In-vitro activity of cefiderocol (S-649266) against multidrug-resistant Enterobacteriaceae from the UK

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INTRODUCTION

- Carbapenem-resistant Enterobacteriaceae have proliferated globally and are a growing problem. Many are resistant to multiple classes of antibiotics[1].
- Cephalosporin/diazabicyclooctanes-inhibitor combinations such as ceftazidime/avibactam are active against most Enterobacteriaceae isolates with Class A or D carbapenamase, but lack activity against those with metallo-beta-lactamases (MBLs)[2, 3].
- Cefiderocol (S-649266) is a novel parenteral siderophore cephalosporin with a catechol moiety on the 3- side chain, now in phase III development.
- Cefiderocol exploits the ferric iron transporter system to enter the Gram-negative cell[4].
- We evaluated cefiderocol's activity against multidrug-resistant clinical isolates of Enterobacteriaceae from the UK.

METHODS

Bacteria

- The test panel were 305 clinical Enterobacteriaceae submitted between 2008 - 2016 and all but 2 were from UK hospitals. The 2 non-UK isolates were from Ireland. The panel was selected to represent diverse carbapenemase producers and those with carbapenem resistance via combinations of porin loss with AmpC or ESBL activity (table 1).
  - Carbapenemase genes were identified by PCR or by whole genome sequencing.
  - Carbapenem resistance due to porin loss combined with ESBL or AmpC activity was inferred from their previous susceptibility results and the absence of carbapenemases.

MIC testing

- MICs were determined using pre-prepared broth microdilution plates (IHMA Inc, Illinois, USA) with antibiotic dilutions in cation-adjusted Mueller Hinton broth (CAMHB)[6].
  - Iron depleted CAMHB (ID-CAMHB) was used for cefiderocol only. ID-CAMHB was prepared by treating CAMHB with cation-binding resin (Chelex, Bio-Rad), followed by removal of resin by filtration and addition of Mg, Ca and Zn ions at concentrations of 20-25 mg/L, 10-12.5 mg/L and 0.5-1.0 mg/L, respectively (IHMA Inc, Illinois, USA).
- Comparator antibiotics comprised meropenem, ceftazidime, ceftazidime-avibactam, cefepime, ceftolozane-tazobactam, aztreonam, colistin, amikacin, ciprofloxacin and tigecycline.
- MICs were interpreted using CLSI guidelines where available, or EUCAST breakpoints for ceftazidime-avibactam, tigecycline and colistin

RESULTS

Table 1. Isolate panel.

	No isolates with										
	NDM	VIM	IMP	KPC	OXA-48-like	Porin loss + ESBL	Porin loss + AmpC	GES	IMI	SME	Total
Klebsiella spp.	20	17	5	20	22	6	7	5			102
Escherichia coli	21	15	5	21	20	11	7				100
Enterobacter spp.	10	8	4	9	9	8	5	3	5		61
Serratia marcescens	1			3	2	1	4	1		5	17
Citrobacter spp.	3	7	1	3	3						17
Providencia spp.	3						1				4
Morganella morganii	2										2
Proteus mirabilis	1										1
Hafnia alvei							1				1
Total	61	47	15	56	56	26	25	9	5	5	305

Table 2. MIC distribution of cefiderocol and comparator.

Antibiotic	No. isolates at MIC (mg/L)													MIC_{50}	MIC_{90}	No. non-susceptible
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128			
Cefiderocol	11	13	19	25	29	71	11	56	41	15	3	5	6	1	8	–
Meropenem				1	5	6	27	43	58	41	44	42	38	16	≥128	293 (96.1%)
Ceftazidime			3	3	5	15	10	6	9	15	21	25	193	≥128	≥128	263 (86.2%)
Ceftazidime-avibactam		1	10	19	41	55	39	10	3	9	10	15	93	2	≥128	127 (41.6%)
Cefepime					11*	2	24	22	22	33	191**			≥32	≥32	268(87.9%)
Ceftolozane-tazobactam				1	6	13	6	13	25	26	14	20	181	≥128	≥128	279 (91.5%)
Azteonam					55*	13	6	9	10	12	23	177**		≥64	≥64	222 (72.8%)
Amikacin								126*	58	38	30	13	40	8	≥128	83 (27.2%)
Ciprofloxacin				68*	13	24	20	14	166**					≥8	≥8	200 (65.6%)
Tigecycline				59*	78	109	26	23	10**					1	4	59 (19.3%)
Colistin					212*	36	4	5	3	45**				≤0.5	≥16	57 (18.7%)

*** ≤ MIC value, ** ≥ MIC value**

Figure 1. Cefiderocol MIC distribution by species

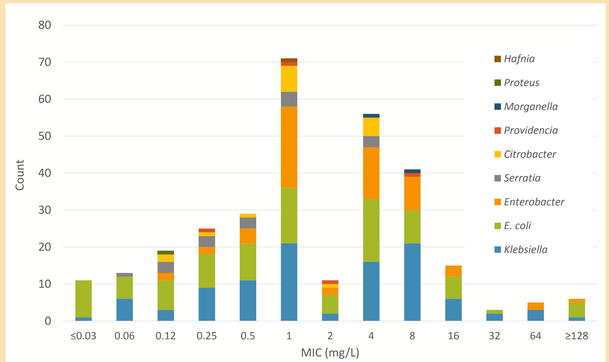
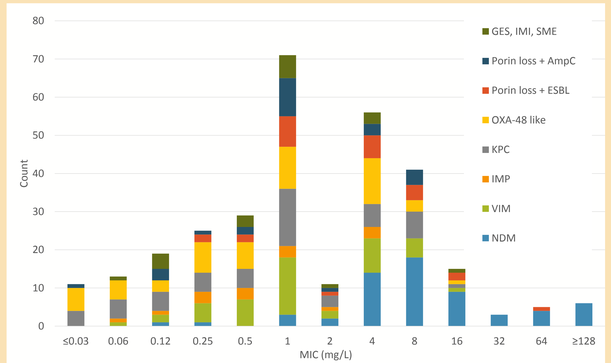


Figure 2. Cefiderocol MIC distribution by resistance mechanism



- MIC distribution are shown in table 2.
- At 8 mg/L cefiderocol inhibited 90.5% of isolates; rates were >95% except for: isolate with NDM MBLs (63.9%) porin loss+ESBL (88.5%) uncommon class A carbapenemases (94.7%) (table 3).
- At 4 mg/L cefiderocol inhibited >80% of isolates in all groups except those with NDM carbapenemases or combinations of ESBL and porin loss.
- No other agent inhibited >90% of isolates at breakpoint; only colistin and tigecycline inhibited >80% of isolates (table 2).
- The activity of cefiderocol against this challenging collection of Enterobacteriaceae was not related to the bacterial species (figure1).
- The MIC distribution for isolates with NDM enzymes, irrespective of species, was extended and raised compared with distributions for isolates with other β-lactamases, including MBLs (figure 2).
- Cefiderocol MICs for isolates with NDM enzymes were independent of aztreonam resistance, indicating that high values did not reflect co-resident ESBL or AmpC (figure 3).

Table 3. Percent susceptibility to cefiderocol at 4 & 8 mg/L in relation to resistance mechanisms.

Isolates with	No. tested	≤4mg/L	≤8mg/L
IMP	15	100%	100%
GES, IMI, SME	19	94.7%	94.7%
OXA-48 like	56	92.9%	98.2%
VIM	47	87.2%	97.9%
KPC	56	85.7%	98.2%
Porin loss + AmpC	25	84.0%	100%
Porin loss + ESBL	26	73.1%	88.5%
NDM	61	34.4%	63.9%

Figure 3. Cefiderocol vs aztreonam MICs for isolates with NDM carbapenemases.

	MIC (mg/L) cefiderocol										
MIC (mg/L) aztreonam	0.12	0.25	1	2	4	8	16	32	64	≥128	Total
≤0.5	1		1	2	4	7	2	1	1		19
1							1				1
2						2					2
4		1			1		1			1	4
8					1		1			1	3
16					1						1
32					1	1		1		1	4
≥64			2		6	8	4	1	3	3	27
Total	1	1	3	2	14	18	9	3	4	6	61

CONCLUSIONS

- At ≤4 or 8 mg/L, cefiderocol inhibited the huge majority of carbapenem-resistant Enterobacteriaceae, irrespective of species, including isolates with IMP, VIM, OXA-48-like and Class A carbapenemases.
- MICs >8 mg/L were seen for around one-third of isolates with NDM carbapenemases; this behaviour was unrelated to aztreonam MICs implying that it relates to the NDM enzymes themselves, not to co-produced ESBLs or AmpC enzymes.
- Cefiderocol is the first catechol b-lactam to reach advanced clinical development. If clinical trials confirm efficacy, the drug has considerable potential to overcome the challenge of carbapenemase-producing Enterobacteriaceae

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TRANPARENCY DECLARATION

DML: Advisory Boards or ad-hoc consultancy Accelerate, Achaogen, Adenium, Allecra, AstraZeneca, Auspherix, Basilea, BioVersys, Centauri, Discuva, Meiji, Pfizer, Roche, Shionogi, Tetraphase, VenatoRx, Wockhardt, Zambon, Zealand, Paid lectures – Astellas, AstraZeneca, Cardiome, Cepheid, Merck and Nordic. Relevant shareholdings in– Dechra, GSK, Merck, Perkin Elmer, Pfizer collectively amounting to <10% of portfolio value. All others: No personal interests to declare. However, PHE's AMRHAI Reference Unit has received financial support for conference attendance, lectures, research projects or contracted evaluations from numerous sources, including: Achaogen, Allecra, Amplex, AstraZeneca, AusDiagnostics, Becton Dickinson, The BSAC, Cepheid, Check-Points, Cubist Pharmaceuticals, Department of Health, Enigma Diagnostics, Food Standards Agency, GlaxoSmithKline Service, Henry Stewart Talks, IHMA Ltd, Merck Sharpe & Dohme, Meiji Seika Kiasya, Momentum Biosciences, Roche, Nordic, Norgine, Rempex, Rokitan Ltd, Smith & Nephew, VenatoRx and Wockhardt Ltd.