JAC Antimicrob Resist
doi:10.1093/jacamr/dlab081

JAC-Antimicrobial Resistance

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

Thierry Naas [1,2,3]*, Gerard Lina[4,5], Anne Santerre Henriksen [6], Christopher Longshaw[7] and Francois Jehl[8]

[1]Team ReSIST, INSERM U1184, School of Medicine Université Paris-Saclay, LabEx LERMIT, Le Kremlin-Bicêtre, France; [2]Bacteriology-Hygiene unit, Assistance Publique/Hôpitaux de Paris, Bicêtre Hospital, Le Kremlin-Bicêtre, France; [3]French National Reference Center for Antibiotic Resistance: Carbapenemase-producing Enterobacteriaceae, Le Kremlin-Bicêtre, France; [4]CIRI Centre International de Recherche en Infectiologie, Inserm U1111, Université Lyon 1, Ecole Normale Supérieure de Lyon, CNRS UMR, 5308, Lyon, France; [5]Institut des Agent infectieux, Hôpital de la Croix Rousse, Hospices Civils de Lyon, Lyon, France; [6]Maxel Consulting ApS, Jyllinge, Denmark; contractor for Shionogi BV, London, UK; [7]Infectious Diseases, Shionogi B.V, London, UK; [8]Laboratory of Bacteriology, School of Medicine and University Hospital, Strasbourg, France

*Corresponding author. E-mail: thierry.naas@aphp.fr

Received 29 January 2021; accepted 14 May 2021

Objectives: Over recent years, France has experienced an increase of infections caused by carbapenem-resistant Gram-negative (GN) pathogens. Cefiderocol is approved in Europe for the treatment of aerobic GN infections in adults with limited treatment options. This study evaluated the *in vitro* activity of cefiderocol and comparators against GN clinical isolates from France.

Methods: MICs were determined by broth microdilution, according to International Organization for Standardization guidelines. Cefiderocol was tested using iron-depleted CAMHB. Susceptibility rates were based on EUCAST breakpoints. In the absence of a species-specific breakpoint, pharmacokinetic/pharmacodynamic breakpoints were used.

Results: Of 2027 isolates, 1344 (66.3%) were Enterobacterales and 683 (33.7%) were non-fermenters. The most common pathogen was *Pseudomonas aeruginosa* (16.8%), followed by *Escherichia coli* (16.0%), *Klebsiella pneumoniae* (13.1%), *Acinetobacter baumannii* (7.9%) and *Stenotrophomonas maltophilia* (5.1%). Isolates represented a range of infection sources including nosocomial pneumonia (33.6%), complicated urinary tract infection (24.3%), bloodstream infection (13.1%) and complicated intra-abdominal infection (18.0%). In total, 135/2027 (6.7%) isolates were meropenem resistant (MIC >8 mg/L); 133/135 (98.5%) were non-fermenters. Overall, 1330/1344 (99.0%) Enterobacterales and 681/683 (99.7%) non-fermenters were cefiderocol susceptible, including 100% of meropenem-resistant *S. maltophilia* ($n = 98$) and *P. aeruginosa* ($n = 18$) isolates. Susceptibility to cefiderocol was significantly higher ($P < 0.01$) in nosocomial pneumonia isolates (681/682 [99.9%]) than susceptibility to meropenem (586/682 [85.9%]), ceftolozane/tazobactam (593/682 [87.0%]), ceftazidime/avibactam (612/682 [89.7%]) and colistin (538/682 [78.9%]).

Conclusions: Cefiderocol demonstrated high *in vitro* susceptibility rates against a wide range of Gram-negative pathogens, including meropenem-resistant strains, and was significantly more active than comparators against pneumonia isolates.

Introduction

Antibiotic resistance among Gram-negative bacteria (GNB) poses a substantial global threat to patients and healthcare systems, often leading to increased hospital stays, higher medical costs and increased rates of mortality.[1–3] Across Europe, the burden of antimicrobial-resistant bacteria is substantial and the estimated number of infections is increasing.[4–7] Carbapenems are considered one of the few last-resort antibiotics for the treatment of infections

caused by MDR GNB.[8] However, these agents are now challenged by increasing dissemination of carbapenemase genes that confer antimicrobial resistance.[8,9] Notable pathogens with increasing or high levels of carbapenem resistance are ESBL-producing Enterobacterales such as *Klebsiella pneumoniae* and the glucose non-fermenters *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[10]

In France there has been a steady increase in the spread of carbapenemase-producing Enterobacterales (CPE) over recent years.[4] Carbapenemases or loss of porin function plus overexpression of *amp*C and efflux pumps are the major mechanisms of carbapenem resistance.[11] Carbapenemases reported among CPE include KPC, NDM, VIM and OXA-48, and although KPC is prevalent in other European countries, OXA-48 remains the most common carbapenemase in France.[12] Furthermore, a 2018 report from the French National Reference Center (F-NRC) for CPEs showed a notable increase in isolates producing MBLs such as NDM and VIM, as well as ongoing diversification of OXA-48-type carbapenemases, especially OXA-181 and OXA-244 variants.[12] These findings, along with the first isolation of IMP-producing GNB in 2007,[13] highlight the evolving and challenging epidemiology of carbapenemases among Enterobacterales in France.

Although the prevalence of infections caused by non-fermenting GNB such as *A. baumannii*, *P. aeruginosa* and *Stenotrophomonas maltophilia* has remained relatively low in France, rates of carbapenem resistance among these pathogens are considerably higher than those reported for Enterobacterales.[14] Among the 954 *P. aeruginosa* isolates submitted to F-NRC of antibiotic resistances in 2018, 16.2% produced an ESBL (PER-1, SHV-2a, GES, VEB, OXA), 15.1% were carbapenemase producers (VIM, IMP, DIM, GES) and 2.8% of isolates produced both.[12] Similarly, among the 379 isolates of *A. baumannii*, 96.6% expressed at least one carbapenemase (primarily OXA-23, OXA-72, NDM-1), together with an ESBL in 2.1% of the isolates.[12] The high levels of resistance among non-fermenters, particularly to carbapenems, reduce the arsenal of effective therapeutics, often making treatment more problematic.[14,15]

Therapeutic options for carbapenem-resistant (CR) GNB infections in general are limited,[16] and many CR pathogens exhibit MDR phenotypes, including resistance to all β-lactams (e.g. cephalosporins and penicillins) and other common drug classes such as aminoglycosides and fluoroquinolones.[8] Furthermore, there has been a consistent rise in the annual number of XDR CPEs identified in France since 2012.[4] These emerging pathogens are resistant even to last-resort antibiotics such as colistin, or to newly released antibiotics, and are a source of great concern for the future treatment of patients.[17]

Cefiderocol is a novel siderophore cephalosporin developed for the treatment of infections caused by GNB, including those resistant to carbapenems.[18] Cefiderocol is approved in the USA for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, hospital-acquired pneumonia and ventilator-associated pneumonia caused by susceptible Gram-negative microorganisms,[18] and has recently been approved in Europe for the treatment of infections caused by aerobic GNB in adults with limited or no alternative treatment options.[19] The structure of cefiderocol is based around a cephalosporin backbone with the addition of a catechol moiety at the 3-position side chain.[20] The cephalosporin core enables cefiderocol to act like other cephalosporins, binding primarily to penicillin-binding proteins and killing bacterial cells by inhibition of peptidoglycan cell wall biosynthesis. Cefiderocol differs from other cephalosporins in that the catechol moiety chelates ferric (Fe-III) iron, mimicking natural siderophores, allowing cefiderocol to exploit the bacteria's own active receptor-mediated iron transport system to cross the outer membrane.[20,21] The resulting increase in periplasmic concentration circumvents non-specific resistance due to porin loss or efflux and enhances cefiderocol's activity relative to carbapenems, other cephalosporins and β-lactam/β-lactamase inhibitor combinations.[22] Cefiderocol is active against CR GNB, including those with derepressed *amp*C and/or ESBLs plus porin/efflux pump resistance mechanisms as well as those harbouring carbapenemases from different Ambler classes, including KPC, VIM, IMP, NDM and OXA carbapenemases.[22–24] Activity has also been demonstrated against meropenem-resistant and MDR *P. aeruginosa* and *A. baumannii*.[24–26]

The SIDERO-WT surveillance studies assessed the activity of cefiderocol and comparators against clinical isolates of CR and MDR GNB. Previous reports have shown potent *in vitro* activity of cefiderocol against carbapenemase-producing and carbapenemase-negative meropenem-non-susceptible Gram-negative pathogens, including MBL producing isolates.[11,27,28] Additionally, in the SIDERO-CR study, cefiderocol demonstrated potent activity against carbapenem-non-susceptible Gram-negative pathogens, MDR Gram-negative pathogens and a wide variety of MBL- and serine-β-lactamase-producing strains, including non-fermenters.[24]

This article reports on the activity of cefiderocol and comparators against clinical isolates of GNB collected from hospitals in France as part of the SIDERO-WT surveillance studies.

Materials and methods

Detailed methodology for the SIDERO-WT studies and molecular characterization of isolates using PCR has been reported previously.[11,27,28] In this analysis, pooled data from the SIDERO-WT studies for French isolates only were assessed. From 2014 to 2018, 10 central laboratories across France (see Supplementary Materials and methods, available as Supplementary data at *JAC-AMR* Online, for details of participating sites) collected clinical GNB isolates from patients with documented intra-abdominal infections (IAI), urinary tract infections (UTI), skin and soft tissue infections, lower respiratory tract infections or bloodstream infections (BSI). As this was an *in vitro* surveillance study, the isolates were selected by the nature of the clinical sample rather than any clinical definition. No other inclusion or exclusion criteria were applied. Unlike other species, *Proteus* spp., *Morganella* spp. and *Burkholderia* spp. were not initially included in the study but were collected from 2015 onwards. Only one isolate per patient per bacterial species was accepted into the study, and all isolates were from an unselected isolate population, collected independently of their antimicrobial susceptibility phenotype. All isolates were shipped to International Health Management Associates Inc. (IHMA, Schaumburg, IL, USA) for testing. Isolates were identified using MALDI-TOF MS (Bruker Daltonics, Billerica, MA, USA). Characterization of β-lactamases for a specific subset of isolates that were considered clinically relevant was carried out using PCR methodology as published previously.[11,28] β-Lactamase genes included Ambler class A ESBLs (e.g. SHV, CTX-M) and carbapenemases (e.g. KPC, GES), class B MBLs (e.g. NDM, VIM), class C plasmid-mediated *amp*C-type β-lactamases and Class D β-lactamases (e.g. oxacillinases).

Isolates were identified by source of infection and subgroups were created for nosocomial pneumonia (NP), cUTI, BSI and complicated IAI (cIAI) (see Supplementary Materials and methods for details of infection sources).

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was conducted using broth microdilution. MICs were determined for meropenem, ceftazidime/avibactam, ceftolozane/tazobactam, colistin and meropenem/vaborbactam by broth microdilution according to International Organization for Standardization (ISO) guidelines,[29] and for cefiderocol using EUCAST guidelines.[30] Aztreonam/avibactam was tested using ISO guidelines for aztreonam,[29] with a fixed concentration of avibactam of 4 mg/L.

Data for meropenem/vaborbactam and aztreonam/avibactam were only collected between 2017 and 2018. Susceptibilities of all antibiotics, with the exception of aztreonam/avibactam, which is currently under clinical development, were interpreted using EUCAST breakpoints.[31] Isolates were defined as meropenem resistant with a breakpoint of >8 mg/L and were classified as susceptible (susceptible, increased exposure) to meropenem if they had an MIC of ≤8 mg/L (relating to high-dose extended-infusion [2 g, 3 h infusion] meropenem), based on EUCAST recommendations. Where EUCAST breakpoints were not available, pharmacokinetic/pharmacodynamic breakpoints were used, including ≤4 mg/L for ceftolozane/tazobactam, ≤8 mg/L for ceftazidime/avibactam and ≤2 mg/L for colistin.[31]

Enterobacterales and *P. aeruginosa* were considered susceptible to cefiderocol at MIC ≤2 mg/L (resistant >2 mg/L), based on EUCAST breakpoints; other pathogens were assessed using the pharmacokinetic/pharmacodynamic breakpoint (≤2 mg/L).[31] Cefiderocol was tested using iron-depleted CAMHB (ID-CAMHB),[30] while all other antimicrobial agents were tested using standard CAMHB, and quality control testing was performed on each day of testing.

Statistical analysis

Post-hoc statistical analysis was carried out. Overall, statistical significance was determined using an OR with a 95% CI, assuming the OR was log-normally distributed. Significance was determined by the null value (1) being outside the CI. Results were not adjusted for multiple comparisons and the analysis was simple and comparative. At an individual species level, the number of isolates was too small to conduct a comparison, therefore it was decided to consider trends across infection sources.

Ethics

Ethics approval was not required as all *in vitro* samples were anonymized.

Results

Pathogen characteristics

The *in vitro* activity of cefiderocol and comparators was assessed in 2027 Gram-negative isolates collected from 10 participating laboratories across the majority of French regions, with the exception of Eastern and Northern France. In total, 1344 (66.3%) isolates were Enterobacterales and 683 (33.7%) were non-fermenters. The most common Enterobacterales included *Escherichia coli* (324/1344, 24.1%), *K. pneumoniae* (266/1344, 19.8%) and *Serratia marcescens* (165/1344, 12.3%). The majority of non-fermenters were *P. aeruginosa* (341/683, 49.9%), followed by *A. baumannii* (161/683, 23.6%) and *S. maltophilia* (103/683, 15.1%).

Nosocomial pneumonia was the most common source of isolates (682/2027, 33.6%), of which *P. aeruginosa* (166/682, 24.3%), *S. marcescens* (90/682, 13.2%) and *S. maltophilia* (78/682, 11.4%) were the most frequently identified (Table S1); cUTI was the next most common source of isolates (493/2027, 24.3%), followed by cIAI (364/2027, 18.0%), BSI (265/2027, 13.1%) and other infection sources (223/2027, 11.0%). *E. coli* and *K. pneumoniae* were the most common pathogens isolated from cUTIs (105/493 [21.3%] and 103/493 [20.9%], respectively) and from BSI (38/265 [14.3%] and 37/265 [14.0%], respectively), while in cIAI cases *E. coli* and *P. aeruginosa* were most prevalent (115/364 [31.6%] and 54/364 [14.8%], respectively) (Table S1).

The isolate collection contained some species with intrinsic resistance to certain comparators, including *Proteus* spp., *Providencia* spp., *Morganella* spp., *Serratia* spp. and *Burkholderia* spp. with intrinsic resistance to colistin,[32] and *S. maltophilia* with intrinsic resistance to meropenem.[33]

Activity of cefiderocol

Cefiderocol exhibited *in vitro* activity against the vast majority of isolates irrespective of infection source (Table 1). Among non-fermenting GNB, 100% susceptibility to cefiderocol was reported in isolates from all species with the exception of *A. baumannii,* where just two (2/161, 1.2%) isolates showed resistance, one from a patient with BSI (cefiderocol MIC 4 mg/L) and one from a patient with NP (cefiderocol MIC 8 mg/L).

Cefiderocol activity among meropenem-resistant isolates

Meropenem resistance (MIC >8 mg/L) was most frequently noted in isolates from patients with nosocomial pneumonia, the majority (134/135, 99.3%) of which were susceptible to cefiderocol (Table 2). Meropenem resistance was more common in non-fermenting GNB (133/683 [19.5%]) than in Enterobacterales (2/1344 [0.1%]).

Among meropenem-resistant non-fermenters, intrinsically resistant *S. maltophilia* were the most common isolates (98/133 [73.7%]), followed by *P. aeruginosa* (18/133 [13.5%]), *A. baumannii* (16/133 [12.0%]) and *B. cepacia* (1/133 [0.8%]). Overall, 132/133 (99.2%) meropenem-resistant non-fermenters were susceptible to cefiderocol; all *P. aeruginosa* and *S. maltophilia* isolates were cefiderocol susceptible (Tables 1 and 2), including meropenem-resistant isolates. The meropenem-resistant isolate also resistant to cefiderocol (MIC 8 mg/L) was *A. baumannii* and was only susceptible to colistin (1 mg/L).

There were too few meropenem-resistant Enterobacterales isolates to enable sub-analyses. The two isolates identified consisted of one *Klebsiella aerogenes* (meropenem MIC 64 mg/L) and one *S. marcescens* (meropenem MIC 32 mg/L), both of which were negative for known β-lactamases/carbapenemases and were susceptible to cefiderocol (MICs of 2 mg/L and 0.06 mg/L, respectively).

Overall, more isolates of meropenem-resistant non-fermenters were susceptible to cefiderocol than to any of the other comparator antimicrobials tested (Table 2). Colistin was the only other agent with similar activity to cefiderocol against meropenem-resistant isolates of *P. aeruginosa* and *A. baumannii*; however, susceptibility to colistin was lower than to cefiderocol among *S. maltophilia* (72.8% versus 100%, respectively), which comprised the majority of meropenem-resistant non-fermenters in this study.

Molecular characterization of the mechanism of meropenem resistance was carried out for 14 isolates (seven *A. baumannii*, five *P. aeruginosa*, one *K. aerogenes* and one *S. marcescens*). Of the

Table 1. *In vitro* activity of cefiderocol against Gram-negative SIDERO-WT-2014–2018 isolates collected from hospitals in France, by infection source

	All isolates			NP			cUTI			BSI			cIAI		
Pathogen	*n*	*N*	%S	*n*	*N*	%S	*n*	*N*	%S	*n*	*N*	%S	*n*	*N*	%S
Enterobacterales	1330	1344	99.0	344	344	100	383	388	98.7	166	172	96.5	300	302	99.3
E. coli	322	324	99.4	48	48	100	104	105	99.0	38	38	100	114	115	99.1
K. pneumoniae	260	266	97.7	65	65	100	101	103	98.1	35	37	94.6	43	44	97.7
Klebsiella oxytoca	96	96	100	24	24	100	17	17	100	13	13	100	31	31	100
K. aerogenes	90	91	98.9	40	40	100	17	18	94.4	14	14	100	11	11	100
Klebsiella variicola	18	18	100	5	5	100	5	5	100	1	1	100	5	5	100
E. cloacae	89	90	98.9	13	13	100	24	24	100	13	14	92.9	21	21	100
Enterobacter asburiae	9	11	81.8	2	2	100	1	2	50.0	2	3	66.7	1	1	100
Serratia spp.	167	167	100	90	90	100	20	20	100	30	30	100	10	10	100
Citrobacter spp.	137	139	98.6	28	28	100	55	55	100	15	17	88.2	32	32	100
Proteus spp.	89	89	100	17	17	100	27	27	100	3	3	100	19	19	100
M. morganii	37	37	100	11	11	100	3	3	100	1	1	100	12	12	100
Providencia rettgeri	16	16	100	1	1	100	9	9	100	1	1	100	1	1	100
Non-fermenters	681	683	99.7	337	338	99.7	105	105	100	92	93	98.9	62	62	100
P. aeruginosa	341	341	100	166	166	100	42	42	100	30	30	100	54	54	100
Pseudomonas otitidis	1	1	100	—	—		—	—		—	—		1	1	100
A. baumannii	159	161	98.8	66	67	98.5	34	34	100	32	33	97.0	1	1	100
other *Acinetobacter* spp.	71	71	100	23	23	100	23	23	100	17	17	100	2	2	100
S. maltophilia	103	103	100	78	78	100	6	6	100	11	11	100	4	4	100
Burkholderia spp.	6	6	100	4	4	100	—	—		2	2	100	—	—	
Total	2011	2027	99.2	681	682	99.9	488	493	99.0	258	265	97.4	362	364	99.5

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

Table 2. *In vitro* activity of cefiderocol and comparators against meropenem-resistant (MIC >8 mg/L) Gram-negative pathogens isolated from hospitals in France

		MIC (mg/L)			MIC interpretation (% susceptible)
Species (*n*)[a]	Antimicrobial agent	range	MIC_{50}	MIC_{90}	
S. maltophilia[b] (98)	cefiderocol	0.004 to 1	0.06	0.25	100
	ceftazidime/avibactam	0.5 to >64	32	64	39.8
	ceftolozane/tazobactam	0.5 to >64	32	64	28.6
	colistin	<0.25 to >8	1	>8	72.4
P. aeruginosa (18)	cefiderocol	0.015 to 2	0.25	2	100
	ceftazidime/avibactam	4 to >64	4	32	72.2
	ceftolozane/tazobactam	1 to >64	2	>64	77.8
	colistin	<0.25 to 2	1	2	100
A. baumannii (16)	cefiderocol	0.008 to 8	0.25	2	93.8
	ceftazidime/avibactam	8 to >64	64	>64	18.8
	ceftolozane/tazobactam	2 to >64	16	>64	12.5
	colistin	0.5 to 1	0.5	1	100

≤8 mg/L breakpoint used to determine susceptibility.
[a]Where $n > 10$ isolates.
[b]*S. maltophilia* is intrinsically resistant to meropenem.

seven *A. baumannii* isolates, although two did not have known acquired β-lactamase genes identified, five were found to carry OXA-23 carbapenemase genes (two co-carried ESBL genes). While no acquired β-lactamase was found in 4/5 *P. aeruginosa* isolates (isolates with likely porin D2 loss[22]), the remaining *P. aeruginosa* isolate harboured the MBL VIM-2. Other characterized isolates had no acquired β-lactamase genes identified.

Activity of cefiderocol and comparators

The MIC_{50} and MIC_{90} values for cefiderocol and comparators are reported by pathogen in Table 3 and by infection source in Table S1. The MIC_{90} value of cefiderocol against all Enterobacterales and all non-fermenters was 0.5 mg/L. Among all Enterobacterales, cefiderocol (99.0%) demonstrated comparable susceptibility rates to those of meropenem (99.9%) and ceftazidime/avibactam (99.8%); more Enterobacterales isolates were susceptible to cefiderocol (99.0%) than to ceftolozane/tazobactam (92.4%) and colistin (76.6%). Among non-fermenting GNB, 99.7% of isolates were susceptible to cefiderocol, which was higher than all other comparators including meropenem (73.9%), ceftazidime/avibactam (83.6%) and ceftolozane/tazobactam (85.2%).

Overall, a significantly ($P < 0.01$) higher proportion of non-fermenting GNB were susceptible to cefiderocol (99.7%) than to meropenem (80.5%) ceftazidime/avibactam (83.6%) ceftolozane/tazobactam (85.2%) and colistin (94.4%) (Table 4). In particular, against all non-fermenter isolates from patients with NP, cefiderocol demonstrated significantly ($P < 0.01$) higher activity than comparators; additionally, activity against NP Enterobacterales was significantly ($P < 0.01$) higher for cefiderocol than colistin (Table 4). Activity of cefiderocol against BSI isolates was significantly ($P < 0.01$) greater than colistin for Enterobacterales and for other agents versus non-fermenters.

Comparator data for meropenem/vaborbactam and aztreonam/avibactam were generated between 2017 and 2018 ($n = 188$). All Enterobacterales ($n = 120$) and 83.8% of non-fermenters ($n = 68$) were susceptible to meropenem/vaborbactam, with MIC_{90} values of <0.06 mg/L and >32 mg/L, respectively. The MIC_{90} for aztreonam/avibactam was 0.25 mg/L among Enterobacterales and >8 mg/L among non-fermenters.

Discussion

In this SIDERO-WT-2014–2018 subset of isolates from France, cefiderocol demonstrated substantial *in vitro* activity against Gram-negative isolates from different infection sources, including meropenem-resistant non-fermenters. Notably, cefiderocol demonstrated potent activity against all isolates of *P. aeruginosa* and intrinsically meropenem-resistant *S. maltophilia*, where all other comparators demonstrated lower susceptibility rates. Overall, more isolates were susceptible to cefiderocol than to a key subset of other currently available antimicrobial agents including the β-lactam/β-lactamase inhibitor combinations ceftazidime/avibactam and ceftolozane/tazobactam, and colistin, which is often considered an agent of last resort. Notably, isolates in the current study collected in France from 2014 to 2016 (~1433) will have been included in previously published global analysis[34] as part of the overall isolate set; however, this study reports a more detailed breakdown of a larger set of isolates only from France, collected from 2014 to 2018.

The study had some limitations. Firstly, the pooled isolates included very few meropenem-resistant Enterobacterales, making it impossible to assess cefiderocol activity versus comparators in these pathogens. Secondly, the majority of isolates were collected from patients with nosocomial pneumonia, with low representation for other infection sources. This represents a gap for future studies, particularly for infections such as BSI, where selecting the most effective therapy at the earliest timepoint is critical for patient survival.[35] Finally, while the geographical spread of collected isolates was generally representative of most regions in France, there were no collection sites in Eastern or Central regions. As epidemiology may vary between hospitals, the isolate collection may not necessarily be regionally representative, as there may be considerable heterogeneity in the numbers and types of pathogens and mechanisms of resistance from hospital to hospital. However, the isolate population is in line with previous published reports for France, with larger proportions of carbapenem resistance seen in non-fermenting GNB compared with Enterobacterales.[14]

Carbapenem resistance among GNB in France is steadily rising[5] and poses a substantial threat to patients and healthcare systems, often leading to greater rates of mortality and morbidity and increased burden on hospitals.[1–3] There is now increasing concern over the emergence of OXA-48-mediated resistance to new antibiotic regimens such as ceftazidime/avibactam.[36] Therefore there is a continued need for new antibiotics and antibiotic regimens with activity against OXA-48-like producers, among others. Despite the dominance of OXA-48 in France, over recent years there has been a notable shift in resistance mechanisms with an increase in MBL producers, such as NDM and VIM,[12] and the first isolation of IMP-producing GNB.[13] This shift to MBL-mediated resistance is of concern as new β-lactam/β-lactamase inhibitor combination therapies, including ceftazidime/avibactam, ceftolozane/tazobactam and meropenem/vaborbactam,[37,38] are known to lack efficacy against MBLs. As such, these agents cannot be used with confidence as empirical treatments against infections that are suspected to involve MBL-producing GNB.[37,38] Previous reports from the SIDERO-WT studies have shown potent *in vitro* activity of cefiderocol against carbapenemase-producing isolates including a majority of MBL producers.[27] These findings demonstrate the potential for cefiderocol in these types of infection, particularly in countries such as France where MBL producers represented 25% of CR Enterobacterales in 2019.[12] Furthermore, in instances where resistance is not due to carbapenemase production, cefiderocol has demonstrated *in vitro* activity against isolates with *ampC*, ESBLs, porin mutations and efflux pump upregulation.[20–24] Although the number of isolates that underwent molecular characterization in the current study was small, it is reflective of that observed across France,[39] i.e. OXA-23 for *A. baumannii* and no acquired β-lactamases for *P. aeruginosa*.

Although the prevalence of infections caused by non-fermenting GNB currently remains relatively low in France, there is growing concern regarding the high propensity of these isolates to develop resistance,[14,40] and the resulting depletion of available effective treatment options. In this study, cefiderocol activity exceeded that of all tested comparators except colistin against meropenem-resistant isolates of *S. maltophilia*, *P. aeruginosa* and *A. baumannii*. These findings are in line with a previous report by Oueslati *et al.*,[41]

Table 3. *In vitro* activity of cefiderocol and comparators against Gram-negative SIDERO-WT-2014–2018 isolates from France

Pathogen (*n*)[a]	Antibiotic	MIC (mg/L)			MIC interpretation (% susceptible)
		range	MIC_{50}	MIC_{90}	
Enterobacterales (1344)	cefiderocol	<0.002 to 4	0.12	0.5	99.0
	meropenem	<0.06 to 64	<0.06	<0.06	99.9
	colistin	<0.25 to >8	0.5	≥8	76.4
	ceftazidime/avibactam	<0.03 to >64	0.12	0.5	99.8
	ceftolozane/tazobactam	<0.06 to >64	0.25	2	92.4
	meropenem/vaborbactam (*n* = 120)	<0.06 to 0.12	<0.06	<0.06	100
	aztreonam/avibactam (*n* = 120)	<0.12 to 1	<0.12	0.25	NA
E. coli (324)	cefiderocol	<0.002 to 4	0.12	0.5	99.4
	meropenem	<0.06 to 8	<0.06	<0.06	100
	colistin	<0.25 to >8	0.5	1	99.7
	ceftazidime/avibactam	<0.03 to >64	0.12	0.25	99.1
	ceftolozane/tazobactam	<0.06 to 32	0.25	0.5	98.5
	meropenem/vaborbactam (*n* = 30)	<0.06 to <0.06	<0.06	<0.06	100
	aztreonam/avibactam (*n* = 30)	<0.12 to 0.25	<0.12	<0.12	NA
Klebsiella spp. (471)	cefiderocol	<0.002 to 4	0.12	1	98.5
	meropenem	<0.06 to 64	<0.06	<0.06	99.8
	colistin	<0.25 to >8	0.5	1	98.9
	ceftazidime/avibactam	<0.03 to 8	0.12	0.5	100
	ceftolozane/tazobactam	<0.06 to >64	0.25	2	90.0
	meropenem/vaborbactam (*n* = 46)	<0.06 to <0.06	<0.06	<0.06	100
	aztreonam/avibactam (*n* = 46)	<0.12 to 1	<0.12	<0.12	NA
K. pneumoniae (266)	cefiderocol	<0.002 to 4	0.12	1	97.7
	meropenem	<0.06 to 8	<0.06	<0.06	100
	colistin	<0.25 to >8	0.5	1	98.5
	ceftazidime/avibactam	<0.03 to 4	0.12	0.5	100
	ceftolozane/tazobactam	<0.06 to >64	0.25	2	92.5
	meropenem/vaborbactam (*n* = 25)	<0.06 to <0.06	<0.06	<0.06	100
	aztreonam/avibactam (*n* = 25)	0.12 to 0.5	<0.12	<0.12	NA
Serratia spp.[b] (167)	cefiderocol	0.008 to 1	0.12	0.25	100
	meropenem	<0.06 to 32	<0.06	<0.06	99.4
	colistin	0.5 to >8	≥8	≥8	6.0
	ceftazidime/avibactam	<0.06 to 2	0.12	0.5	100
	ceftolozane/tazobactam	0.12 to 8	0.5	1	99.4
	meropenem/vaborbactam (*n* = 20)	<0.06 to 0.12	<0.06	<0.06	100
	aztreonam/avibactam (*n* = 20)	<0.12 to 0.25	<0.06	0.25	NA
Citrobacter spp. (139)	cefiderocol	<0.002 to 4	0.25	0.5	98.6
	meropenem	<0.06 to 0.25	<0.06	<0.06	100
	colistin	<0.25 to 2	0.5	1	100
	ceftazidime/avibactam	<0.06 to 4	0.12	0.5	100
	ceftolozane/tazobactam	<0.06 to 64	0.25	8	82.7
	meropenem/vaborbactam (*n* = 10)	<0.06 to <0.06	NA	NA	100
	aztreonam/avibactam (*n* = 10)	<0.12 to <0.12	NA	NA	NA
Enterobacter spp. (101)	cefiderocol	0.008 to 4	0.5	2	97.0
	meropenem	<0.06 to 0.5	<0.06	0.12	100
	colistin	<0.25 to >8	0.5	≥8	84.2
	ceftazidime/avibactam	<0.06 to 2	0.25	0.5	100
	ceftolozane/tazobactam	<0.06 to >64	0.5	8	75.2
	meropenem/vaborbactam (*n* = 14)	<0.06 to 0.06	NA	NA	100
	aztreonam/avibactam (*n* = 14)	<0.12 to 1	NA	NA	NA
Morganellaceae[b] (142)	cefiderocol	<0.002 to 0.5	0.015	0.12	100
	meropenem	<0.06 to 0.12	<0.06	0.12	100

Continued

Table 3. *Continued*

Pathogen (*n*)[a]	Antibiotic	MIC (mg/L) range	MIC_{50}	MIC_{90}	MIC interpretation (% susceptible)
	colistin	<0.25 to >8	≥8	≥8	2.9
	ceftazidime/avibactam	<0.06 to 0.25	0.06	0.12	100
	ceftolozane/tazobactam	0.12 to 1	0.25	0.5	100
M. morganii[b] (37)	cefiderocol	0.015 to 0.5	0.06	0.25	100
	meropenem	<0.06 to 0.12	<0.06	0.12	100
	colistin	<0.25 to >8	>8	>8	2.7
	ceftazidime/avibactam	<0.06 to 0.12	<0.06	0.12	100
	ceftolozane/tazobactam	0.12 to 1	0.25	0.5	100
Proteus spp.[b] (89)	cefiderocol	<0.002 to 0.25	0.015	0.06	100
	meropenem	<0.06 to 0.12	<0.06	0.12	100
	colistin	0.5 to >8	>8	>8	3.4
	ceftazidime/avibactam	<0.06 to 0.12	<0.06	0.12	100
	ceftolozane/tazobactam	0.12 to 1	0.25	0.5	100
Providencia spp.[b] (16)	cefiderocol	0.004 to 0.12	0.008	0.06	100
	meropenem	<0.06 to 0.12	<0.06	0.12	100
	colistin	>8 to >8	>8	>8	0
	ceftazidime/avibactam	<0.06 to 0.25	<0.06	0.25	100
	ceftolozane/tazobactam	0.12 to 0.25	0.25	0.25	100
Non-fermenters (683)[c]	cefiderocol	<0.002 to 8	0.12	0.5	99.7
	meropenem	<0.06 to >64	0.5	≥64	80.5
	colistin	<0.25 to >8	1	2	94.4
	ceftazidime/avibactam	<0.06 to >64	4	32	83.6
	ceftolozane/tazobactam	<0.06 to >64	0.5	16	85.2
	meropenem/vaborbactam (*n* = 68)	<0.06 to >32	0.5	>32	83.8
	aztreonam/avibactam (*n* = 68)	0.5 to >8	8	>8	NA
Acinetobacter spp. (232)	cefiderocol	0.004 to 8	0.06	0.5	99.1
	meropenem	<0.06 to >64	0.25	1	93.1
	colistin	<0.25 to 2	0.5	1	100
	ceftazidime/avibactam	<0.06 to >64	8	32	80.2
	ceftolozane/tazobactam	<0.06 to >64	0.5	4	91.4
	meropenem/vaborbactam (*n* = 29)	<0.06 to 1	0.25	0.5	100
	aztreonam/avibactam (*n* = 29)	2 to >8	>8	>8	NA
A. baumannii (161)	cefiderocol	0.004 to 8	0.06	0.25	98.8
	meropenem	<0.06 to >64	0.25	8	90.1
	colistin	0.25 to 2	0.5	1	100
	ceftazidime/avibactam	<0.06 to >64	4	32	82.6
	ceftolozane/tazobactam	<0.06 to >64	0.5	8	87.6
	meropenem/vaborbactam (*n* = 14)	<0.06 to 1	NA	NA	100
	aztreonam/avibactam (*n* = 14)	2 to >8	NA	NA	NA
Pseudomonas spp. (342)	cefiderocol	<0.002 to 2	0.12	0.5	100
	meropenem	<0.06 to >64	0.25	8	94.7
	colistin	<0.25 to >8	1	1	98.8
	ceftazidime/avibactam	0.12 to >64	2	4	98.0
	ceftolozane/tazobactam	0.12 to >64	0.5	2	97.4
	meropenem/vaborbactam (*n* = 29)	<0.06 to 16	0.25	4	93.1
	aztreonam/avibactam (*n* = 29)	0.5 to >8	8	8	NA
P. aeruginosa (341)	cefiderocol	<0.002 to 2	0.12	0.5	100
	meropenem	<0.06 to >64	0.25	8	94.7
	colistin	<0.25 to >8	1	1	98.8
	ceftazidime/avibactam	0.12 to >64	2	4	97.9
	ceftolozane/tazobactam	0.12 to >64	0.5	2	97.4

Continued

Table 3. *Continued*

Pathogen (*n*)[a]	Antibiotic	MIC (mg/L) range	MIC$_{50}$	MIC$_{90}$	MIC interpretation (% susceptible)
	meropenem/vaborbactam (*n* = 28)	<0.06 to 16	0.25	4	92.9
	aztreonam/avibactam (*n* = 28)	0.5 to >8	8	8	NA
S. maltophilia[d] (103)	cefiderocol	0.004 to 1	0.06	0.25	100
	meropenem	0.12 to >64	≥64	≥64	4.9
	colistin	<0.25 to >8	1	>8	72.8
	ceftazidime/avibactam	0.5 to >64	16	64	42.7
	ceftolozane/tazobactam	0.5 to >64	16	64	31.1
	meropenem/vaborbactam (*n* = 9)	>32 to >32	NA	NA	0
	aztreonam/avibactam (*n* = 9)	2 to 8	NA	NA	NA

MIC$_n$, MIC for *n*% of isolates tested; NA, not applicable (fewer than 20 isolates or no breakpoint available).
[a]Where $n \geq 15$ isolates.
[b]Intrinsically resistant to colistin.
[c]Includes 6 *Burkholderia* spp. isolates intrinsically resistant to colistin.
[d]Intrinsically resistant to meropenem.

Table 4. Susceptibility of cefiderocol and comparators against Enterobacterales, non-fermenters and overall, by infection source

Infection source	Pathogen group (*n*)	Antimicrobial agent (% susceptible) CFDC	MEM[a]	C/T	CZA	CST	MVB[b] (*n*)
Overall	Enterobacterales (1344)	99.0	99.9	92.4**	99.8	76.4**	100 (120)
	non-fermenters (683)	99.7	80.5**	85.2**	83.6**	94.4**	83.8 (68)
	all (2027)	99.2	93.3**	90.0**	94.3**	82.5**	94.1 (188)
NP	Enterobacterales (344)	100	99.7	94.2	99.4	64.8**	100 (31)
	non-fermenters (338)	99.7	71.9**	79.6**	79.9**	93.2**	77.4 (31)
	all (682)	99.9	85.9**	87.0**	89.7**	78.9**	88.7 (62)
cUTI	Enterobacterales (388)	98.7	100	86.6**	100	84.2**	100 (25)
	non-fermenters (105)	100	90.5†	89.5†	83.8†	95.2†	87.5 (16)
	all (493)	99.0	98.0	87.2**	96.6*	86.6**	95.1 (41)
BSI	Enterobacterales (172)	96.5	100	93.6	100	79.1**	100 (28)
	non-fermenters (93)	98.9	84.9**	86.0**	83.9**	94.6	83.3 (12)
	all (265)	97.4	94.7	90.9**	94.3	84.5**	95.0 (40)
cIAI	Enterobacterales (302)	99.3	99.7	90.7**	100	86.4**	100 (35)
	non-fermenters (62)	100	88.7†	90.3†	90.3†	95.2†	100 (7)
	all (364)	99.5	97.8	90.7**	98.4	87.9**	100 (42)

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.
Isolates intrinsically resistant to colistin (*n* = 315) and meropenem (*n* = 103) are included in the dataset.
58 Enterobacterales not included in NP, cUTI, BSI or cIAI categories were colistin resistant (mostly wound or abscess related). Only 1/58 (MIC 4 mg/L) was cefiderocol resistant. Aztreonam/avibactam was not included as there is no clinical breakpoint at present.
[a]≤8 mg/L breakpoint used to determine susceptibility.
[b]Isolates collected in 2018 only (*N* = 188), no statistical analysis available.
*$P < 0.05$ versus cefiderocol; **$P < 0.01$ versus cefiderocol; †insufficient data to provide measure of significance.

which demonstrated potent *in vitro* activity of cefiderocol against MDR *A. baumannii*, MDR *P. aeruginosa*, *S. maltophilia* and *B. cepacia* isolates, with >93% of all isolates displaying cefiderocol MICs of ≤4 mg/L. Interestingly, their findings showed that cefiderocol was the only agent to which 100% of *P. aeruginosa* isolates were susceptible, and the only other agent with comparable activity was colistin (96%).[41] Additionally, novel agents recently approved for antimicrobial-resistant GNB are effective against KPC producers but have limited or no efficacy against CR *A. baumannii*.[40] In recent years we have witnessed importation from Italy and Portugal of

avibactam-resistant KPC producers.[17,42] These findings highlight a vital area of focus for antibiotic development and an area where cefiderocol may provide vital treatment coverage.

Overall, there are very few antimicrobial agents available to clinicians to treat patients infected with CR GNB, and the agents that are available are often associated with considerable toxicities and increasing resistance. Colistin is effective against a wide range of CR GNB, and in this study colistin was the only agent with comparable activity to cefiderocol against non-fermenters collected from patients with nosocomial pneumonia or BSI. However, colistin is commonly associated with nephrotoxicity[43] and several species of Enterobacterales have demonstrated intrinsic colistin resistance.[44,45] Also, in this study, fewer meropenem-resistant *S. maltophilia* isolates were susceptible to colistin than to cefiderocol.

Conclusions

The increasing incidence and diversification of carbapenem resistance among GNB is of growing concern in France, as a shift toward more difficult-to-treat pathogens is putting pressure on the already limited available treatment options. Cefiderocol demonstrates substantial and broad *in vitro* activity against a wide range of GNB, including carbapenem resistant strains, from multiple infection sources. The findings from this study in combination with previous reports suggest that cefiderocol may offer an invaluable treatment option for clinicians in the fight against antimicrobial-resistant GNB, particularly for carbapenem-resistant non-fermenters and MBL producers, for which there are currently few approved effective therapies.

Acknowledgements

We would like to thank all investigators and participating sites for the provision of clinical isolates. Coordination of the SIDERO-WT studies including generation of the *in vitro* MIC data was carried out by Meredith A. Hackel, Krystyna M. Kazmierczak and Daniel F. Sahm of International Health Management Associates Inc. (IHMA), Schaumburg, IL, USA. Medical writing support was provided by Sarah Rossall, PhD, of Ashfield Healthcare, part of UDG Healthcare plc, and was funded by Shionogi & Co. Ltd., Osaka, Japan.

Funding

This work was funded by Shionogi & Co. Ltd., Osaka, Japan.

Transparency declarations

T.N. reports non-financial support from Pfizer and personal fees and non-financial support from Shionogi, outside the submitted work. G.L. has none to declare. A.S.H. is a contract employee and C.L. is a full-time employee of Shionogi B.V., London, UK. F.J. reports personal fees and non-financial support from Shionogi, outside the submitted work.

Author contributions

All authors contributed to the analysis of study data, drafting and revising the manuscript and approved the final version for submission.

Supplementary data

Supplementary Materials and methods and Table S1 are available as Supplementary data at *JAC-AMR* Online.

References

1 Cassini A, Högberg LD, Plachouras D *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.

2 WHO. Prioritization of Pathogens to Guide Discovery, Research and Development of new Antibiotics for Drug Resistant Bacterial Infections, Including Tuberculosis. 2017. https://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf.

3 CDC. Antibiotic Resistance Threats in the United States. 2019. https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf.

4 Colomb-Cotinat M, Soing-Altrach S, Leon A *et al*. Emerging extensively drug-resistant bacteria (eXDR) in France in 2018. *Med Mal Infect* 2020; **50**: 715–22.

5 Brolund A, Lagerqvist N, Byfors S *et al*. Worsening epidemiological situation of carbapenemase-producing Enterobacteriaceae in Europe, assessment by national experts from 37 countries, July 2018. *Euro Surveill* 2019; **24**: pii=1900123.

6 ECDC. Carbapenem-Resistant Enterobacteriaceae Risk Assessment. 2019. https://www.ecdc.europa.eu/en/publications-data/carbapenem-resistant-enterobacteriaceae-second-update.

7 Surveillance of Antimicrobial Resistance in Europe. 2018. https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2018.

8 Morrill HJ, Pogue JM, Kaye KS *et al*. Treatment options for carbapenem-resistant Enterobacteriaceae infections. *Open Forum Infect Dis* 2015; **2**: ofv050.

9 Livermore DM. Current epidemiology and growing resistance of gram-negative pathogens. *Korean J Intern Med* 2012; **27**: 128–42.

10 ECDC. *Surveillance of Antimicrobial Resistance in Europe: Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)*. ECDC, 2017.

11 Kazmierczak KM, Tsuji M, Wise MG *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.

12 Plésiat PC, V, Bonnet R, Naas T *et al*. *Rapport d'Activité 2018*. Centre Nationale de Référence de la Résistance aux Antibiotiques, 2018.

13 Neuwirth C, Siebor E, Robin F *et al*. First occurrence of an IMP metallo-β-lactamase in *Aeromonas caviae*: IMP-19 in an isolate from France. *Antimicrob Agents Chemother* 2007; **51**: 4486–8.

14 Nordmann P, Poirel L. Epidemiology and diagnostics of carbapenem resistance in Gram-negative bacteria. *Clin Infect Dis* 2019; **69**: S521–8.

15 Kerr KG, Snelling AM. *Pseudomonas aeruginosa*: a formidable and ever-present adversary. *J Hosp Infect* 2009; **73**: 338–44.

16 Sheu CC, Chang YT, Lin SY *et al*. Infections caused by carbapenem-resistant Enterobacteriaceae: an update on therapeutic options. *Front Microbiol* 2019; **10**: 80.

17 Oueslati S, Iorga BI, Tlili L *et al*. Unravelling ceftazidime/avibactam resistance of KPC-28, a KPC-2 variant lacking carbapenemase activity. *J Antimicrob Chemother* 2019; **74**: 2239–46.

18 Shionogi & Co. Ltd. Fetroja (cefiderocol) Prescribing Information. 2020. https://www.shionogi.com/content/dam/shionogi/si/products/pdf/fetroja.pdf.

19 Shionogi & Co. Ltd. Fetcroja. Summary of Product Characteristics. 2020. https://www.ema.europa.eu/en/documents/product-information/fetcroja-epar-product-information_en.pdf.

20 Ito A, Nishikawa T, Matsumoto S *et al.* Siderophore cephalosporin cefiderocol utilizes ferric iron transporter systems for antibacterial activity against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2016; **60**: 7396–401.

21 Ito A, Kohira N, Bouchillon SK *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.

22 Ito A, Sato T, Ota M *et al. In vitro* antibacterial properties of cefiderocol, a novel siderophore cephalosporin, against Gram-negative bacteria. *Antimicrob Agents Chemother* 2017; **62**: e01454-17.

23 Ito A, Nishikawa T, Ota M *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.

24 Longshaw C, Manissero D, Tsuji M *et al. 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.

25 Kohira N, West J, Ito A *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.

26 Ito-Horiyama T, Ishii Y, Ito A *et al.* Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases. *Antimicrob Agents Chemother* 2016; **60**: 4384–6.

27 Hackel MA, Tsuji M, Yamano Y *et al. 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**: e00093-17.

28 Karlowsky JA, Hackel MA, Tsuji M *et al. 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.

29 International Organization for Standardization. ISO 20776-1:2019. 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. 2019. https://www.iso.org/standard/70464.html.

30 EUCAST. Guidance Document on Broth Microdilution Testing of Cefiderocol. 2020. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Guidance_documents/Cefiderocol_MIC_testing_EUCAST_guidance_document_201217.pdf.

31 EUCAST. Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 11.0. 2021. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.pdf.

32 Olaitan AO, Morand S, Rolain J-M. Mechanisms of polymyxin resistance: acquired and intrinsic resistance in bacteria. *Front Microbiol* 2014; **5**: 643–61.

33 Brooke JS. *Stenotrophomonas maltophilia*: an emerging global opportunistic pathogen. *Clin Microbiol Rev* 2012; **25**: 2–41.

34 Hackel MA, Tsuji M, Yamano Y *et al. In vitro* activity of the siderophore cephalosporin, cefiderocol, against carbapenem-nonsusceptible and multidrug-resistant isolates of Gram-negative bacilli collected worldwide in 2014 to 2016. *Antimicrob Agents Chemother* 2018; **62**: e01968-17.

35 Kumar A, Ellis P, Arabi Y *et al.* Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest* 2009; **136**: 1237–48.

36 Fröhlich C, Sørum V, Thomassen AM *et al.* OXA-48-mediated ceftazidime-avibactam resistance is associated with evolutionary trade-offs. *mSphere* 2019; **4**: e00024-19.

37 Kazmierczak KM, Biedenbach DJ, Hackel M *et al.* Global dissemination of *blaKPC* into bacterial species beyond *Klebsiella pneumoniae* and *in vitro* susceptibility to ceftazidime-avibactam and aztreonam-avibactam. *Antimicrob Agents Chemother* 2016; **60**: 4490–500.

38 de Jonge BL, Karlowsky JA, Kazmierczak KM *et al. In vitro* susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible Enterobacteriaceae isolates collected during the INFORM global surveillance study (2012 to 2014). *Antimicrob Agents Chemother* 2016; **60**: 3163–9.

39 Centre National de Référence de la Résistance aux Antibiotiques, 2019 report. https://maquette.cnr-resistance-antibiotiques.fr/ressources/pages/Rapport_CNR_RA_2019_resume.pdf.

40 Isler B, Doi Y, Bonomo RA *et al.* New treatment options against carbapenem-resistant *Acinetobacter baumannii* infections. *Antimicrob Agents Chemother* 2019; **63**: e01110-18.

41 Oueslati S, Naas T. *In vitro* activity of the siderophore cephalosporin, cefiderocol, against multidrug-resistant isolates of Gram-negative bacilli from France. *RICAI* 2019, Paris, France. Poster 12.

42 Oueslati S, Tlili L, Exilie C *et al.* Different phenotypic expression of KPC β-lactamase variants and challenges in their detection. *J Antimicrob Chemother* 2020; **75**: 769–71.

43 Ordooei JA, Shokouhi S, Sahraei Z. A review on colistin nephrotoxicity. *Eur J Clin Pharmacol* 2015; **71**: 801–10.

44 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing—Thirtieth Edition: M100*. 2020.

45 Dortet L, Girlich D, Ponties V *et al.* Investigation of NDM-1-producing *Morganella morganii* outbreak using whole genome sequencing. *ECCMID* 2016, Amsterdam, Netherlands. ePoster 0183.