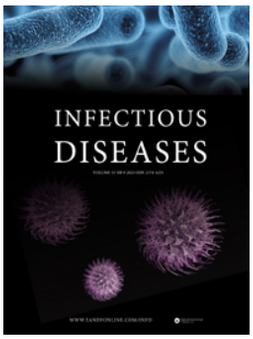

Infectious Diseases

ISSN: (Print) (Online) Journal homepage: informahealthcare.com/journals/infd20

Higher rates of cefiderocol resistance among NDM producing *Klebsiella* bloodstream isolates applying EUCAST over CLSI breakpoints

Burcu Isler, Cansel Vatansever, Berna Özer, Güle Çınar, Abdullah Tarık Aslan, Caitlin Falconer, Michelle J. Bauer, Brian Forde, Funda Şimşek, Necla Tülek, Hamiyet Demirkaya, Şirin Menekşe, Halis Akalin, İlker İnanç Balkan, Mehtap Aydın, Elif Tükenmez Tigen, Safiye Koçulu Demir, Mahir Kapmaz, Şiran Keske, Özlem Doğan, Çiğdem Arabacı, Serap Yağcı, Gülşen Hazırolan, Veli Oğuzalp Bakır, Mehmet Gönen, Neşe Saltoğlu, Alpay Azap, Özlem Azap, Murat Akova, Önder Ergönül, Füsun Can, David L. Paterson & Patrick N. A. Harris

To cite this article: Burcu Isler, Cansel Vatansever, Berna Özer, Güle Çınar, Abdullah Tarık Aslan, Caitlin Falconer, Michelle J. Bauer, Brian Forde, Funda Şimşek, Necla Tülek, Hamiyet Demirkaya, Şirin Menekşe, Halis Akalin, İlker İnanç Balkan, Mehtap Aydın, Elif Tükenmez Tigen, Safiye Koçulu Demir, Mahir Kapmaz, Şiran Keske, Özlem Doğan, Çiğdem Arabacı, Serap Yağcı, Gülşen Hazırolan, Veli Oğuzalp Bakır, Mehmet Gönen, Neşe Saltoğlu, Alpay Azap, Özlem Azap, Murat Akova, Önder Ergönül, Füsun Can, David L. Paterson & Patrick N. A. Harris (2023) Higher rates of cefiderocol resistance among NDM producing *Klebsiella* bloodstream isolates applying EUCAST over CLSI breakpoints, Infectious Diseases, 55:9, 607-613, DOI: 10.1080/23744235.2023.2226709

To link to this article: https://doi.org/10.1080/23744235.2023.2226709

Taylor & Francis
Taylor & Francis Group

INFECTIOUS DISEASES,
2023; VOL. 55,
NO. 9, 607–613

https://doi.org/10.1080/23744235.2023.2226709

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Higher rates of cefiderocol resistance among NDM producing *Klebsiella* bloodstream isolates applying EUCAST over CLSI breakpoints

Burcu Isler[a,b], Cansel Vatansever[c], Berna Özer[c], Güle Çınar[d], Abdullah Tarık Aslan[e], Caitlin Falconer[a], Michelle J. Bauer[a], Brian Forde[a], Funda Şimşek[f], Necla Tülek[g], Hamiyet Demirkaya[h], Şirin Menekşe[i], Halis Akalin[j], İlker İnanç Balkan[k], Mehtap Aydın[l], Elif Tükenmez Tigen[m], Safiye Koçulu Demir[n], Mahir Kapmaz[o], Şiran Keske[c,p], Özlem Doğan[c], Çiğdem Arabacı[q], Serap Yağcı[r], Gülşen Hazırolan[s], Veli Oğuzalp Bakır[t], Mehmet Gönen[u], Neşe Saltoğlu[k], Alpay Azap[d], Özlem Azap[h], Murat Akova[e], Önder Ergönül[c,v], Füsun Can[c,v], David L. Paterson[a] and Patrick N. A. Harris[a]

[a]UQ Centre for Clinical Research, Faculty of Medicine, University of Queensland, Brisbane, Australia; [b]Infection Management Services, Princess Alexandra Hospital, Brisbane, Australia; [c]Infectious Diseases and Clinical Microbiology, School of Medicine, Koç University, Istanbul, Turkey; [d]Infectious Diseases and Clinical Microbiology, School of Medicine, Ankara University Ankara, Turkey; [e]Infectious Diseases and Clinical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey; [f]Infectious Diseases and Clinical Microbiology, University of Health Sciences, Ministry of Health Prof Dr Cemil Taşçıoğlu City Hospital, Istanbul, Turkey; [g]Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Atilim University, Ankara, Turkey; [h]Infectious Diseases and Clinical Microbiology, Ankara Hospital, Başkent University, Ankara, Turkey; [i]Infectious Diseases, Koşuyolu Kartal Heart Training and Research Hospital, Istanbul, Turkey; [j]Infectious Diseases and Clinical Microbiology, School of Medicine, Uludağ University, Bursa, Turkey; [k]Infectious Diseases and Clinical Microbiology, School of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey; [l]Infectious Diseases and Clinical Microbiology, Ümraniye Training and Research Hospital, University of Health Sciences, Istanbul, Turkey; [m]Infectious Diseases and Clinical Microbiology, Pendik Training and Research Hospital, Marmara University, Istanbul, Turkey; [n]Infectious Diseases and Clinical Microbiology, Demiroglu Bilim University, Istanbul, Turkey; [o]Infectious Diseases and Clinical Microbiology, Koç University Hospital, Istanbul, Turkey; [p]Infectious Diseases, VKV American Hospital, Istanbul, Turkey; [q]Clinical Microbiology, Ministry of Health Prof Dr Cemil Taşçıoğlu City Hospital, University of Health Sciences, Istanbul, Turkey; [r]Clinical Microbiology, Ankara Training and Research Hospital, Ankara, Turkey; [s]Clinical Microbiology, Hacettepe University School of Medicine, Ankara, Turkey; [t]Graduate School of Sciences and Engineering, Koç University, Istanbul, Turkey; [u]Industrial Engineering, College of Engineering, Koç University, Istanbul, Turkey; [v]Koç University İş Bank Centre for Infectious Diseases (KUISCID), Istanbul, Turkey

ABSTRACT

Background: Cefiderocol is generally active against carbapenem-resistant *Klebsiella* spp. (CRK) with higher MICs against metallo-beta-lactamase producers. There is a variation in cefiderocol interpretive criteria determined by EUCAST and CLSI. Our objective was to test CRK isolates against cefiderocol and compare cefiderocol susceptibilities using EUCAST and CLSI interpretive criteria.

Methods: A unique collection ($n = 254$) of mainly OXA-48-like- or NDM-producing CRK bloodstream isolates were tested against cefiderocol with disc diffusion (Mast Diagnostics, UK). Beta-lactam resistance genes and multilocus sequence types were identified using bioinformatics analyses on complete bacterial genomes.

Results: Median cefiderocol inhibition zone diameter was 24 mm (interquartile range [IQR] 24–26 mm) for all isolates and 18 mm (IQR 15–21 mm) for NDM producers. We observed significant variability between cefiderocol susceptibilities using EUCAST and CLSI breakpoints, such that 26% and 2% of all isolates, and 81% and 12% of the NDM producers were resistant to cefiderocol using EUCAST and CLSI interpretive criteria, respectively.

Conclusions: Cefiderocol resistance rates among NDM producers are high using EUCAST criteria. Breakpoint variability may have significant implications on patient outcomes. Until more clinical outcome data are available, we suggest using EUCAST interpretive criteria for cefiderocol susceptibility testing.

Supplemental data for this article can be accessed online at https://doi.org/10.1080/23744235.2023.2226709.

KEYWORDS
Cefiderocol
NDM
EUCAST
CLSI
Klebsiella
bloodstream

ARTICLE HISTORY
Received 16 December 2022
Revised 7 June 2023
Accepted 14 June 2023

CONTACT
Burcu Isler
burcu.isler@uq.edu.au
UQ Centre for Clinical Research, Faculty of Medicine, University of Queensland,
Building 71/918. Royal Brisbane and Women's Hospital Campus Herston, QLD 4029, Brisbane, Australia

Introduction

Carbapenem resistant *Klebsiella* (CRK) infections are associated with significant morbidity and mortality for the vulnerable hospitalised patients. This is partly explained by the underlying patient comorbidities, and is largely contributed by the lack of active antibiotics against CRK. Several new antibiotics have been approved recently for the treatment of OXA-48-like- and KPC-producing CRK infections. However, metallo-beta-lactamase-producing CRK remains as a challenging group with few treatment options [1]. Cefiderocol is a new generation cephalosporin with *in vitro* activity against all clinically important carbapenemases including metallo-beta-lactamases [2]. However, cefiderocol MICs were reported to be higher for the metallo-beta-lactamase producers [3]. Real life data evaluating cefiderocol use for metallo-beta-lactamase-producing CRK are limited [4].

Accurate antimicrobial susceptibility testing (AST) is important to guide treatment. Cefiderocol AST remains challenging due to the requirement for iron-depleted media for broth microdilution (BMD). Disc diffusion has been accepted as a robust alternative to BMD for cefiderocol AST and is the most practical method applied by the clinical laboratories [5,6]. Another challenging aspect of cefiderocol AST is the substantial difference between EUCAST and CLSI interpretive criteria. Isolates with a cefiderocol MIC of >2 mg/L and ≥ 16 mg/L are categorised as resistant according to EUCAST and CLSI, respectively (Table 1) [7,8]. EUCAST does not have an 'I' (susceptible, increased exposure) category and has an area of technical uncertainty (ATU) for the isolates with a inhibition zone diameter of 18–22 mm, whereas CLSI has a range (9–15 mm) for 'I' (intermediate) category but no ATU. The difference between the MIC breakpoints is the reason for different zone diameter breakpoints, as the latter are calibrated to MIC breakpoints.

The objective of this study was to test a large collection of CRK bloodstream isolates that were collected as part of a multicentre observational study, against cefiderocol to demonstrate its *in vitro* activity against OXA-48-like and metallo-beta-lactamase producing CRK isolates. We aimed to compare EUCAST and CLSI breakpoints, and demonstrate discrepancies that would arise from breakpoint variability.

Table 1. Comparison of EUCAST and CLSI interpretive criteria for Enterobacterales.

	Broth micro dilution, mg/L			Disc diffusion, mm			
	S	I	R	S	I	R	ATU
EUCAST	≤ 2	NA	>2	≥ 22	NA	<22	18-22
CLSI	≤ 4	8	≥ 16	≥ 16	12–15	≤ 11	NA

S: susceptible; I: intermediate; R: resistant; ATU: area of technical uncertainty; NA: not available

Methods

Isolate selection

Isolates were collected as part of a multicentre observational study between June 2018 and June 2019 from 13 tertiary care centres in Turkey [9]. The study was approved by the Koc University Institutional Review Board (approval number: 2018.151.IRB1.018). Carbapenem resistance was defined as being non-susceptible to at least one carbapenem according to EUCAST 2018 breakpoints (i.e. MIC >2 μg/mL for meropenem or imipenem, and >0.5 μg/mL for ertapenem). Carbapenem resistance was detected by automated methods at participating laboratories and was confirmed with Etest (bioMérieux, France) in the central laboratory (University of Queensland Centre for Clinical Research laboratories). Species identification was performed using MALDI-TOF MS (Bruker, Bremen, Germany). Whole genome sequencing was performed at Australian Centre for Ecogenomics using Illumina NextSeq500 (Illumina Inc., San Diego, CA) instrument. Carbapenemase genes were detected on whole bacterial genomes using Abricate version 0.8.10 (https://github.com/tseemann/abricate) with the NCBI database [10]. Lineage STs were assigned using MLST (https://github.com/tseemann/mlst) with MLST profiles from pubMLST (https://pubmlst.org/).

Susceptibility testing

Cefiderocol susceptibility testing was performed using 30 μg cefiderocol discs (Mast Diagnostics, UK) according to EUCAST 2021 criteria [7]. Briefly, isolates were grown on non-selective blood agar at 35 ± 1 °C for 18 ± 2 h. A single colony was suspended in 0.9% NaCl for a McFarland of 0.5. This was streaked onto standard Mueller-Hinton agar (Thermo Fisher Scientific, Swindon, UK) and plates were incubated in aerobic air at 35 ± 1 °C for 16–18 h. Quality control organisms (i.e. *Escherichia coli* ATCC 25922) were prepared each day of testing. All experiments were performed in duplicates on the same day. In the event of a discordance between the results of the first two experiments, a third experiment was performed. Discordance was defined as discrepancies resulting in assignment of bacterial isolates to adjacent interpretative category (i.e. susceptible to intermediate, intermediate to susceptible, intermediate to resistant, resistant to intermediate, susceptible to resistant, resistant to susceptible). Inhibition zone diameters were read using the innermost colony-free zone when pinpoint colonies were observed within the zone. Results were interpreted by applying EUCAST and CLSI breakpoints (Table 1).

Results

Isolate characteristics

There were 254 *Klebsiella* spp. isolates (92% *Klebsiella pneumoniae*, 6% *Klebsiella variicola*, 0.4% *Klebsiella quasipneumoniae* and 0.4% *Klebsiella oxytoca*). Fifty (20%) isolates were found to be carbapenem susceptible in the central laboratory and did not harbour any carbapenemases. The majority of the remaining isolates were OXA-48-like producers (145/204, 70%), followed by metallo-beta-lactamase/OXA-48-like co-producers (31/204, 15%), single metallo-beta-lactamase producers (11/204, 5%), no-carbapenemase producers (13/204, 6%) and KPC producers (4/204, 2%). All metallo-beta-lactamases, except a single VIM, were NDM.

SHV was the main extended spectrum beta-lactamase (ESBL) class detected in this collection (232/254, 91%), followed by CTX-M (196/254, 77%) and TEM (109/254, 43%). Predominant SHV, CTX-M and TEM types were SHV-106 (90/232, 36%), CTX-M-15 (184/196, 73%) and TEM-150 (105/109, 96%), respectively (data not shown).

ST2096 was the main multilocus sequence type (66/254, 26%) followed by ST101 (37/254, 15%) and ST14 (28/254, 11%). The majority (58/66, 88%) of ST2096 strains carried OXA-232 and the majority (20/28, 71%) of ST14 strains carried an NDM and an OXA-48-like concomitantly.

Inhibition zone diameters

Median cefiderocol disc zone diameter was 24 mm (interquartile range [IQR] 24–26 mm) for all isolates, 24 mm (IQR 23–26 mm) for OXA-48-like producers, 18 mm (IQR 15–21 mm) for metallo-beta-lactamase producers, 25 mm (IQR 22–26 mm) for KPC producers, 26 mm (IQR 24–27 mm) for none-carbapenemase-producers and 28 mm (IQR 26–28 mm) for carbapenem susceptible isolates (Table 2, Figure 1).

Interpretive criteria

Cefiderocol susceptibility was demonstrated for 189 (74%) and 236 (93%) of all isolates using EUCAST and CLSI interpretive criteria, respectively ($p < 0.001$) (Table 3). About 90% (47/52) of those that were categorised as resistant by EUCAST were categorised as susceptible by CLSI. Susceptible percentages using EUCAST and CLSI interpretive criteria for OXA-48-like, metallo-beta-lactamase and KPC producers were 81% and 97%, 19% and 67%, and

Table 2. Cefiderocol inhibition zone diameter according to the carbapenemase type.

		Disc zone diameter, mm			EUCAST interpretive criteria, *n* (%)		
	Number	Median	IQR	Range	S	R	ATU
OXA-48-like	145	24	23–26	13–30	118 (81)	27 (19)	30 (21)
OXA-48	64	25	23–27	13–29	55 (86)	9 (14)	10 (16)
OXA-232	59	23	21–25	17–28	44 (75)	15 (25)	18 (31)
OXA-244	17	24	24–25	16–27	16 (94)	1 (6)	0
OXA-181	5	23	18–28	18–30	3 (60)	2 (40)	2 (40)
MBL[a]	42	18	15–21	6–26	8 (19)	34 (81)	16 (38)
MBL with OXA-48- like[b]	31	17	14–21	6–26	5 (16)	26 (84)	10 (32)
MBL single	11	20	18–23	14–26	3 (27)	8 (73)	6 (55)
KPC	4	25	22–26	19–26	3 (75)	1 (25)	1 (25)
No-carbapenemase	13	26	24–27	17–29	11 (85)	2 (15)	1 (7)
Carbapenem susceptible	50	28	26–28	21–27	48 (98)	2 (2)	1 (2)
Total	254	24	24–26	6–37	189 (74)	65 (26)	49 (19)

[a]NDM ($n = 41$) and VIM ($n = 1$); [b]OXA-48 ($n = 27$), OXA-232 ($n = 3$), OXA-244 ($n = 1$); IQR: interquartile range; MBL: metallo-beta-lactamase; CRK; carbapenem resistant *Klebsiella* spp.; ATU: area of technical uncertainty.

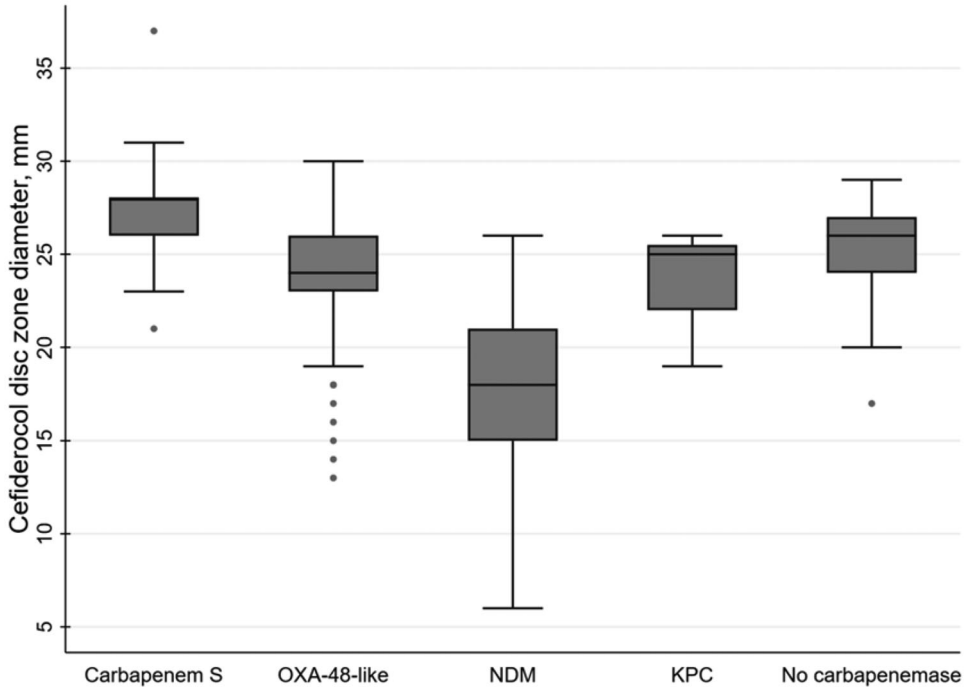

Figure 1. Box plot graph of cefiderocol inhibition zone diameter according to carbapenem resistance mechanism. S: susceptible.

Table 3. Comparison of interpretive categories when using EUCAST and CLSI inhibition zone diameter breakpoints for cefiderocol according to carbapenem resistance mechanism.

Carbapenem resistance mechanism	Number of isolates	R (%)		I (%)	S (%)	
		EUCAST	CLSI	CLSI	EUCAST	CLSI
OXA-48-like	145	27 (19)	0	4 (3)	118 (81)	141 (97)
MBL*	42	34 (81)	5 (12)	9 (21)	8 (19)	28 (67)
KPC-2	4	1 (25)	0	0	3 (75)	4 (100)
No-carbapenemase	13	2 (15)	0	0	11 (85)	13 (100)
carbapenem susceptible	50	1 (2)	0	0	49 (98)	50 (100)
Total	254	65 (26)	5 (2)	13 (5)	189 (74)	236 (93)

S: susceptible; I: intermediate; R: resistant; MBL: metallo-beta-lactamase; CRK: carbapenem resistant *Klebsiella* spp.
*31 of 42 MBL producing isolates also produce an OXA-48-like carbapenemase.

75% and 100%; respectively. Majority of the non-carbapenemase producers and all carbapenem susceptible isolates remained susceptible to cefiderocol using EUCAST and CLSI interpretive criteria, respectively (Table 3). Forty-nine (19%) isolates fell into EUCAST ATU category (Table 2). The percentage of isolates in the ATU category were higher for the metallo-beta-lactamase producers (16/42, 38%).

Cefiderocol susceptibility according to MLST

ST14 and ST101 were the sequence types with the highest and lowest cefiderocol resistance rates, respectively, according to EUCAST interpretive criteria (27/28, 96% and 1/37, 3%; respectively). Cefiderocol resistance rate was 29% (19/66) for the predominant sequence type ST2096 (Supplementary Figure).

Cefiderocol susceptibility according to ESBL type

ESBL presence was more common among cefiderocol resistant isolates as compared to cefiderocol susceptible isolates according to EUCAST criteria. CTX-M, SHV and TEM were present in 94%, 100% and 58% of the cefiderocol resistant isolates, and 71%, 88% and 38% of the cefiderocol susceptible isolates, respectively (Table 4). SHV and TEM carriage rates were similar for cefiderocol susceptible and resistant OXA-48-like producers, whereas CTX-M carriage rate was higher for cefiderocol resistant OXA-48-like producers as compared to their susceptible counterparts (100% *vs.* 80%). CTX-M and TEM carriage rates were similar for cefiderocol susceptible and resistant metallo-beta-lactamase producers, whereas SHV carriage was higher for cefiderocol resistant metallo-beta-lactamase producers as compared to their susceptible counterparts (100% *vs.* 75%) (Table 4).

Table 4. ESBL type according to cefiderocol susceptibility as per EUCAST.

ESBL type, *n* (%)	Total ($n = 254$)			OXA48 ($n = 145$)			MBL ($n = 42$)			KPC ($n = 4$)			No-carbapenemase producer ($n = 13$)			Carbapenem susceptible ($n = 50$)		
	CDRO R ($n = 65$)	CDRO S ($n = 189$)	*p*	CDRO R ($n = 27$)	CDRO S ($n = 118$)	*p*	CDRO R ($n = 34$)	CDRO S ($n = 8$)	*p*	CDRO R ($n = 1$)	CDRO S ($n = 3$)	*p*	CDRO R ($n = 2$)	CDRO S ($n = 11$)	*p*	CDRO R ($n = 1$)	CDRO S ($n = 49$)	*p*
CTX-M	61 (94)	135 (71)	0.000	27 (100)	94 (80)	0.01	31 (91)	6 (75)	0.2	0 (0)	3 (100)	0.05	2 (100)	8 (72)	0.4	1 (100)	24 (49)	0.31
SHV	65 (100)	167 (88)	0.004	27 (100)	108 (92)	0.12	34 (100)	6 (75)	0.003	1 (100)	3 (100)	NA	2 (100)	10 (91)	0.66	1 (100)	40 (82)	0.64
TEM	38 (58)	71 (38)	0.003	17 (63)	66 (56)	0.51	20 (59)	3 (38)	0.28	1 (100)	3 (100)	NA	1 (50)	1 (9)	0.14	0 (0)	1 (2)	0.88

CDRO: cefiderocol; S: susceptible; R: resistant

Discussion

In this study, majority of OXA-48-like producers remained susceptible to cefiderocol using disc diffusion, in accordance with the previous reports [2]. There was a striking variation in resistance rates, particularly for metallo-beta-lactamase producers, using EUCAST *vs.* CLSI breakpoints, with significantly higher resistance rates with the former. The range of inhibition zones was large (e.g. 14–26 mm for metallo-beta-lactamase producers), suggesting the presence of additional resistance mechanisms contributing to cefiderocol resistance.

Elevated cefiderocol MICs for NDM producers were previously demonstrated in *in vitro* surveillance studies and the co-presence of an ESBL, particularly CTX-M, was found to be more frequent among cefiderocol-resistant metallo-beta-lactamase producers [3]. In this study, copresence of an ESBL, particularly SHV, was more frequent among cefiderocol-resistant metallo-beta-lactamase producers. We also observed an association between the MLST type and cefiderocol resistance, such that all except one of the ST14 isolates and all except one of the ST101 isolates were cefiderocol resistant and susceptible, respectively. This may partially be explained by the carbapenemase types, as 75% of the isolates in the ST14 group harboured a metallo-beta-lactamase, whereas only 5% of the ST101 isolates harboured a metallo-beta-lactamase.

More recently, cefiderocol resistance development under cefiderocol exposure was demonstrated in a clinical isolate recovered from a patient who was treated with cefiderocol for an intra-abdominal infection caused by NDM-5 producing *E. coli* [11]. Cefiderocol resistance development in this study was demonstrated to be associated with an increase in the blaNDM-5 copy number. A number of other mechanisms were found to be associated with cefiderocol MIC increase in *Enterobacterales*, such as the deletions of the bacterial iron transport system components, mutations in the signal transduction and energy transduction systems [12,13], and mutations in the chromosomal AmpC enzymes [14,15]. The molecular resistance mechanisms contributing to cefiderocol resistance in this study are yet to be described.

In vitro studies and earlier PK/PD studies demonstrated favourable outcomes with cefiderocol against metallo-beta-lactamase-producers with MICs <16 mg/L [16,17]. In the CREDIBLE-CR trial, there were 23 patients infected with metallo-beta-lactamase-producing pathogens (including the non-fermenters) and the clinical cure rates were higher with cefiderocol as compared to the

best available therapy (75% *vs.* 29%, respectively) [17]. A recent analysis of the outcomes of the patients with metallo-beta-lactamase producing CRK infections from the APEKS-NP and CREDIBLE-CR trials demonstrated numerically higher clinical cure for NDM infections treated with cefiderocol [18]. It is important to note, however, that the greatest cefiderocol MIC was 4 mg/L for the isolates randomised to the cefiderocol arm, and the majority of the patients with elevated cefiderocol MICs had an APACHE score of <15. The numbers are too small to draw strong conclusions and more clinical outcome data are required to assess the effectiveness of cefiderocol for metallo-beta-lactamase producing CRK infections, particularly in patients with higher disease severity. However, it is important to note that breakpoint variability may have significant implications on patient outcomes. If CLSI breakpoints are more clinically relevant, using the more conservative EUCAST criteria would limit the use of a potent active treatment option, whereas if it is the other way around, using cefiderocol might result in treatment failure.

The major limitation of this study is that disc diffusion results were not compared to BMD. Previous studies demonstrated good correlation between disc diffusion and BMD, with 90% categorical agreement and no very major errors [5]. There may be a resistance overcall by disc diffusion as major error rate was reported as 14% in a previous study comparing disc diffusion and BMD [5]. However, our results were in line with the previous studies, where high susceptibility rates were observed against OXA-48-like producers using CLSI criteria. Another limitation of this study is that genomic mechanisms behind cefiderocol resistance were not elucidated.

In conclusion, this, to our knowledge is the largest collection of CRK BSI isolates tested against cefiderocol. Cefiderocol resistance rate varied widely, particularly for metallo-beta-lactamase producers, depending on the interpretive criteria used. The majority of the metallo-beta-lactamase producers were categorised as cefiderocol resistant using the more conservative EUCAST criteria. More clinical outcome data are required to ascertain which breakpoints are more clinically relevant. Until such data are available, we advise using the more cautious approach for this group of infections.

Author contributions

Conceptualisation, B.I., S.K., O.D., O.E., F.C., P.H., D.P.; Methodology, B.I., B.O., C.V., C.F., B.F., O.D., F.C.; Software, V.B. and M.G.; Formal Analysis, B.I. C.F., B.F.; Investigation and data curation, B.I., B.O., C.V., G.C., A.T.A, F.S., N.T., H.D., S.M., H.A., I.I.B., M.A., E.T.T., S.K.D., M.K., S.K., O.D., C.A., S.Y., G.H., N.S., A.A., O.A., M. A.; Resources, B.I., P.H., O.E., D.P. F.C.; Data Curation, B.I.; Writing – Original Draft Preparation, B.I., Writing – Review & Editing, B.I., B.O., C.V., A.S., G.C., A.T.A, C.F., B.F., P.S., F.S., N.T., H.D., S.M., H.A., I.I.B., M.A., E.T.T., S.K.D., M.K., S.K., O.D., C.A., S.Y., G.H., N.S., A.A., O.A., M.A., P.H., O.E., D.P., F.C.; Supervision, P.H., O.E., D.P., F.C.; Project Administration, B.I., B.O., C.V., O.D., F.C., O.E.; Funding Acquisition, B.I., D.P.

Disclosure statement

Dr. Isler received honoraria from Pfizer. Dr. Paterson reports research grants from Merck, Pfizer and Shionogi. David Paterson has received honoraria for advisory board membership from Merck, Pfizer, Shionogi, GSK, QPex, Entasis, VenatoRx, BioMerieux and Accelerate. Dr Harris has received research grants from Sandoz, Merck/MSD and Shionogi, speaker's fees from Pfizer and honoraria for advisory board membership from Merck/MSD, OpGen and Sandoz, paid to the University of Queensland. All others have no conflict of interest to declare.

Institutional Review Board statement

The study was approved by the Koc University Institutional Review Board (approval number: 2018.151.IRB1.018).

Funding

This work was supported by Pfizer Global Medical Grants [grant number 56644459]. Dr Brian Forde's research is supported by Advance Queensland Industry Research Fellowship from the Queensland Government.

Data availability statement

The genomic dataset generated during this study is available in the public database [i.e. US National Library of Medicine (NLM) National Centre for Biotechnology Information (NCBI), PRJNA789336].

References

[1] Isler B, Aslan AT, Akova M, et al. Treatment strategies for OXA-48-like and NDM producing Klebsiella pneumoniae infections. Expert Rev Anti Infect Ther. 2022;20(11):1389–1400. doi:10.1080/14787210.2022.2128764.

[2] 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(2):177–184. doi:10.1016/j.ijantimicag.2018.10.007.

[3] Kohira N, Hackel MA, Ishioka Y, et al. Reduced susceptibility mechanism to cefiderocol, a siderophore cephalosporin, among clinical isolates from a global surveillance

programme (SIDERO-WT-2014). J Glob Antimicrob Resist. 2020;22:738–741. doi:10.1016/j.jgar.2020.07.009.

[4] Bassetti M, Echols R, Matsunaga Y, 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(2):226–240. doi:10.1016/S1473-3099(20)30796-9.

[5] Morris CP, Bergman Y, Tekle T, et al. Cefiderocol antimicrobial susceptibility testing against Multidrug-Resistant Gram-Negative bacilli: a comparison of disk diffusion to broth microdilution. J Clin Microbiol. 2020;59(1):e01649-20. doi:10.1128/JCM.01649-20.

[6] Matuschek E, Longshaw C, Takemura M, et al. Cefiderocol: EUCAST criteria for disc diffusion and broth microdilution for antimicrobial susceptibility testing. J Antimicrob Chemother. 2022;77(6):1662–1669. doi:10.1093/jac/dkac080.

[7] European Committee on Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters, version 11.0. 2021. [accessed 2022 Feb 10]. Available from: https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_11.0_Breakpoint_Tables.pdf

[8] Clinical and laboratory standards institute (CLSI). M100-ED31. Performance Standards for Antimicrobial Susceptibility Testing, 31st ed. Table 2A. Zone Diameter and MIC Breakpoints for Enterobacterales. 2021.

[9] Isler B, Özer B, Çınar G, et al. Characteristics and outcomes of carbapenemase harbouring carbapenem-resistant Klebsiella spp. bloodstream infections: a multicentre prospective cohort study in an OXA-48 endemic setting. Eur J Clin Microbiol Infect Dis. 2022;41(5):841–847. doi:10.1007/s10096-022-04425-4.

[10] Feldgarden M, Brover V, Haft DH, et al. Validating the AMRFinder tool and resistance gene database by using antimicrobial resistance Genotype-Phenotype correlations in a collection of isolates. Antimicrob Agents Chemother. 2019;63(11):e00483-19. doi:10.1128/AAC.00483-19.

[11] Simner PJ, Mostafa HH, Bergman Y, et al. Progressive development of cefiderocol resistance in Escherichia coli during therapy is associated with increased blaNDM-5 copy number and gene expression. Clin Infect Dis. 2021;75:47–54.

[12] 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. 2018;62(1):e01454-17. doi:10.1128/AAC.01454-17.

[13] Yamano Y, Takemura M, Nakamura R, et al. Frequency of resistance acquisition and resistance mechanisms to cefiderocol. Presented at: ID Week Annual Meeting; 2020 October 22–25; Online conference; Poster 1455.

[14] Kawai A, McElheny CL, Iovleva A, et al. Structural basis of reduced susceptibility to Ceftazidime-Avibactam and cefiderocol in Enterobacter cloacae due to AmpC R2 loop deletion. Antimicrob Agents Chemother. 2020;64(7):e00198-20. doi:10.1128/AAC.00198-20.

[15] Shields RK, Iovleva A, Kline EG, et al. Clinical evolution of AmpC-Mediated Ceftazidime-Avibactam and cefiderocol resistance in Enterobacter cloacae complex following exposure to cefepime. Clin Infect Dis. 2020;71(10):2713–2716. doi:10.1093/cid/ciaa355.

[16] Katsube T, Echols R, Wajima T. Pharmacokinetic and pharmacodynamic profiles of cefiderocol, a novel siderophore cephalosporin. Clin Infect Dis. 2019;69(7):S552–S558. doi:10.1093/cid/ciz828.

[17] Tan X, Kim HS, Baugh K, et al. Therapeutic options for metallo-β-Lactamase-Producing enterobacterales. Infect Drug Resist. 2021;14:125–142. doi:10.2147/IDR.S246174.

[18] Timsit JF, Paul M, Shields RK, et al. Cefiderocol for the treatment of infections due to Metallo-Beta-Lactamase-Producing pathogens in the CREDIBLE-CR and APEKS-NP phase 3 randomized studies. Clin Infect Dis. 2022;75:1081–1084.