<0.06 to >64	2	8	91.5
	Colistin	<0.25 to >8	1	2	98.4
	Meropenem/vaborbactam (n = 73)	<0.06–64	0.5	16	89.0
	Aztreonam/avibactam (n = 73)	0.25 to >8	8	>8	NA
Acinetobacter spp. (271)	Cefiderocol	0.004–4	0.12	1	97.4
	Meropenem	<0.06 to >64	64	>64	35.1
	Ceftolozane/tazobactam	<0.06 to >64	8	64	37.6
	Ceftazidime/avibactam	1 to >64	16	64	38.7
	Colistin	<0.25 to >8	0.5	2	95.6
	Meropenem/vaborbactam (n = 54)	0.12 to >64	64	64	42.6
	Aztreonam/avibactam (n = 54)	1 to >8	>8	>8	NA
Acinetobacter baumannii (255)	Cefiderocol	0.004–4	0.12	1	97.3
	Meropenem	0.12 to >64	64	>64	31.4
	Ceftolozane/tazobactam	<0.06 to >64	8	64	33.7
	Ceftazidime/avibactam	1 to >64	32	64	35.7
	Colistin	<0.25 to >8	0.5	2	95.3
	Meropenem/vaborbactam (n = 49)	0.12 to >64	64	64	36.7
	Aztreonam/avibactam (n = 49)	8 to >8	>8	>8	NA
Burkholderia spp. [b] (31)	Cefiderocol	<0.002–32	0.03	0.25	96.8
	Meropenem	2–32	8	16	83.9
	Ceftolozane/tazobactam	0.5 to >64	8	>64	45.2
	Ceftazidime/avibactam	0.25–32	4	16	83.9
	Colistin	8 to >8	>8	>8	0
	Meropenem/vaborbactam (n = 12)	1–16	NA	NA	91.7
	Aztreonam/avibactam (n = 12)	2–8	NA	NA	NA
Stenotrophomonas maltophilia [c] (123)	Cefiderocol	0.008–64	0.06	0.25	99.2
	Meropenem	1 to >64	>64	>64	2.4
	Ceftolozane/tazobactam	0.12 to >64	16	>64	30.1
	Ceftazidime/avibactam	0.5 to >64	16	>64	35.8
	Colistin	<0.25 to >8	2	8	71.5
	Meropenem/vaborbactam (n = 25)	32 to >32	>32	>32	0
	Aztreonam/avibactam (n = 25)	1–8	4	8	NA

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC of 50% and 90% of the tested isolates, respectively; NA, not applicable (<20 isolates or no breakpoint available); %S, percent susceptible.

[a] Where $n \geq 20$ isolates.

[b] Intrinsically resistant to colistin.

[c] Intrinsically resistant to meropenem.

colistin-susceptible, 28 were ceftazidime/avibactam-susceptible and 8 were ceftolozane/tazobactam-susceptible. In total, 12/801 (1.5%) non-fermenters were resistant to cefiderocol (10 isolates with MIC of 4 mg/L and one each with MIC of 32 mg/L and 64 mg/L), including 7 *A. baumannii* and 3 *P. aeruginosa*. Of these cefiderocol-resistant non-fermenters, 1 was meropenem-susceptible, 10 were colistin-susceptible, 1 was ceftazidime/avibactam-susceptible, 1 was ceftolozane/tazobactam-susceptible and 1 was aztreonam/avibactam-susceptible. The most common infection source of cefiderocol-resistant isolates was NP (n = 20).

3.1.4. Cefiderocol versus comparators

The isolate collection contained a wide range of pathogens, including some species that display intrinsic resistance to specific comparators; *Proteus* spp., *Providencia* spp., *Morganella* spp., *Serratia* spp. and *Burkholderia* spp. are intrinsically resistant to colistin [9], while *S. maltophilia* is intrinsically resistant to meropenem [25]. *In vitro* activity data for cefiderocol and comparators are shown in Table 3. Susceptibility to all antimicrobials was generally similar in species that are not intrinsically resistant to certain agents. However, susceptibility to cefiderocol was greater than ceftolozane/tazobactam in *Klebsiella* spp., *Citrobacter* spp. and *Enterobacter* spp. In addition, susceptibility to cefiderocol was greater than β-lactam/β-lactamase inhibitor combinations in non-fermenters, especially *Acinetobacter* spp. and *S. maltophilia*.

A significantly ($P < 0.01$) higher proportion of isolates was susceptible to cefiderocol [2260/2303 (98.1%)] compared with comparators overall and across all infection sources (Table 4). The proportion of Enterobacterales susceptible to cefiderocol ranged from 95.3% (301/316) in NP to 99.3% (403/406) in cIAI, and was significantly ($P < 0.01$) greater than the proportion of Enterobacterales susceptible to ceftolozane/tazobactam overall (97.9% vs. 90.5%) and for all infection sources. Susceptibility to cefiderocol in Enterobacterales was similar to meropenem and ceftazidime/avibactam overall and across all infection sources. Due to intrinsic resistance to *Proteus* spp., *Providencia* spp., *Morganella* spp. and *Serratia* spp., colistin showed variation across infection sources for Enterobacterales. The proportion of all Enterobacterales isolates susceptible to cefiderocol was significantly ($P < 0.01$) higher than to colistin [1176/1502 (78.3%)] overall. However, excluding *Proteus* spp., *Providencia* spp., *Morganella* spp. and *Serratia* spp., susceptibility to cefiderocol in Enterobacterales [1180/1210 (97.5%)] was similar to colistin [1164/1210 (96.2%)].

A significantly ($P < 0.01$) greater proportion of non-fermenters was susceptible to cefiderocol than all other antimicrobials tested. Susceptibility to cefiderocol [789/801 (98.5%)] was significantly ($P < 0.01$) greater than to ceftolozane/tazobactam [500/801 (62.4%)]

Table 4
In vitro susceptibility of cefiderocol and comparators against Enterobacterales, non-fermenters and overall, by infection source, for SIDERO-WT-2014–2018 isolates from Spain

Infection source	Pathogen group (n) [a]	Antimicrobial agent (% susceptible)					
		CFDC	MEM	C/T	CZA	CST	MVB [b] (n)
Overall	Enterobacterales (1502)	97.9	98.9	90.5 **	98.7	78.3 **	99.7 (311)
	Non-fermenters (801)	98.5	56.2 **	62.4 **	64.8 **	89.5 **	60.6 (165)
	All (2303)	98.1	84.0 **	80.8 **	86.9 **	82.2 **	86.1 (476)
NP	Enterobacterales (316)	95.3	98.7	86.1 **	97.8	67.1 **	98.7 (77)
	Non-fermenters (425)	98.8	53.6 **	59.3 **	62.6 **	86.4 **	57.1 (1684)
	All (741)	97.3	72.9 **	70.7 **	77.6 **	78.1 **	77.0 (161)
cUTI	Enterobacterales (207)	97.1	99.0	90.9 *	99.0	81.6 **	100 (42)
	Non-fermenters (76)	98.7	51.3 **	65.8 **	68.4 **	93.4	43.8 (16)
	All (283)	97.5	86.2 **	84.5 **	90.8 **	84.8 **	84.5 (58)
BSI	Enterobacterales (286)	98.6	99.0	90.9 **	99.0	80.8 **	100 (77)
	Non-fermenters (67)	100	58.2 †	67.2 †	67.2 †	83.6 †	50.0 (18)
	All (353)	98.9	91.2 **	86.4 **	92.9 **	81.3 **	90.5 (95)
cIAI	Enterobacterales (406)	99.3	99.0	91.1 **	98.8	88.4 **	98.0 (51)
	Non-fermenters (62)	96.8	58.1 **	58.1 **	58.1 **	93.5	100 (1)
	All (468)	98.9	93.6 **	86.8 **	93.4 **	89.1 **	98.1 (52)

BSI, bloodstream infection; CFDC, cefiderocol; cIAI, complicated intra-abdominal infection; CST, colistin; C/T, ceftolozane/tazobactam; cUTI, complicated urinary tract infection; CZA, ceftazidime/avibactam; MEM, meropenem; MVB, meropenem/vaborbactam; NP, nosocomial pneumonia.

[a] Enterobacterales includes isolates with intrinsic colistin resistance (n = 323); non-fermenters includes isolates with intrinsic meropenem resistance (n = 123) and those with intrinsic colistin resistance (n = 31).

[b] Isolates collected in 2017/2018 only (n = 476), no statistical analysis available.

* $P < 0.05$ versus cefiderocol;

** $P < 0.01$ versus cefiderocol;

† insufficient data to provide measure of significance.

Table 5
In vitro activity of cefiderocol and comparators against meropenem-resistant (MIC > 8 mg/L) SIDERO-WT-2014–2018 isolates from Spain

Species (n) [a]	Antimicrobial agent	MIC (mg/L)			MIC interpretation (%S)
		Range	MIC_{50}	MIC_{90}	
Acinetobacter baumannii (175)	Cefiderocol	0.015–4	0.25	1	96.6
	Ceftazidime/avibactam	4 to >64	32	>64	14.9
	Ceftolozane/tazobactam	2 to >64	16	>64	9.7
	Colistin	<0.25 to >8	0.5	2	96.6
Pseudomonas aeruginosa (50)	Cefiderocol	0.06–4	0.25	2	96.0
	Ceftazidime/avibactam	4 to >64	16	>64	40.0
	Ceftolozane/tazobactam	0.5 to >64	4	>64	50.0
	Colistin	<0.25–4	1	1	94.0
Stenotrophomonas maltophilia (123) [b]	Cefiderocol	0.015–1	0.06	0.25	100
	Ceftazidime/avibactam	1 to >64	16	>64	35.0
	Ceftolozane/tazobactam	0.25 to >64	16	>64	29.2
	Colistin	<0.25 to >8	2	8	71.7

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC of 50% and 90% of the tested isolates, respectively; %S, percent susceptible.

[a] Where $n \geq 20$ isolates.

[b] Intrinsically resistant to meropenem.

and ceftazidime/avibactam [519/801 (64.8%)] in non-fermenters overall and across NP, cUTI and cIAI infection sources. Susceptibility to cefiderocol was also substantially numerically higher than both β-lactam/β-lactamase combinations in BSI non-fermenters, but significance could not be determined due to the low number of available isolates. The proportion of non-fermenters susceptible to cefiderocol [789/801 (98.5%)] was significantly ($P < 0.01$) greater than to colistin against non-fermenters overall [717/801 (89.5%)] and in NP. Excluding intrinsically colistin-resistant *Burkholderia* spp. from the non-fermenters, cefiderocol retained higher activity than colistin overall [cefiderocol, 759/770 (98.6%); colistin, 717/770 (93.1%)] and in NP [cefiderocol, 397/401 (99.0%); colistin, 367/401 (91.5%)].

Aztreonam/avibactam and meropenem/vaborbactam were tested only against isolates from 2018 (n = 476) (Table 3). The aztreonam/avibactam MIC_{90} was 0.25 mg/L against Enterobacterales (n = 311) and >8 mg/L against non-fermenters (n = 165). The meropenem/vaborbactam MIC_{90} was <0.06 mg/L against Enterobacterales and 64 mg/L against non-fermenters. Susceptibility to meropenem/vaborbactam was substantially higher in Enterobacterales (99.7%) compared with non-fermenters (60.6%).

3.2. Meropenem-resistant isolates

Of the 2303 isolates tested, 368 (16.0%) were meropenem-resistant (MIC > 8 mg/L) (Table 5). A higher proportion of NP isolates was meropenem-resistant [201/741 (27.1%)] compared with other infection sources [cUTI, 39/283 (13.8%); BSI, 31/353 (8.8%); cIAI, 30/468 (6.4%)]. Only 1.1% (17/1502) of Enterobacterales were meropenem-resistant. By contrast, 43.8% (351/801) of non-fermenters were meropenem-resistant [50/375 (13.3%) of *P. aeruginosa* and 175/255 (68.6%) of *A. baumannii*]. Excluding *S. maltophilia* isolates with expected intrinsic resistance (n = 123), 11.4% (248/2180) of isolates were meropenem-resistant.

A high proportion of meropenem-resistant *A. baumannii, P. aeruginosa* and *S. maltophilia* isolates remained susceptible to cefiderocol (Table 5). Susceptibility to cefiderocol was similar to that of colistin against *A. baumannii* (cefiderocol, 96.6%; colistin, 96.6%) and *P. aeruginosa* (cefiderocol, 96.0%; colistin, 94.0%), while susceptibility to cefiderocol was numerically higher versus *S. maltophilia* (cefiderocol, 100%; colistin, 71.7%). Ceftazidime/avibactam and ceftolozane/tazobactam did not demonstrate high levels of activity against meropenem-resistant non-fermenters and it is notable that 50% of meropenem-resistant *P. aeruginosa* were resistant to ceftolozane/tazobactam.

Only *S. maltophilia* isolates collected in 2018 ($n = 25$) were tested against trimethoprim/sulfamethoxazole. One *S. maltophilia* isolate was resistant to trimethoprim/sulfamethoxazole (MIC = 4 mg/L) and all other comparator antimicrobials with the exception of cefiderocol (MIC = 0.06 mg/L); no aztreonam/avibactam breakpoint was available, but the MIC was 1 mg/L. The remaining 24 *S. maltophilia* isolates had trimethoprim/sulfamethoxazole MICs in the range between ≤0.012 mg/L and 1 mg/L.

Molecular characterisation was carried out for 102 meropenem-resistant isolates. The majority ($n = 76$) were *A. baumannii*, all of which were susceptible to cefiderocol; 37 OXA-23 and 37 OXA-24 carriers were identified, and 2 had no transferable β-lactamase genes. Of 20 *P. aeruginosa* isolates, 6 had VIM identified (3 VIM-20, 2 VIM-2 and 1 VIM-4), all of which were susceptible to cefiderocol, and 14 isolates had no transferable β–lactamases detected, with 1 isolate being resistant to cefiderocol. Identified genes in the four *K. pneumoniae* isolates were two OXA-48-like and two VIM-1; one VIM-1-producer was cefiderocol-resistant (MIC = 4 mg/L). The remaining two isolates were both susceptible to cefiderocol—one VIM–1 *Enterobacter asburiae* and one *Serratia marcescens* with no transferable β-lactamases detected.

4. Discussion

In this subset of Spanish isolates from the SIDERO-WT-2014–2018 study, cefiderocol demonstrated *in vitro* activity against GNB isolates from different infection sources. A significantly ($P < 0.01$) higher proportion of isolates was susceptible to cefiderocol compared with all comparators, and cefiderocol activity was similar across infection sources (Table 4). Susceptibility to cefiderocol in Enterobacterales was significantly ($P < 0.01$) greater than to ceftolozane/tazobactam and colistin, but similar to meropenem and ceftazidime/avibactam, while susceptibility to cefiderocol in non-fermenters was significantly ($P < 0.01$) greater than comparators. Of particular note is the fact that cefiderocol activity was significantly ($P < 0.01$) greater than all comparators against isolates from patients with NP. Few isolates were cefiderocol-resistant [43/2303 (1.9%)]. It is worth noting that 30/31 (96.8%) of cefiderocol-resistant Enterobacterales had an MIC of 4 mg/L and would be interpreted as susceptible using US Food and Drug Administration (FDA) or Clinical and Laboratory Standards Institute (CLSI) breakpoints [26,27]. Cefiderocol retained activity against meropenem-resistant isolates.

The study is limited by the fact that there are low numbers of isolates for some species by infection source, in particular non-fermenters in cUTI, BSI and cIAI sites. Furthermore, species such as *Proteus* spp., *Providencia* spp., *Morganella* spp. and *Burkholderia* spp. were not collected for the full duration of the study, and newer β-lactam/β-lactamase combinations (meropenem/vaborbactam and aztreonam/avibactam) were only included as comparators in 2018, so data are limited. Data on mechanisms of resistance are also incomplete, as molecular characterisation was only carried out for a subset of isolates. Participating sites were located primarily in cities, with one site in Mallorca; a third of the sites were located in Madrid, and no sites were located in the North-West region of Spain.

The general epidemiology for isolates from Spain is very similar to the SIDERO-WT overall European epidemiology, with the proportion of Enterobacterales in Spain [1502/2303 (65.2%)] similar to that for all of Europe [13 926/20 909 (66.6%)]. This is also comparable with data from the PIRASOA programme which found that 750/1243 isolates (60.3%) tested were Enterobacterales [6].

In this analysis, Enterobacterales are less relevant than non-fermenters for clinicians in Spain as a smaller proportion of Enterobacterales were meropenem-resistant compared with non-fermenters. In the SIDERO-WT-2014–2018 study, the overall prevalence of meropenem-resistant Enterobacterales in Spain [17/1502 (1.1%)] was similar to the European average [384/13 926 (2.8%)]. Meropenem resistance was much more prevalent in non-fermenters from Spain [351/801 (43.8%)] than Enterobacterales but was also similar to the European average [2847/6983 (40.8%)]. Of the EU5 (France, Germany, Italy, Spain and UK), only Italy [516/927 (55.7%)] had a higher prevalence of meropenem-resistant non-fermenter isolates than Spain.

The proportions of meropenem-resistant isolates for key species in SIDERO-WT are relatively consistent with previously published reports on the prevalence of carbapenem resistance for *K. pneumoniae* [SIDERO-WT, 3.9% (10/256); ECDC, 3.8%; Cantón, 2.7%], *P. aeruginosa* [SIDERO-WT, 13.3% (50/375); ECDC, 18.6%; Cantón, 18.4%] and *A. baumannii* [SIDERO-WT, 68.6% (175/255); ECDC, 53.4% *Acinetobacter* spp.; Cantón, 68.2% *Acinetobacter* spp.) [1,3].

Ceftolozane/tazobactam is commonly used to treat infections caused by *P. aeruginosa*, although activity against other non-fermenter species is generally limited [28,29]. In this study, susceptibility to ceftolozane/tazobactam (92.3%) for *P. aeruginosa* was higher than to ceftazidime/avibactam (91.5%) and meropenem (86.7%), but lower than that of colistin (98.4%) and cefiderocol (99.2%). Overall susceptibility to ceftolozane/tazobactam in non-fermenters was 62.4% due to the low susceptibility of other non-fermenter species (*Acinetobacter* spp., 37.6%; *Burkholderia* spp., 45.2%; *S. maltophilia*, 30.1%). Susceptibility to ceftazidime/avibactam (64.8%) was similar to ceftolozane/tazobactam (62.4%) overall versus non-fermenters.

The SUPERIOR multicentre study from intensive care units in Spain reported that 95.7% (44/46; MIC_{90} = 4 mg/L) of *P. aeruginosa* isolates from cUTI were susceptible to ceftolozane/tazobactam [30]. Similarly, the SIDERO-WT studies found that 93.9% (31/33; MIC_{90} = 1 mg/L) of *P. aeruginosa* isolates from cUTI were susceptible to ceftolozane/tazobactam. The SUPERIOR study also reported that 85.3% (29/34; MIC_{90} = 64 mg/L) of *P. aeruginosa* isolates from cIAI were susceptible to ceftolozane/tazobactam [30], while the proportion of cIAI *P. aeruginosa* isolates susceptible to ceftolozane/tazobactam [33/35 (94.3%); MIC_{90} = 1 mg/L] in SIDERO-WT was higher. The SUPERIOR study reported no activity of ceftolozane/tazobactam against carbapenemase-producing isolates [30]. In contrast to this, 48/50 (96.0%) of meropenem-resistant *P. aeruginosa* isolates were susceptible to cefiderocol in this study. As expected, the MIC_{90} for both aztreonam/avibactam and meropenem/vaborbactam was lower in Enterobacterales (0.25 mg/L and <0.06 mg/L, respectively) than in non-fermenters (>8 mg/L and 64 mg/L, respectively). Vaborbactam is active against GNB pathogens producing class A carbapenemases [31] but is not able to inhibit class B or D carbapenemases frequently detected in non-fermenters [31].

The prevalence of MBL-producing GNB is increasing, particularly in the south of Spain. For example, between 2014 and 2018 the prevalence of MBLs increased substantially from 1.5% (2/133) to 45.5% (166/365) in carbapenemase-producing GNB isolates collected from hospitals participating in the PIRASOA surveillance programme in Andalusia [6]. Longshaw et al. report from an *in*

vitro isolate study that cefiderocol demonstrated favourable activity when tested against a set of CR and MDR isolates harbouring a range of MBLs [20]. Of the antimicrobials tested, only cefiderocol and colistin had susceptibility rates of >50% versus VIM-producing Enterobacterales (cefiderocol, 79.0%; colistin, 93.5%), NDM-producing Enterobacterales (cefiderocol, 51.4%; colistin, 78.4%) and VIM- and GES-producing *P. aeruginosa* (cefiderocol, 100%; colistin, 100%) [20]. Similarly, among the meropenem-resistant Spanish isolates in the SIDERO-WT studies with available mechanisms of resistance data, 5/6 isolates with VIM genes detected that were tested were susceptible to cefiderocol and 5/6 were susceptible to colistin; none were susceptible to ceftazidime/avibactam or ceftolozane/tazobactam.

This study confirms previous reports that cefiderocol is active against a broad range of GNB from all types of infections [21–23]. However, there were low numbers of isolates highly resistant to other antimicrobials, meaning that many of the isolates in this study have other therapeutic alternatives. Full molecular characterisation was carried out for only a subset of meropenem-resistant isolates. The high number of isolates susceptible to antimicrobials tested may be due to low numbers of MBL-producing or ESBL-producing isolates. The PIRASOA programme reported a high prevalence (45.5%) of MBLs in 2018 [6]. Notably, MBL production was substantially lower (1.5%) in 2014 at the start of the PIRASOA programme [6]. Although the SIDERO-WT isolates were collected at the same time as the PIRASOA isolates, the SIDERO-WT isolates were unselected and were taken from multiple sites across Spain, meaning that it is not appropriate to compare prevalence data.

Cefiderocol is a promising alternative when few other treatment options for CR-GNB infections are available. Of particular importance is the activity of cefiderocol against MBL-producing GNB; the number of infections caused by MBL-producing GNB is increasing, but there are very few effective treatment options for such infections. Cefiderocol is active against MBL-producers and therefore could be a promising therapeutic option where MBL production is suspected [20].

A particular issue in Spain at present is the rapid dissemination of high-risk clones of GNB. Spread of KPC-producing *K. pneumoniae* clones ST11, ST101 and ST512 has occurred across multiple regions; ST101 is of particular concern owing to its hypervirulence and extensive resistance profile [32]. High-risk clones of *P. aeruginosa* (ST235, ST111 and ST175) in Spain have also been characterised [33]. It is concerning that *P. aeruginosa* ST235 is resistant to aminoglycosides, β-lactams and carbapenems and has been associated with transferable resistance [33]. Although strain information on the isolates in the SIDERO-WT studies are not available, cefiderocol is active against the vast majority of *K. pneumoniae* and *P. aeruginosa* isolates tested, including 96.0% of meropenem-resistant *P. aeruginosa* isolates, indicating the potential utility of cefiderocol in the clinical setting in Spain, regardless of strain identity.

An important aspect of controlling the spread of antimicrobial resistance is antibiotic stewardship. Carbapenems are widely considered to be a last-line treatment for patients with MDR-GNB infections. However, resistance to carbapenems is increasing and diversification of antibiotics is needed. While other options for CR-GNB infections exist, such as polymyxins, there are concerns about neurotoxicity and nephrotoxicity associated with these treatments [34]. Published clinical trial data on cefiderocol demonstrate that it is well tolerated and has a safety profile similar to other β-lactams [35,36]. Therefore, cefiderocol could be used in patients who are unable to tolerate polymyxins and other classes of antimicrobials.

The broad range of GNB susceptible to cefiderocol and its relative safety profile mean it is a promising option for empirical therapy in immunocompromised patients. However, cefiderocol also demonstrates potency against specific difficult-to-treat GNB, including those that are CR. Cefiderocol could therefore be used as a broad-spectrum empirical therapy where antimicrobial resistance is suspected or likely, or could be used as a targeted treatment against MDR-GNB once resistance profiles are available.

In conclusion, cefiderocol demonstrates high levels of activity against a wide range of GNB pathogens from multiple infection sources, including those resistant to meropenem. Cefiderocol was active against a range of isolates, including all classes of carbapenemase-producing Enterobacterales and MDR non-fermenters such as *A. baumannii, P. aeruginosa, Burkholderia* spp. and *S. maltophilia*, and is a potential therapeutic option for these organisms against which few other treatment options exist.

Data access

Data are available upon reasonable request from Shionogi & Co., Ltd.

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Competing interests

EC has participated in educational meetings sponsored by MSD and Pfizer; CL is an employee of Shionogi; RP is a former employee of Shionogi; ASH is a contract employee of Shionogi; AP reports grants from MSD and grants and personal fees from Shionogi, outside of the submitted work. LC declares no competing interests.

Ethical approval

Not required; all *in vitro* samples were anonymised and no patient specimens were analysed, only bacterial isolates from routine diagnostic culture.

References

[1] European Centre for Disease Prevention and Control (ECDC) Surveillance of antimicrobial resistance in Europe 2018, Stockholm, Sweden: ECDC; 2019. https://www.ecdc.europa.eu/sites/default/files/documents/surveillance-antimicrobial-resistance-Europe-2018.pdf [accessed 11 December 2020].

[2] Brolund A, Lagerqvist N, Byfors S, Struelens MJ, Monnet DL, Albiger B, et al. Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018. Euro Surveill 2019;24:1900123. doi:10.2807/1560-7917.ES.2019.24.9.1900123.

[3] Cantón R, Huarte R, Morata L, Trillo-Mata JL, Muñoz R, González J, et al. Determining the burden of infectious diseases caused by carbapenem-resistant Gram-negative bacteria in Spain. Enferm Infecc Microbiol Clin (Engl Ed) 2021;39:179–83. doi:10.1016/j.eimc.2020.04.009.

[4] Horcajada JP, Salavert M, De La Torre Cisneros J, Gracia-Ahufinger I, Paño Pardo JR, Vilchez Rueda HH, et al. A retrospective study to evaluate the epidemiology, standard of care, outcomes and resource utilisation in patients with

confirmed or suspected infection by a carbapenem-resistant Gram-negative organism in Spain: the CARBAR study part 1, epidemiology of Gram-negative organisms 30th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) Abstract Book. ESCMID; 2020. [abstract 4912] https://markterfolg.de/ESCMID/Abstractbook2020.pdf [accessed 11 December 2020].

[5] Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC) *Registro hospitalario de pacientes afectados por las resistencias bacterianas* [*Hospital registry of patients affected by bacterial resistance*]. SEIMC; 2018. https://seimc.org/contenidos/referencias/seimc-Registro_de_Pacientes_BMR.pdf [accessed 26 July 2021].

[6] López-Hernández I, Delgado-Valverde M, Fernández-Cuenca F, López-Cerero L, Machuca J, Pascual Á. Carbapenemase-producing Gram-negative bacteria in Andalusia, Spain 2014–2018. Emerg Infect Dis 2020;26:2218–22. doi:10.3201/eid2609.191772.

[7] Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis 2019;19:56–66. doi:10.1016/S1473-3099(18)30605-4.

[8] Ordooei Javan A, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. Eur J Clin Pharmacol 2015;71:801–10. doi:10.1007/s00228-015-1865-4.

[9] Olaitan AO, Morand S, Rolain J-M. Mechanisms of polymyxin resistance: acquired and intrinsic resistance in bacteria. Front Microbiol 2014;5:643. doi:10.3389/fmicb.2014.00643.

[10] Castanheira M, Mills JC, Costello SE, Jones RN, Sader HS. Ceftazidime–avibactam activity tested against Enterobacteriaceae isolates from U.S. hospitals (2011 to 2013) and characterization of β-lactamase-producing strains. Antimicrob Agents Chemother 2015;59:3509–17. doi:10.1128/AAC.00163-15.

[11] Shionogi & Co. Ltd Fetcroja. Summary of product characteristics. Shionogi & Co Ltd; 2020. https://www.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_en.pdf [accessed 11 December 2020].

[12] Shionogi & Co. Ltd Fetroja (cefiderocol) prescribing information. Shionogi & Co Ltd; 2020. https://www.shionogi.com/content/dam/shionogi/si/products/pdf/fetroja.pdf [accessed 11 December 2020].

[13] Ito A, Kohira N, Bouchillon SK, West J, Rittenhouse S, Sader HS, et al. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. J Antimicrob Chemother 2016;71:670–7. doi:10.1093/jac/dkv402.

[14] Ito A, Nishikawa T, Matsumoto S, Yoshizawa H, Sato T, Nakamura R, et al. Siderophore cephalosporin cefiderocol utilizes ferric iron transporter systems for antibacterial activity against *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 2016;60:7396–401. doi:10.1128/AAC.01405-16.

[15] Ito A, Nishikawa T, Ota M, Ito-Horiyama T, Ishibashi N, Sato T, et al. Stability and low induction propensity of cefiderocol against chromosomal AmpC β-lactamases of *Pseudomonas aeruginosa* and *Enterobacter cloacae*. J Antimicrob Chemother 2018;73:3049–52 Erratum in: J Antimicrob Chemother 2019;74:539. doi: 10.1093/jac/dky482. doi:10.1093/jac/dky317.

[16] International Organization for Standardization (ISO) Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices—part 1: broth micro-dilution reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases. ISO; 2019. https://www.iso.org/standard/70464.html [accessed 11 December 2020].

[17] European Committee on Antimicrobial Susceptibility Testing (EUCAST) Guidance document on broth microdilution testing of cefiderocol. EUCAST; 2020. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Cefiderocol_MIC_testing_EUCAST_guidance_document_201217.pdf [accessed 4 January 2021].

[18] Kohira N, West J, Ito A, Ito-Horiyama T, Nakamura R, Sato T, et al. In vitro antimicrobial activity of a siderophore cephalosporin, S-649266, against Enterobacteriaceae clinical isolates, including carbapenem-resistant strains. Antimicrob Agents Chemother 2016;60:729–34. doi:10.1128/AAC.01695-15.

[19] Ito-Horiyama T, Ishii Y, Ito A, Sato T, Nakamura R, Fukuhara N, et al. Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases. Antimicrob Agents Chemother 2016;60:4384–6. doi:10.1128/AAC.03098-15.

[20] Longshaw C, Manissero D, Tsuji M, Echols R, Yamano Y. In vitro activity of the siderophore cephalosporin, cefiderocol, against molecularly characterized, carbapenem-non-susceptible Gram-negative bacteria from Europe. JAC Antimicrob Resist 2020;2:dlaa060. doi:10.1093/jacamr/dlaa060.

[21] Hackel MA, Tsuji M, Yamano Y, Echols R, Karlowsky JA, Sahm DF. In vitro activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant Gram-negative bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 Study). Antimicrob Agents Chemother 2017;61:e00093. doi:10.1128/AAC.00093-17.

[22] Kazmierczak KM, Tsuji M, Wise MG, Hackel M, Yamano Y, Echols R, et al. In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible Gram-negative bacilli, including serine carbapenemase- and metallo-β-lactamase-producing isolates (SIDERO-WT-2014 Study). Int J Antimicrob Agents 2019;53:177–84. doi:10.1016/j.ijantimicag.2018.10.007.

[23] Karlowsky JA, Hackel MA, Tsuji M, Yamano Y, Echols R, Sahm DF. In vitro activity of cefiderocol, a siderophore cephalosporin, against Gram-negative bacilli isolated by clinical laboratories in North America and Europe in 2015–2016: SIDERO-WT-2015. Int J Antimicrob Agents 2019;53:456–66. doi:10.1016/j.ijantimicag.2018.11.007.

[24] European Committee on Antimicrobial Susceptibility Testing (EUCAST) Breakpoint tables for interpretation of MICs and zone diameters. EUCAST; 2021. *Version 11.0, 2021* https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.pdf [accessed 4 January 2021].

[25] Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. Clin Microbiol Rev 2012;25:2–41. doi:10.1128/CMR.00019-11.

[26] Clinical and Laboratory Standards Institute (CLSI) Performance standards for antimicrobial susceptibility testing. 30th ed. Wayne, PA: CLSI; 2020. CLSI supplement M100. https://clsi.org/media/3481/m100ed30_sample.pdf, [accessed 2 August 2021].

[27] US Food and Drug Administration (FDA) *Cefiderocol injection—FDA identified breakpoints*. FDA; 2020. https://www.fda.gov/drugs/development-resources/cefiderocol-injection [accessed 5 January 2021].

[28] Forrester JB, Steed LL, Santevecchi BA, Flume P, Palmer-Long GE, Bosso JA. In vitro activity of ceftolozane/tazobactam vs nonfermenting, Gram-negative cystic fibrosis isolates. Open Forum Infect Dis 2018;5:ofy158. doi:10.1093/ofid/ofy158.

[29] Livermore DM, Mushtaq S, Meunier D, Hopkins KL, Hill R, Adkin R, et al. Activity of ceftolozane/tazobactam against surveillance and 'problem' Enterobacteriaceae, *Pseudomonas aeruginosa* and non-fermenters from the British Isles. J Antimicrob Chemother 2017;72:2278–89. doi:10.1093/jac/dkx136.

[30] García-Fernández S, García-Castillo M, Bou G, Calvo J, Cercenado E, Delgado M, et al. Activity of ceftolozane/tazobactam against *Pseudomonas aeruginosa* and Enterobacterales isolates recovered from intensive care unit patients in Spain: the SUPERIOR multicentre study. Int J Antimicrob Agents 2019;53:682–8. doi:10.1016/j.ijantimicag.2019.02.004.

[31] Novelli A, Del Giacomo P, Rossolini GM, Tumbarello M. Meropenem/vaborbactam: a next generation β-lactam β-lactamase inhibitor combination. Expert Rev Anti Infect Ther 2020;18:643–55. doi:10.1080/14787210.2020.1756775.

[32] Oteo J, Pérez-Vázquez M, Bautista V, Ortega A, Zamarrón P, Saez D, et al. The spread of KPC-producing Enterobacteriaceae in Spain: WGS analysis of the emerging high-risk clones of *Klebsiella pneumoniae* ST11/KPC-2, ST101/KPC-2 and ST512/KPC-3. J Antimicrob Chemother 2016;71:3392–9. doi:10.1093/jac/dkw321.

[33] Oliver A, Mulet X, López-Causapé C, Juan C. The increasing threat of *Pseudomonas aeruginosa* high-risk clones. Drug Resist Updat 2015;21–22:41–59. doi:10.1016/j.drup.2015.08.002.

[34] Wagenlehner F, Lucenteforte E, Pea F, Soriano A, Tavoschi L, Steele VR, et al. Systematic review on estimated rates of nephrotoxicity and neurotoxicity in patients treated with polymyxins. Clin Microbiol Infect 2021;27:681–6. doi:10.1016/j.cmi.2020.12.009.

[35] Portsmouth S, Van Veenhuyzen D, Echols R, Machida M, Arjona Ferreira JC, Ariyasu M, et al. Cefiderocol versus imipenem–cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. Lancet Infect Dis 2018;18:1319–28. doi:10.1016/S1473-3099(18)30554-1.

[36] Bassetti M, Echols R, Matsunaga Y, Ariyasu M, Doi Y, Ferrer R, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. Lancet Infect Dis 2021;21:226–40. doi:10.1016/S1473-3099(20)30796-9.