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ORIGINAL ARTICLE

Activity of the novel siderophore cephalosporin cefiderocol against multidrug-resistant Gram-negative pathogens

J. Dobias[1,2,3,4] · **V. Dénervaud-Tendon**[1,2,3,4] · **L. Poirel**[1,2,3,4] · **P. Nordmann**[1,2,3,4,5]

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Abstract The novel siderophore cephalosporin cefiderocol (S-649266) with potent activity against Gram-negative pathogens was recently developed (Shionogi & Co., Ltd.). Here, we evaluated the activity of this new molecule and comparators against a collection of previously characterized Gram-negative isolates using broth microdilution panels. A total of 753 clinical multidrug-resistant Gram-negative isolates collected from hospitals worldwide were tested against cefiderocol and antibiotic comparators (ceftolozane–tazobactam [CT], meropenem [MEM], ceftazidime [CAZ], ceftazidime–avibactam [CZA], colistin [CST], aztreonam [ATM], amikacin [AMK], ciprofloxacin [CIP], cefepime [FEP], and tigecycline [TGC]) for their susceptibility. The collection included *Escherichia coli* (n = 164), *Klebsiella pneumoniae* (n = 298), *Enterobacter* sp. (n = 159), *Pseudomonas aeruginosa* (n = 45), and *Acinetobacter baumannii* (n = 87). Resistance mechanisms included producers of carbapenemases and extended-spectrum β-lactamases (ESBLs). In addition, a series of colistin-resistant enterobacterial isolates (n = 74), including 15 MCR-1 producers, were tested. The MIC_{90} of cefiderocol was 2 mg/L, while those of comparative drugs were >64 mg/L for CT, MEM, CAZ, CZA, and AMK, >32 mg/L for ATM, >16 mg/L for FEP, 8 mg/L for CST, and 2 mg/L for TGC. The MIC_{50} of cefiderocol was 0.5 mg/L, while those of other drugs were >64 mg/L for CAZ, 64 mg/L for CT, >32 mg/L for ATM, >16 mg/L for FEP, 8 mg/L for MEM and AMK, >4 mg/L for CIP, 1 mg/L for CZA, 0.5 mg/L for TGC, and <0.5 mg/L for CST. Only 20 out of 753 strains showed MIC values of cefiderocol ≥8 μg/mL. Compared to the other drugs tested, cefiderocol was more active, with the exception of colistin and tigecycline showing equivalent activity against certain subgroups of bacteria.

✉ P. Nordmann
patrice.nordmann@unifr.ch

1 Emerging Antibiotic Resistance Unit, University of Fribourg, Fribourg, Switzerland

2 National Reference Center for Emerging Antibiotic Resistance (Switzerland), University of Fribourg, Fribourg, Switzerland

3 French INSERM European Unit (LEA/IAME), University of Fribourg, Fribourg, Switzerland

4 Medical and Molecular Microbiology Unit, Department of Medicine, University of Fribourg, rue Albert Gockel 3, 1700 Fribourg, Switzerland

5 Institute for Microbiology, University of Lausanne and University Hospital Centre, Lausanne, Switzerland

Introduction

Gram-negative bacteria that produce extended-spectrum β-lactamases (ESBLs) are a major concern in healthcare due to their ability to spread globally [1]. ESBLs are a major group of enzymes that confer resistance to several generations of β-lactam antibiotics, including third-generation cephalosporins [2, 3]. ESBL-encoding genes that are primarily plasmid-encoded include mostly TEM-, SHV-, and CTX-M-type enzymes [4]. Enterobacteriaceae, such as *Klebsiella pneumoniae* and *Escherichia coli*, are the main ESBL producers that have been reported globally. Carbapenems are mostly used for the treatment of infections due to ESBL-producing bacteria, but carbapenemase-producing bacteria are now extensively reported [5, 6]. Polymyxins (e.g., colistin and polymyxin B) are now more frequently used as last-resort antibiotics for treating patients with multidrug-resistant bacterial infections [7]. However, a recent report shows that a novel gene (*mcr-1*) as a source of plasmid-encoded resistance encoded on a plasmid in *E. coli* may quickly spread to other bacterial strains or species [8–10]. Therefore, due to the increasing threat of

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multidrug-resistant and pandrug-resistant bacteria, there is a need for novel molecules. Cefiderocol (CFDC) is a novel parenteral siderophore cephalosporin also known as S-649266. It possesses a unique mechanism for penetrating efficiently into Gram-negative pathogens. It uses a "Trojan horse" strategy by binding free iron and is then actively transported into bacterial cells across the outer membrane of Gram-negative bacteria by way of the iron-transport system [11, 12]. Cefiderocol is a cephalosporin molecule with an attached catechol moiety on the 3-position side chain which binds to ferric iron [11]. Once across the outer membrane, the iron dissociates and the cephalosporin binds to penicillin-binding proteins (PBP), mainly PBP3, as other cephalosporins do to disrupt cell wall synthesis [11, 13], contributing to a potent antimicrobial activity against Gram-negative bacteria. In addition, this antimicrobial activity of cefiderocol is enhanced by the high stability of cefiderocol to hydrolysis by nearly all β-lactamases, including both the serine and metallo-carbapenemases [14]. The ability to cross the outer membrane through the active iron-transport system overcomes resistance due to porin channel mutations and efflux pump overproducers. It results that cefiderocol exhibits potent in vitro and in vivo activity against all species of Gram-negative bacteria, including carbapenem-resistant strains of Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, and even *Stenotrophomonas maltophilia* [15]. Here, we evaluated the antimicrobial activity of cefiderocol and other Gram-negative antibiotics (aztreonam, amikacin, cefepime, ceftazidime, ceftazidime–avibactam, ceftolozane–tazobactam, ciprofloxacin, meropenem, colistin, and tigecycline) against a panel of 753 multidrug-resistant bacterial isolates from human clinical sources with characterized antibiotic resistance mechanisms.

Materials and methods

Bacterial isolates

A total of 753 clinical multidrug-resistant isolates were evaluated in this study (Table 1). They were representative of the most widespread and broad-spectrum mechanisms of resistance currently observed worldwide in Gram-negative bacteria. The strains were collected from hospitals worldwide (42 countries) from 2000 to 2016, with a majority dating from the 2012–2016 period. They were of various origins (not always recorded) but mostly from urines, broncho-alveolar specimens, blood, pus, and stools.

In vitro susceptibility test methods

Minimum inhibitory concentrations (MICs) were determined following the Clinical and Laboratory Standards Institute (CLSI) broth microdilution (BMD) guidelines [16]. Frozen 96-well broth microdilution panels with pre-loaded antibiotic-growth medium were supplied by International Health Management Associates, Inc. (Schaumburg, IL, USA). Cefiderocol was tested in iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB) [17], as recently approved by the CLSI (http://clsi.org/standards/micro/microbiology-files/), whereas comparators were tested in cation-adjusted Mueller–Hinton broth (CAMHB). Quality

Table 1 Bacterial strains tested in this study

Genus (species)	Number of tested isolates	Characterized resistance
Escherichia coli (164)		
	43	OXA (-1/48/181/204)
	22	VIM (-1/2/4/19), IMP (-1/8)
	45	NDM (-1/4/5/6/7)
	11	KPC (-2/3)
	25	CTX-M (-1/3/15)
	15	MCR-1
	3	Non-MCR-1 colistin resistant
Klebsiella pneumoniae (298)		
	101	KPC (-2/3/11)
	89	OXA (-48/162/163/181/204/232)[a]
	18	NDM[b] (-1/4)
	20	VIM (-1/4/19), IMP (-1/4/8)
	25	CTX-M (-3/15)
	45	Colistin R
Enterobacteriaceae (159)		
	26	OXA (-48/163)
	10	NDM-1
	5	VIM-1
	14	IMP (-1/8)
	14	KPC-2
	49	CTX-M (-3/15)
	7	VEB-1
	14	SHV-12
	9	Plasmid-mediated AmpC and overproducer of AmpC
	11	Colistin R
Pseudomonas aeruginosa (45)		
	6	PER-1
	9	SHV (-2a/5/12), GES (-1/9)
	20	IMP (-1/2/10/13/15/19/29), KPC-2
	10	VIM (-1/2), SPM-1, GIM-1
Acinetobacter baumannii (87)		
	85	OXA-23/40/58/72
	2	NDM-1, IMP-4
Total	753	

[a] Five strains are OXA-48 producers and colistin resistant

[b] Five strains are NDM producers and colistin resistant

Table 2 In vitro activities of cefiderocol (CFDC), ceftolozane–tazobactam (CT), meropenem (MEM), ceftazidime (CAZ), ceftazidime–avibactam (CZA), colistin (CST), aztreonam (ATM), amikacin (AMK), ciprofloxacin (CIP), cefepime (FEP), and tigecycline (TGC) against *E. coli*, *K. pneumoniae*, *Enterobacter* sp., *P. aeruginosa*, and *A. baumannii*

Organism group/ antimicrobial agent	MIC range (mg/L)	No.	MIC_{50}[a]	MIC_{90}[a]
All species				
CFDC	0.03–64	753	0.5	2
CT	0.03–64	753	64	>64
CAZ	0.03–64	753	>64	>64
CZA	0.03–64	753	1	>64
FEP	0.05–16	753	>16	>16
MEM	0.03–64	753	8	>64
CIP	0.25–4	753	>4	>4
ATM	0.05–32	753	>32	>32
AMK	4–64	753	8	>64
CST	0.5–8	753	≤0.5	8
TGC	0.25–4	753	0.5	2
Escherichia coli				
CFDC	0.03–64	164	0.5	4
CT	0.03–64	164	8	>64
CAZ	0.03–64	164	64	>64
CZA	0.03–64	164	0.5	>64
FEP	0.05–16	164	>16	>16
MEM	0.03–64	164	2	>64
CIP	0.25–4	164	>4	>4
ATM	0.05–32	164	>32	>32
AMK	4–64	164	≤4	>64
CST	0.5–8	164	≤0.5	2
TGC	0.25–4	164	≤0.25	≤0.25
Klebsiella pneumoniae				
CFDC	0.03–64	298	1	2
CT	0.03–64	298	64	>64
CAZ	0.03–64	298	>64	>64
CZA	0.03–64	298	1	>64
FEP	0.05–16	298	>16	>16
MEM	0.03–64	298	16	>64
CIP	0.25–4	298	>4	>4
ATM	0.05–32	298	>32	>32
AMK	4–64	298	8	64
CST	0.5–8	298	≤0.5	16
TGC	0.25–4	298	0.5	1
Enterobacter sp.				
CFDC	0.03–64	159	0.5	4
CT	0.03–64	159	16	>64
CAZ	0.03–64	159	>64	>64
CZA	0.03–64	159	0.5	>64
FEP	0.05–16	159	>16	>16
MEM	0.03–64	159	0.5	16
CIP	0.25–4	159	>4	>4
ATM	0.05–32	159	>32	>32
AMK	4–64	159	≤4	16
CST	0.5–8	159	≤0.5	8
TGC	0.25–4	159	0.5	1

Table 2 (continued)

Organism group/ antimicrobial agent	MIC range (mg/L)	No.	MIC_{50}[a]	MIC_{90}[a]
Pseudomonas aeruginosa				
CFDC	0.03–64	45	0.5	2
CT	0.03–64	45	64	>64
CAZ	0.03–64	45	>64	>64
CZA	0.03–64	45	16	>64
FEP	0.05–16	45	>16	>16
MEM	0.03–64	45	32	>64
CIP	0.25–4	45	>4	>4
ATM	0.05–32	45	16	>32
AMK	4–64	45	8	>64
CST	0.5–8	45	≤0.5	1
TGC	0.25–4	45	>4	>4
Acinetobacter baumannii				
CFDC	0.03–64	87	0.12	4
CT	0.03–64	87	16	>64
CAZ	0.03–64	87	>64	>64
CZA	0.03–64	87	16	64
FEP	0.05–16	87	>16	>16
MEM	0.03–64	87	32	64
CIP	0.25–4	87	>4	>4
ATM	0.05–32	87	>32	>32
AMK	4–64	87	64	>64
CST	0.5–8	87	≤0.5	1
TGC	0.25–4	87	1	2

[a] MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively

control (QC) strains (*E. coli* ATCC 25922, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853) were tested regularly to ensure the stability of the panels and validity of the test methods. The acceptable concentration range for QC strains is 0.06–0.5 mg/L for *E. coli* and *P. aeruginosa* and not yet defined for *K. pneumoniae*.

All isolates were tested against the following antibiotics for the given concentration range: cefiderocol (S-649266) (CFDC, 0.03–64 mg/L), aztreonam (ATM, 0.5–32 mg/L), cefepime (FEP, 0.5–16 mg/L), ceftolozane–tazobactam (CT, 0.03–64 mg/L), meropenem (MEM, 0.03–64 mg/L), ceftazidime (CAZ, 0.03–64 mg/L), ceftazidime–avibactam (CZA, 0.03–64 mg/L), colistin (CST, 0.5–8 mg/L), amikacin (AMK, 4–64 mg/L), ciprofloxacin (CIP, 0.25–4 mg/L), and tigecycline (TGC, 0.25–4 mg/L).

The strains were grown overnight on a non-selective agar medium and two to three colonies were solubilized in 3 mL sterile 0.85% NaCl. The turbidity was adjusted to 0.5 McFarland with a McFarland densitometer DEN-1B from Grant Bio (Grant instruments Ltd., Cambridge, UK). One milliliter of inoculum was then diluted in 29 mL of sterile ddH_2O and 10 μL were added to each BMD panel well. The panels were incubated for 16–20 h at 35 °C. To ensure an even thermal distribution during incubation, the panels were stacked no more than four high. The MIC reading was then done according to the CLSI guidelines [18].

Results and discussion

The susceptibility test results are listed in Tables 2–7. The MIC_{90} (MIC value that inhibits 90% of the isolates) of cefiderocol was 2 mg/L (Table 2), while those of comparative drugs were >64 mg/L for CT, MEM, CAZ, CZA, and AMK, >32 mg/L for ATM, >16 mg/L for FEP, 8 mg/L for CST, and 2 mg/L for TGC. The MIC_{50} of CFDC was at 0.5 mg/L, while those of other drugs were >64 mg/L for CAZ, 64 mg/L for CT, >32 mg/L for ATM, >16 mg/L for FEP, 8 mg/L for MEM and AMK, >4 mg/L for CIP, 1 mg/L for CZA, 0.5 mg/L for TGC, and ≤0.5 mg/L for CST. The addition of 4 μg/mL of avibactam restored the activities of ceftazidime against the majority of the tested enterobacterial isolates.

The MIC_{50} and MIC_{90} of CFDC for Enterobacteriaceae producing KPC carbapenemases were ≤1 μg/mL and ≤2 mg/L, respectively (Table 3). The only competitive comparators were ceftazidime–avibactam ($MIC_{50/90}$) (1/4), colistin (≤0.5/

Table 3 In vitro activities of cefiderocol (CFDC), ceftolozane–tazobactam (CT), ceftazidime (CAZ), ceftazidime–avibactam (CZA), cefepime (FEP), meropenem (MEM), ciprofloxacin (CIP), aztreonam (ATM), amikacin (AMK), colistin (CST), and tigecycline (TGC) against Enterobacteriaceae (*E. coli*, *K. pneumoniae*, and *Enterobacter* sp.) producing a KPC-type carbapenemase

Organism group/antimicrobial agent	MIC range (mg/L)	No.	MIC_{50}[a]	MIC_{90}[a]
Total Enterobacteriaceae				
CFDC	0.03–64	127	1	2
CT	0.03–64	127	64	>64
CAZ	0.03–64	127	>64	>64
CZA	0.03–64	127	1	4
FEP	0.05–16	127	>16	>16
MEM	0.03–64	127	32	>64
CIP	0.25–4	127	>4	>4
ATM	0.05–32	127	>32	>32
AMK	4–64	127	16	32
CST	0.5–8	127	≤0.5	>8
TGC	0.25–4	127	0.5	1
Escherichia coli				
CFDC	0.03–64	12	0.5	1
CT	0.03–64	12	32	>64
CAZ	0.03–64	12	64	>64
CZA	0.03–64	12	1	4
FEP	0.05–16	12	>16	>16
MEM	0.03–64	12	8	64
CIP	0.25–4	12	>4	>4
ATM	0.05–32	12	64	64
AMK	4–64	12	≤4	>64
CST	0.5–8	12	≤0.5	≤0.5
TGC	0.25–4	12	≤0.25	≤0.25
Klebsiella pneumoniae				
CFDC	0.03–64	101	1	2
CT	0.03–64	101	64	>64
CAZ	0.03–64	101	>64	>64
CZA	0.03–64	101	2	4
FEP	0.05–16	101	>16	>16
MEM	0.03–64	101	64	>64
CIP	0.25–4	101	>4	>4
ATM	0.05–32	101	>32	>32
AMK	4–64	101	16	32
CST	0.5–8	101	≤0.5	>8
TGC	0.25–4	101	0.5	1
Enterobacter sp.				
CFDC	0.03–64	14	0.5	1
CT	0.03–64	14	64	>64
CAZ	0.03–64	14	>64	>64
CZA	0.03–64	14	1	2
FEP	0.05–16	14	>16	>16
MEM	0.03–64	14	8	16
CIP	0.25–4	14	>4	>4
ATM	0.05–32	14	>32	>32
AMK	4–64	14	≤4	≤4
CST	0.5–8	14	≤0.5	8
TGC	0.25–4	14	0.5	1

[a] MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively

Table 4 In vitro activities of cefiderocol (CFDC), ceftolozane–tazobactam (CT), ceftazidime (CAZ), ceftazidime–avibactam (CZA), cefepime (FEP) meropenem (MEM), ciprofloxacin (CIP), aztreonam (ATM), amikacin (AMK), colistin (CST), and tigecycline (TGC) against Enterobacteriaceae (*E. coli*, *K. pneumoniae*, and *Enterobacter* sp.) producing an OXA-48-type carbapenemase

Organism group/antimicrobial agent	MIC range (mg/L)	No.	MIC_{50}[a]	MIC_{90}[a]
Total Enterobacteriaceae				
CFDC	0.03–64	154	0.25	2
CT	0.03–64	154	32	>64
CAZ	0.03–64	154	64	>64
CZA	0.03–64	154	0.5	4
FEP	0.05–16	154	>16	>16
MEM	0.03–64	154	1	32
CIP	0.25–4	154	>4	>4
ATM	0.05–32	154	>32	>32
AMK	4–64	154	≤4	16
CST	0.5–8	154	≤0.5	1
TGC	0.25–4	154	≤0.25	1
Escherichia coli				
CFDC	0.03–64	42	0.06	0.5
CT	0.03–64	42	2	32
CAZ	0.03–64	42	4	64
CZA	0.03–64	42	0.25	0.5
FEP	0.05–16	42	8	>16
MEM	0.03–64	42	1	4
CIP	0.25–4	42	≤0.25	>4
ATM	0.05–32	42	32	>32
AMK	4–64	42	≤4	≤4
CST	0.5–8	42	≤0.5	1
TGC	0.25–4	42	≤0.25	≤0.25
Klebsiella pneumoniae				
CFDC	0.03–64	88	0.25	1
CT	0.03–64	88	64	>64
CAZ	0.03–64	88	64	>64
CZA	0.03–64	88	0.5	>64
FEP	0.05–16	88	>16	>16
MEM	0.03–64	88	1	64
CIP	0.25–4	88	>4	>4
ATM	0.05–32	88	>32	>32
AMK	4–64	88	≤4	>64
CST	0.5–8	88	≤0.5	1
TGC	0.25–4	88	0.5	1
Enterobacter sp.				
CFDC	0.03–64	24	1	4
CT	0.03–64	24	32	>64
CAZ	0.03–64	24	>64	>64
CZA	0.03–64	24	0.5	2
FEP	0.05–16	24	>16	>16
MEM	0.03–64	24	1	8
CIP	0.25–4	24	>4	>4
ATM	0.05–32	24	>32	>32
AMK	4–64	24	8	8
CST	0.5–8	24	≤0.5	1
TGC	0.25–4	24	1	1

[a] MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively

Table 5 In vitro activities of cefiderocol (CFDC), ceftolozane–tazobactam (CT), ceftazidime (CAZ), ceftazidime–avibactam (CZA), cefepime (FEP), meropenem (MEM), ciprofloxacin (CIP), aztreonam (ATM), amikacin (AMK), colistin (CST), and tigecycline (TGC) against Enterobacteriaceae (*E. coli*, *K. pneumoniae*, and *Enterobacter* sp.) producing NDM, VIM, or IMP carbapenemases

Organism group/antimicrobial agent	MIC range (mg/L)	No.	MIC_{50}[a]	MIC_{90}[a]
Total Enterobacteriaceae				
CFDC	0.03–64	134	1	4
CT	0.03–64	134	>64	>64
CAZ	0.03–64	134	>64	>64
CZA	0.03–64	134	>64	>64
FEP	0.05–16	134	>16	>16
MEM	0.03–64	134	32	>64
CIP	0.25–4	134	>4	>4
ATM	0.05–32	134	>32	>32
AMK	4–64	134	8	>64
CST	0.5–8	134	≤0.5	1
TGC	0.25–4	134	≤0.25	1
Escherichia coli				
CFDC	0.03–64	67	1	16
CT	0.03–64	67	>64	>64
CAZ	0.03–64	67	>64	>64
CZA	0.03–64	67	>64	>64
FEP	0.05–16	67	>16	>16
MEM	0.03–64	67	64	>64
CIP	0.25–4	67	>4	>4
ATM	0.05–32	67	>32	>32
AMK	4–64	67	8	>64
CST	0.5–8	67	≤0.5	1
TGC	0.25–4	67	≤0.25	≤0.25
Klebsiella pneumoniae				
CFDC	0.03–64	38	1	4
CT	0.03–64	38	>64	>64
CAZ	0.03–64	38	>64	>64
CZA	0.03–64	38	>64	>64
FEP	0.05–16	38	>16	>16
MEM	0.03–64	38	32	>64
CIP	0.25–4	38	>4	>4
ATM	0.05–32	38	>32	>32
AMK	4–64	38	16	>64
CST	0.5–8	38	≤0.5	1
TGC	0.25–4	38	1	2
Enterobacter sp.				
CFDC	0.03–64	29	1	4
CT	0.03–64	29	>64	>64
CAZ	0.03–64	29	>64	>64
CZA	0.03–64	29	>64	>64
FEP	0.05–16	29	>16	>16
MEM	0.03–64	29	16	64
CIP	0.25–4	29	1	>4
ATM	0.05–32	29	16	>32
AMK	4–64	29	≤4	>64
CST	0.5–8	29	≤0.5	≤0.5
TGC	0.25–4	29	0.5	1

[a] MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively

Table 6 In vitro activities of cefiderocol (CFDC), ceftolozane–tazobactam (CT), meropenem (MEM), ceftazidime (CAZ), ceftazidime–avibactam (CZA), colistin (CST), aztreonam (ATM), amikacin (AMK), ciprofloxacin (CIP), cefepime (FEP), and tigecycline (TGC) against *P. aeruginosa* producing a carbapenemase (either IMP, KPC, VIM, SPM, or GIM)

Organism group/antimicrobial agent	MIC range (mg/L)	No.	MIC_{50}[a]	MIC_{90}[a]
Pseudomonas aeruginosa				
CFDC	0.03–64	30	0.5	2
CT	0.03–64	30	>64	>64
CAZ	0.03–64	30	>64	>64
CZA	0.03–64	30	>64	>64
FEP	0.05–16	30	>16	>16
MEM	0.03–64	30	64	>64
CIP	0.25–4	30	>4	>4
ATM	0.05–32	30	8	64
AMK	4–64	30	8	>64
CST	0.5–8	30	≤0.5	1
TGC	0.25–4	30	8	>4

[a] MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively

≥8), and tigecycline (≤0.5/≤1). Elevated MIC_{90} values for colistin were noted for 17 out of 101 strains for *K. pneumoniae* and 2 out of 14 strains for *Enterobacter* sp. For all other antibiotics, the $MIC_{50/90}$ were superior or equal to the upper limit of the concentration range.

OXA-48-like producing Enterobacteriaceae were susceptible to a larger number of antibiotics compared to the KPC producers (Table 4). Again, cefiderocol is one of the antibiotics with the lowest $MIC_{50/90}$ values, at 0.25 and 2 μg/mL, respectively. Direct competitors were ceftazidime–avibactam (0.5/4), meropenem (1/32), amikacin (≤4/16), colistin (≤0.5/1), and tigecycline (≤0.5/≤1). Again, for *Klebsiella* sp., the MIC_{90} of CZA and MEM were affected by outliers and the MIC_{50} values should be considered instead.

For the enterobacterial isolates producing NDM, VIM, or IMP carbapenemases (Table 5), the only antibiotics that had strong activity ($MIC_{50/90}$) were cefiderocol (1/4), colistin (≤0.5/≤1), and tigecycline (≤0.25/≤1).

Colistin-resistant strains, mainly Enterobacteriaceae, had high susceptibility to cefiderocol (≤0.5/≤2) and some activity for ceftolozane–tazobactam in the case of *E. coli* (0.25/>64), ceftazidime–avibactam (0.5/>64), meropenem (0.12/64), amikacin (≤4/16), and tigecycline (≤1/≤1). Except for cefiderocol and tigecycline, the MIC_{90} values were close to or above the upper limit of the concentration range of the tested antibiotics for the Enterobacteriaceae being resistant to colistin. This could be explained by additional resistance traits, such as expression of genes encoding carbapenemases and ESBLs, in particular for *K. pneumoniae* and *Enterobacter* sp. The level of resistance to colistin (MIC_{90} = 2) and of meropenem (MIC_{90} = 1) was lower for *E. coli* than that noted for *K. pneumoniae* and *Enterobacter* sp.

Carbapenemase-producing *P. aeruginosa* were susceptible only to cefiderocol (0.5/2) and colistin (≤0.5/1) (Table 6). The same resistance trend was observed for carbapenemase-producing *A. baumannii* strains [CFDC (0.12/4) and CST

Table 7 In vitro activities of cefiderocol (CFDC), ceftolozane–tazobactam (CT), meropenem (MEM), ceftazidime (CAZ), ceftazidime–avibactam (CZA), colistin (CST), aztreonam (ATM), amikacin (AMK), ciprofloxacin (CIP), cefepime (FEP), and tigecycline (TGC) against *A. baumannii* producing an OXA-type carbapenemase (either OXA-23, -40, -58, or -72)

Organism group/antimicrobial agent	MIC range (mg/L)	No.	MIC_{50}[a]	MIC_{90}[a]
Acinetobacter baumannii				
CFDC	0.03–64	85	0.12	4
CT	0.03–64	85	16	>64
CAZ	0.03–64	85	>64	>64
CZA	0.03–64	85	16	64
FEP	0.05–16	85	>16	>16
MEM	0.03–64	85	32	64
CIP	0.25–4	85	>4	>4
ATM	0.05–32	85	>32	>32
AMK	4–64	85	64	>64
CST	0.5–8	85	0.5	1
TGC	0.25–4	85	1	2

[a] MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC that inhibits 50% and 90% of the isolates, respectively

(0.5/1)], except that they were also susceptible to tigecycline (1/2) (Table 7). The only unexpected result is the overall low activity of ceftolozane–tazobactam against those *P. aeruginosa* isolates.

Among the 753 isolates tested, only 24 isolates exhibited an MIC value of cefiderocol ≥8 μg/mL, among which 45% were NDM producers (n = 11), 30% were OXA-23-producing *A. baumannii* (n = 7), and two VEB-, one SHV-, one VIM-, and one OXA-48-like producers among *K. pneumoniae*, *P. aeruginosa*, and *Enterobacter* sp. Noteworthy, cefiderocol was active against 68 out of 79 NDM producers, while most of the NDM producers co-produced other β-lactam resistance mechanisms, such as ESBLs (mostly CTX-M-15), porin defect, plasmid-mediated cephalosporinases, and other carbapenemases (data not shown). Cefiderocol was more active (MIC_{90} 2–4 mg/L) than the comparators (MIC_{90} >4 to >64 mg/L) (cephalosporins, carbapenem, fluoroquinolone, and monobactam) against all the tested strains. The only comparators with equal activity were colistin and tigecycline, with the limitation that tigecycline was not active against *P. aeruginosa*. Finally, it should be emphasized that cefiderocol displays much favorable pharmacokinetic parameters (tissue diffusion and use in renal impairment) than colistin and tigecycline [19], which will be an important factor for choosing adequate therapy of infections due to multidrug infections.

Compliance with ethical standards

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Conflict of interest None to declare.

Ethical approval Not applicable.

Informed consent Not applicable.

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