



Scientific Letter

***In vitro* Activity of Cefiderocol Against Carbapenem-Resistant *Acinetobacter baumannii* Clinical Isolates: a Single Center Experience**

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**To the editor.**

The introduction should briefly place the study in a broad context and highlight why it is. Infections caused by multi-drug resistant (MDR) Gram-negative bacteria represent one of the main threats to human health worldwide.<sup>1</sup> Since the beginning of the SARS-CoV-2 pandemic, a significant increase of severe infections due to MDR ESKAPE bacteria was observed in our Institution, in particular, due to carbapenem-resistant *Acinetobacter baumannii* (CRAB).<sup>2-4</sup> Cefiderocol (CFDC), approved in 2019 to treat infections sustained by aerobic Gram-negative bacteria, is a novel siderophore cephalosporin with broad-spectrum activity and clinical efficacy against CRAB, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*.<sup>5,6</sup> However, since its introduction in clinical practice, CFDC-resistant Gram-negative bacterial isolates have been reported.<sup>7</sup>

Herein, we evaluated the *in vitro* activity of CFDC against CRAB bloodstream strains isolated in our Teaching Hospital during the last three years.

**Materials and Methods.** This study was conducted in the Microbiology Laboratory “*Mater Domini*” Teaching Hospital, Catanzaro, Italy. CRAB isolates were recovered from blood samples of patients hospitalized between 2020 and 2022 and diagnosed with CRAB bloodstream infections. Only the first CRAB strain isolated from each patient was included.

**Bacterial isolation and identification and Antimicrobial Susceptibility Testing.** CRAB isolates were identified using matrix-assisted laser-desorption ionization time-of-flight mass spectrometry (MALDI-TOF) and Vitek®2 System (bioMérieux, Italy). Antibiotic susceptibility tests for meropenem, amikacin, and trimethoprim/sulfamethoxazole were performed with the Vitek®2 System (whereas the determination of colistin resistance was obtained by broth microdilution

according to EUCAST guidelines.<sup>8</sup>

The Kirby-Bauer disc diffusion test on regular un-supplemented Mueller-Hinton agar (Liofilchem S.R.L., Roseto degli Abruzzi, Italy) was used to assess sensitivity to CFDC, using discs impregnated with 30 micrograms of drug supplied by Liofilchem® (Liofilchem S.R.L., Roseto degli Abruzzi, Italy). Of note, EUCAST evaluated (August 2022) cefiderocol 30 µg disks and regular un-supplemented MH agars from Liofilchem, and no warning concerning their use was reported (unlike other products marketed by other manufacturers).<sup>9</sup> Well-isolated colonies were suspended in saline from an overnight agar plate to achieve a 0.5 McFarland standard turbidity. The inoculum was streaked with a sterile cotton swab over the entire area of the Mueller–Hinton (MH) agar plate. After that, the disc was firmly applied to the surface of the inoculated agar plate and incubated at 35±1 °C for 16–20 h. The diameters of the disk areas were read using the innermost colony-free area. The results were interpreted using the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) experimental breakpoints.<sup>9,10</sup> The EUCAST defined the clinical breakpoints for CFDC against *A. baumannii* complex as susceptible in the range of ≥17mm and resistant of <17 mm, while the CLSI ranges for the determination of susceptibility and resistance are ≥15mm and ≤15 mm, respectively.

**Ethical Statement.** The present retrospective study is based on clinical isolates stored in an anonymous archive without association with clinical data. For this reason, ethics and consent to participate are not applicable. The study was conducted using retrospectively collected and anonymized data according to the Declaration of Helsinki and principles of good clinical practice.

**Table 1.** Summary of cefiderocol disk diffusion susceptibility among analysed carbapenem-resistant *Acinetobacter baumannii* bacterial isolates.

Carbapenem-resistant <i>Acinetobacter baumannii</i> isolates (N=62)	EUCAST breakpoints disk zone diameter (mm)		CLSI breakpoints disk zone diameter (mm)	
	S	R	S	R
	≥17	<17	≥15	<15
	% (N)		% (N)	
	72.5 (45)	27.5 (17)	83.9 (52)	16.1 (10)

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; S, susceptible; I, intermediate; R, resistant.

**Results.** In the last three years, 70 *Acinetobacter baumannii* were isolated from blood samples, and 62 were carbapenem-resistant. 62 CRAB strains were isolated from 62 patients using conventional culture media and tested for susceptibility to CFDC.

The range of diameters and the percentage of susceptible and resistant isolates are shown in **Table 1**, using interpretations of breakpoints recommended by EUCAST and CLSI. CRAB isolates showed higher susceptibility when CLSI breakpoints were applied compared to the EUCAST breakpoints. In particular, seven isolates with a zone diameter ≥15 mm were susceptible according to CLSI guidelines but resistant according to EUCAST breakpoints. When EUCAST breakpoints were applied, the overall susceptibility rate to CFDC was (45/62) 72.5%, whereas it was (52/62) 83.8% using CLSI breakpoints. Antibiotic susceptibility results for amikacin, colistin, and trimethoprim/sulfamethoxazole of CRAB isolates according to susceptibility pattern to CFDC based on EUCAST breakpoints are shown in **Table 2**.

**Discussion.** In the present study, we tested the susceptibility of CRAB isolates to CFDC by using the Kirby-Bauer disc diffusion test on regular un-supplemented Mueller-Hinton agar, considered the gold standard method for this purpose. Then we compared the results to interpretation breakpoints recommended by EUCAST and CLSI guidelines.<sup>10,11</sup> According to EUCAST breakpoints, in our study, resistance to CFDC was observed in 17/62 (27.4%) isolates, whereas by using CLSI guidelines, 10/62 (16.1%) isolates resulted in being resistant to CFDC. In previous epidemiological

studies investigating *in vitro* efficacy of CFDC against CRAB isolates, the overall rates of resistance ranged from 3.1% to 47.4%.<sup>12-20</sup> Therefore, the present results were within the range of literature data, although the range of resistance rates in previous studies was very wide.<sup>12-20</sup>

Furthermore, susceptibility results were interpreted according to breakpoints recommended by EUCAST guidelines in some studies<sup>13,15,16,19</sup> and by CLSI guidelines in others.<sup>12-17</sup> In two of these studies, a disk diffusion test according to EUCAST breakpoints was used to assess the susceptibility of CRAB strains to CFDC, and the resistance rates to CFDC were 5.3%<sup>14</sup> and 22.1%,<sup>16</sup> respectively. Compared to these studies, we found a higher resistance rate to CFDC among CRAB isolates. However, the study of Carcione *et al.*, although conducted in Italy and during a period similar to ours, was based on a total of 19 isolates, and the small sample analyzed could at least partially explain the difference in resistance rate using DD (5%; 1/20) compared to our study.<sup>14</sup> Conversely, the study of Ghebremedhin *et al.* was conducted in a different country (Germany) from 2014 to 2021, so their results could be difficultly comparable to ours.<sup>16</sup>

Furthermore, Morris *et al.* performed DD tests for CFDC by using 30-µg discs produced by two different manufacturers (i.e., FDA-cleared HardyDisks and MASTDISCS [RUO]) on standard MH agar on 14 CRAB strains and compared results by interpreting them according to both EUCAST and CLSI breakpoints; they found rates of resistance which were widely different depending on the type of disc used and interpretation breakpoints used: 35.7% and 57.1% by using

**Table 2.** Antimicrobial susceptibility tests' results of carbapenem-resistant *Acinetobacter baumannii* strains to other choice antibiotics according to susceptibility pattern to cefiderocol based on EUCAST breakpoints.

Carbapenem-resistant <i>Acinetobacter baumannii</i> isolates (N=62)											
Cefiderocol											
Susceptible, % (N)						Resistant, % (N)					
72.5 (45)						27.5 (17)					
AN		CS		SXT		AN		CS		SXT	
S	R	S	R	S	R	S	R	S	R	S	R
% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)	% (N)
9 (4)	91 (41)	100 (45)	0	9 (4)	91 (41)	70 (12)	30 (5)	94 (16)	6 (1)	0	100 (17)

Abbreviations: S, susceptible; R resistant; AN, amikacin; CS, colistin; STX, trimethoprim/sulfamethoxazole.

HardyDisks discs and 7.2% and 64.7% by using MASTDISCS (RUO) discs, according to CLSI and EUCAST breakpoints, respectively; therefore, authors concluded that DD methods (at least with the methodology used in their study) performed poorly for CRAB.<sup>17</sup> Based on these findings, it is possible to speculate that it is difficult to compare our results to those reported in the literature due to the heterogeneity of techniques used to assess the resistance of CRAB to CFDC and different local epidemiology or study periods. Because high rates of clinical failure were reported in patients affected by CFDC-resistant Gram-negative bacteria,<sup>20</sup> optimizing microbiological procedures to assess resistance as part of routine clinical practice is a mandatory task that should be the object of further investigations.

This study is affected by several limitations: i) this is a monocentric study, and the size of samples analysed is relatively small; ii) previous therapy with CFDC was not

evaluated for patients carrying CFDC-resistant CRAB isolates; iii) analysis of the molecular characterization of resistance mechanisms was not conducted; iv) clonal analysis of CRAB isolates to identify possible local outbreak was not performed; this last limitation may have influenced the resistance rate reported in our study.

**Conclusions.** Our results showed a relatively high resistance rate to CFDC among clinical CRAB isolates compared to previous reports. However, several differences in methods, breakpoints interpretation guidelines, and local epidemiology should be considered.

**Author Statement.** Conceptualization, EMT and AQ; methodology, NM and AR; software, CC GGMS; investigation, VS, FS, RL, and VLB data curation, FD and GP; writing—original draft preparation, EMT and AQ; writing, EMT and AQ; supervision, CT and GM.

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Angela Quirino<sup>1</sup>, Claudia Cicino<sup>1</sup>, Vincenzo Scaglione<sup>2</sup>, Nadia Marascio<sup>1</sup>, Francesca Serapide<sup>2</sup>, Giuseppe Guido Maria Scarlata<sup>1</sup>, Rosaria Lionello<sup>2</sup>, Francesca Divenuto<sup>1</sup>, Valentina La Gamba<sup>2</sup>, Grazia Pavia<sup>1</sup>, Alessandro Russo<sup>2</sup>, Carlo Torti<sup>2</sup>, Giovanni Matera<sup>1\*</sup> and Enrico Maria Treçarichi<sup>2</sup>.

<sup>1</sup> Unit of Clinical Microbiology, Department of Health Sciences, “Magna Graecia” University of Catanzaro– “Mater Domini” teaching hospital; Catanzaro, Italy.

<sup>2</sup> Unit of Infectious and Tropical Diseases, Department of Medical and Surgical Sciences, “Magna Graecia” University of Catanzaro – “Mater Domini” teaching hospital; Catanzaro, Italy.

**Competing interests:** The authors declare no conflict of Interest.

Correspondence to: Giovanni Matera. Tel: 09613697760. E-mail: [gm4106@gmail.com](mailto:gm4106@gmail.com)

## References:

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022, 399,629, 655.
2. Reale, M., Strazzulla, A., Quirino, A., Rizzo, C., Marano, V., Postorino, M. C., Mazzitelli, M., Greco, G., Pisani, V., Costa, C., et al. Patterns of multi-drug resistant bacteria at first culture from patients admitted to a third level University hospital in Calabria from 2011 to 2014: implications for empirical therapy and infection control. *Infez Med*. 2017, 25, 98,107.
3. Scaglione, V., Reale, M., Davoli, C., Mazzitelli, M., Serapide, F., Lionello, R., La Gamba, V., Fusco, P., Bruni, A., Procopio, D., et al. Prevalence of Antibiotic Resistance Over Time in a Third-Level University Hospital. *Microb Drug Resist*. 2022, 28, 425,435. <https://doi.org/10.1089/mdr.2021.0109> PMID:34910885 PMCID:PMC9058886
4. Serapide, F., Quirino, A., Scaglione, V., Morrone, H. L., Longhini, F., Bruni, A., Garofalo, E., Matera, G., Marascio, N., Scarlata, G. G. M. et al. Is the Pendulum of Antimicrobial Drug Resistance Swinging Back after COVID-19?. *Microorganisms*. 2022, 10, 957. <https://doi.org/10.3390/microorganisms10050957> PMID:35630400 PMCID:PMC9146770
5. Hsueh SC, Lee YJ, Huang YT, Liao CH, Tsuji M, Hsueh PR. In vitro activities of cefiderocol, ceftolozane/tazobactam, ceftazidime/avibactam and other comparative drugs against imipenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*, all associated with bloodstream infections in Taiwan. *J Antimicrob Chemother*. 2019,74,380, 386. <https://doi.org/10.1093/jac/dky425> PMID:30357343
6. Treçarichi, E. M., Quirino, A., Scaglione, V., Longhini, F., Garofalo, E., Bruni, A., Biamonte, E., Lionello, R., Serapide, F., Mazzitelli, M., et al., Successful treatment with cefiderocol for compassionate use in a critically ill patient with XDR *Acinetobacter baumannii* and KPC-producing *Klebsiella pneumoniae*: a case report. *The Journal of antimicrobial chemotherapy*, 2019, 74, 3399,3401. <https://doi.org/10.1093/jac/dkz318> PMID:31369095
7. Wang C, Yang D, Wang Y, Ni W. Cefiderocol for the Treatment of Multidrug-Resistant Gram-Negative Bacteria: A Systematic Review of Currently Available Evidence. *Frontiers in pharmacology*, 2022, 13, 896971. <https://doi.org/10.3389/fphar.2022.896971> PMID:35496290 PMCID:PMC9039133
8. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 13.0, 2023. <http://www.eucast.org>
9. EUCAST warnings concerning antimicrobial susceptibility testing products or procedures(August 2022) <https://www.eucast.org/ast-of-bacteria/warnings>
10. The European Committee on Antimicrobial Susceptibility Testing. Breakpoints for cefiderocol from EUCAST [https://www.eucast.org/eucast\\_news/news\\_singleview/?tx\\_ttnews%5Btt\\_news%5D=493&cHash=22779384b74c8cf2c55aa3f7fd69d173](https://www.eucast.org/eucast_news/news_singleview/?tx_ttnews%5Btt_news%5D=493&cHash=22779384b74c8cf2c55aa3f7fd69d173)
11. CLSI m100-ed32:2022 performance standards for antimicrobial susceptibility testing, 32<sup>nd</sup> edition
12. Abdul-Mutakabbir, J. C., Nguyen, L., Maassen, P. T., Stamper, K. C., Kebriaei, R., Kaye, K. S., Castanheira, M., & Rybak, M. J. In Vitro Antibacterial Activity of Cefiderocol against Multidrug-Resistant *Acinetobacter baumannii*. *Antimicrobial agents and chemotherapy*, 2021, 65, e0264620 <https://doi.org/10.1128/AAC.02646-20> PMID:34125590 PMCID:PMC8370208
13. Candel, F. J., Santerre Henriksen, A., Longshaw, C., Yamano, Y., & Oliver, A. In vitro activity of the novel siderophore cephalosporin, cefiderocol, in Gram-negative pathogens in Europe by site of infection.

- Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, (2022). 28(3), 447,e1, 447,e6.  
<https://doi.org/10.1016/j.cmi.2021.07.018>  
 PMid:34298176
14. Carcione, D., Siracusa, C., Sulejmani, A., Migliavacca, R., Mercato, A., Piazza, A., Principe, L., Clementi, N., Mancini, N., Leoni, V., et al., In Vitro Antimicrobial Activity of the Siderophore Cephalosporin Cefiderocol against *Acinetobacter baumannii* Strains Recovered from Clinical Samples. *Antibiotics* (Basel, Switzerland), 2021 10(11), 1309.  
<https://doi.org/10.3390/antibiotics10111309>  
 PMid:34827247 PMCid:PMC8614976
  15. Cercenado, E., Cardenoso, L., Penin, R., Longshaw, C., Henriksen, A. S., & Pascual, A. In vitro activity of cefiderocol and comparators against isolates of Gram-negative bacterial pathogens from a range of infection sources: SIDERO WT 2014-2018 studies in Spain. *Journal of global antimicrobial resistance*, 2021 26, 292, 300.  
<https://doi.org/10.1016/j.jgar.2021.06.011>  
 PMid:34274538
  16. Ghebremedhin, B., & Ahmad-Nejad, P. In-Vitro Efficacy of Cefiderocol in Carbapenem-Non-Susceptible Gram-Negative Bacilli of Different Genotypes in Sub-Region of North Rhine Westphalia, Germany. *Pathogens* (Basel, Switzerland), 10 2021 (10), 1258.  
<https://doi.org/10.3390/pathogens10101258>  
 PMid:34684208 PMCid:PMC8540251
  17. Morris, C. P., Bergman, Y., Tekle, T., Fissel, J. A., Tamma, P. D., & Simner, P. J. Cefiderocol Antimicrobial Susceptibility Testing against Multidrug-Resistant Gram-Negative Bacilli: a Comparison of Disk Diffusion to Broth Microdilution. *Journal of clinical microbiology*, 2020, 59(1), e01649,20  
<https://doi.org/10.1128/JCM.01649-20>  
 PMid:32938734 PMCid:PMC7771458
  18. Naas T, Lina G, Santerre Henriksen A, Longshaw C, Jehl F. 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 [published correction appears in *JAC Antimicrob Resist*. 2021;3(2),dlab0 81  
<https://doi.org/10.1093/jacamr/dlab081>  
 PMid:34223140 PMCid:PMC8251251
  19. Wang, Y., Li, Y., Zhao, J., Guan, J., Ni, W., & Gao, Z. Susceptibility of cefiderocol and other antibiotics against carbapenem-resistant, Gram-negative bacteria. *Annals of translational medicine*, (2022). 10(5), 261.  
<https://doi.org/10.21037/atm-22-889>  
 PMid:35402576 PMCid:PMC8987888
  20. Bleibtreu, A., Dortet, L., Bonnin, R. A., Wyplosz, B., Sacleux, S. C., Mihaila, L., Dupont, H., Junot, H., Bunel, V., Grall, N et al., Susceptibility Testing Is Key for the Success of Cefiderocol Treatment: A Retrospective Cohort Study. *Microorganisms*, 2021 9(2), 282.  
<https://doi.org/10.3390/microorganisms9020282>  
 PMid:33573148 PMCid:PMC7911443