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Performance evaluation of the UMIC® Cefiderocol to determine MIC in Gram-negative bacteria

Laurent Dortet [1,2,3]†, Claudia Niccolai[4,5]†, Niels Pfennigwerth [6]†, Stefanie Frisch[7], Camille Gonzalez[1,2], Alberto Antonelli[4,5], Tommaso Giani[4,5], Robert Hoenings[7], Soeren Gatermann[6]†, Gian Maria Rossolini[4,5]† and Thierry Naas [1,2,3]*†

[1]*Team "Resist", INSERM Unit 1184, Faculty of Medicine, Université Paris-Saclay, Service de Bactériologie-Hygiène, Hôpital Bicêtre, 78 rue du Général Leclerc, 94275, Le Kremlin-Bicêtre, France;* [2]*Bacteriology-Hygiene Unit, Assistance Publique-Hôpitaux de Paris, AP-HP Paris-Saclay, Bicêtre Hospital, Le Kremlin-Bicêtre, France;* [3]*Associated French National Reference Center for Antibiotic Resistance, Carbapenemase-Producing Enterobacterales, Bicêtre Hospital, Le Kremlin-Bicêtre, France;* [4]*Department of Microbiology and Virology, University of Florence, Florence, Italy;* [5]*Microbiology and Virology Unit, Careggi University Hospital, Florence, Italy;* [6]*National Reference Centre for Multidrug-Resistant Gram-Negative Bacteria, Ruhr-Universität Bochum, Bochum, Germany;* [7]*Microbiology and Diagnostics, Bruker Daltonics GmbH & Co. KG, Bremen, Germany*

*Corresponding author. E-mail: thierry.naas@aphp.fr
†Authors contributed equally.

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Background: Cefiderocol is a catechol-substituted cephalosporin with potent *in vitro* activity against carbapenem-resistant (CR) Gram-negative bacteria (GNB). Cefiderocol susceptibility testing is complex because iron concentrations need to be taken into consideration. Here, we assessed the clinical performance of Bruker's UMIC® Cefiderocol and corresponding iron-depleted CAMHB to determine MIC by broth microdilution (BMD) for clinically relevant GNB.

Methods: MICs of cefiderocol for 283 GN clinical isolates were determined by BMD using iron-depleted CAMHB. Frozen panels were used as a reference. The concentration range of cefiderocol was 0.03–32 mg/L. The isolates, with different degrees of susceptibility to cefiderocol, included Enterobacterales ($n=180$), *Pseudomonas aeruginosa* ($n=49$), *Acinetobacter baumannii* ($n=44$) and *Stenotrophomonas maltophilia* ($n=10$).

Results: The rates of categorical agreement (CA), essential agreement (EA) and bias were calculated to evaluate the performance of the UMIC® Cefiderocol, as compared with the reference method. Overall, the UMIC® Cefiderocol showed 90.8% EA (95% CI: 86.9%–93.7%) with a bias of −14.5% and a CA of 90.1% (95% CI: 86.1%–93.1%). For Enterobacterales, the UMIC® Cefiderocol showed 91.7% EA (95% CI: 86.7%–94.9%) with a bias of −25.0% and a CA of 87.8% (95% CI: 82.2%–91.8%). For non-fermenters, the UMIC® Cefiderocol showed 89.3% EA (95% CI: 81.9%–93.9%) (not significantly different from 90.0%, Student *t*-test) with a bias of −3.9% and a CA of 94.2% (95% CI: 87.7%–97.3%).

Conclusions: UMIC® Cefiderocol is a valid method for the determination of cefiderocol MICs even if higher than expected discrepancies were observed with NDM-producing Enterobacterales, which presented in most cases MIC values close to the breakpoint.

Introduction

Therapeutic options for carbapenem-resistant (CR) Gram-negative bacteria (GNB) infections in general are limited,[1] and even more so with the consistent rise worldwide of XDR Gram-negatives that are resistant even to last-resort antibiotics such as colistin, or to newly released antibiotics.[1–3]

Cefiderocol, a novel siderophore cephalosporin, is approved in the USA and in Europe for severe cases of infections caused by susceptible Gram-negative microorganisms.[4,5] 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. The catechol moiety chelates ferric (FeIII) iron, mimicking natural siderophores, allowing cefiderocol to exploit the bacteria's own active receptor-mediated iron transport system to cross the outer membrane.[6]

Even though resistance to cefiderocol has been described, global resistance rates are low. Depending on the tested collection,

resistance rates range from 2% up to 20% when MDR or XDR isolates are considered.[7–11] Cefiderocol remains active against a wide range of GNB, including MDR and XDR isolates, with some regional variations. Reliable assays for susceptibility testing are mandatory to initiate cefiderocol therapy on carbapenemase-producers.[12,13]

The reference method for *in vitro* susceptibility testing of cefiderocol is broth microdilution (BMD) in iron-depleted CAMHB (CLSI, EUCAST).[14–17] Preparation of iron-depleted CAMHB is time-consuming and not appropriate for the daily workflow of a clinical microbiology laboratory. Various commercial systems for cefiderocol susceptibility testing have been developed, but they have been affected by major accuracy issues,[18,19] resulting in a recent warning by EUCAST (https://www.eucast.org/ast-of-bacteria/warnings). Disc diffusion was found to be useful for screening, but due to a large area of technical uncertainty a substantial number of isolates may need to be retested using BMD to assess definitive categorization.[14,18]

UMIC® strips (Bruker Daltonics GmbH & Co. KG, Bremen, Germany) are single MIC BMD strips with dried antibiotics that have been shown useful for several critically important antibiotics, such as colistin, piperacillin/tazobactam, vancomycin/teicoplanin, daptomycin and linezolid.[20,21] They offer long shelf-life, room temperature storage, the possibility of testing one single isolate per time, and for UMIC® Cefiderocol dedicated ready-to-use iron-depleted CAMHB vials.

The objective of the study was to assess the analytical and clinical performances of the UMIC® Cefiderocol assay (using dedicated iron-depleted CAMHB) on a collection of clinical isolates of Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*.

Material and methods

Bacterial isolates

A collection of 283 clinical GNB, representing different degrees of susceptibility to cefiderocol, was used to perform this study. These isolates originated from the laboratory collection of the Clinical Microbiology laboratory of the Department of Experimental and Clinical Medicine, University of Florence, Italy and from the French and German National Reference Centres for Gram-negative Bacteria (Kremlin-Bicêtre, France and Bochum, Germany, respectively). Each site contributed equally, and 30% were either fresh or recent and 70% were stock isolates as per ISO 20776-2:2007 definitions.[22] The collection included 180 Enterobacterales and 103 non-fermenters. For details, please refer to Table S1 (available as Supplementary data at *JAC* Online). All isolates were identified by the respective laboratories using either MALDI TOF or WGS. Clinical isolates were tested once unless discrepancy testing was required. Quality control strains *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were included on each testing day. A panel of 10 isolates (Table S2) was tested for the reproducibility and repeatability assays.

UMIC® Cefiderocol and BMD reference method to determine cefiderocol MIC

Bacterial isolates were grown on blood agar plates at 35–37°C for no longer than 24 h. Bacterial cells were resuspended in 5 mL 0.9% sodium chloride solution to a McFarland standard of 0.5. Quantities of 25 µL (for UMIC® Cefiderocol strip; Bruker Daltonics GmbH & Co. KG) or 50 µL (for frozen reference panels, prepared and stored according to EN ISO 20776-1:2019[23] and CLSI document M07[15]) of this bacterial suspension were used to inoculate 5 mL iron-depleted CAMHB (Bruker Daltonics GmbH & Co. KG). Into each well of the UMIC® Cefiderocol strip, 100 µL of the inoculated iron-depleted CAMHB was pipetted, and 50 µL of inoculated iron-depleted CAMHB was pipetted into each well of the thawed reference plates. Incubation was done for 18–24 h at 35–37°C. UMIC® Cefiderocol strip testing, which was done in parallel with the reference method, started from the same bacterial suspension. Incubation was done inside a humidity chamber (UMIC® Incubation Box, Bruker Daltonics GmbH & Co. KG). After incubation at 35–37°C under aerobic conditions for 18–24 h, MIC results were read visually.

Clinical breakpoints used for cefiderocol results interpretation were those of EUCAST for Enterobacterales and *Pseudomonas* [values of susceptible (S) ≤2 mg/L and resistant (R) >2 mg/L], and for *Acinetobacter* spp. and *S. maltophilia* were non-species-related pharmacokinetic/pharmacodynamic (PK/PD) values (≤2 mg/L).[14,15]

Analytical performance

A panel of eight characterized strains of clinical origin (Table S2) plus two reference ATCC strains with known MIC ranges of cefiderocol were used for analytical performance determination. Strains were used to test day-to-day, run-to-run, site-to-site, operator-to-operator and lot-to-lot reproducibility as well as within-run repeatability. Each strain of the predefined panel (10 strains in total) was tested in triplicates with the UMIC® Cefiderocol and iron-depleted CAMHB, and the testing was repeated on four following days (five days in total).

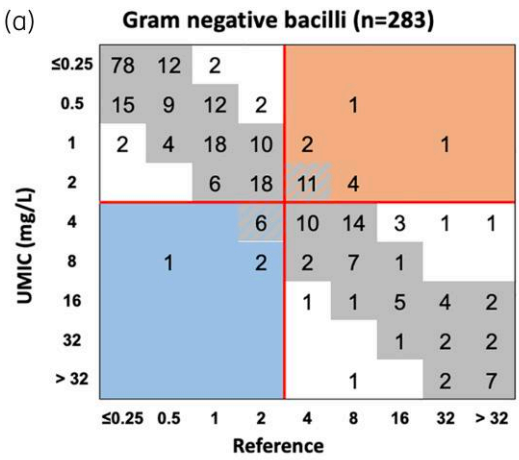
Clinical performance

As recommended in the ISO 20776-2:2021 document, essential agreement (EA) and bias were calculated to evaluate the performance of the UMIC® Cefiderocol.[23] Congruent expected performances were: EA ≥ 90%, −30% ≤ bias ≤ +30%. Rates of categorical agreement (CA), major errors (ME) and very major errors (VME) were also calculated following the definitions from ISO 20776-2:2007.[22,24]

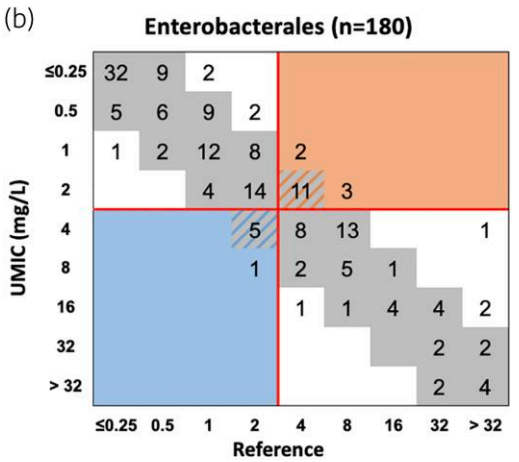
Results and discussion

Analytical performance

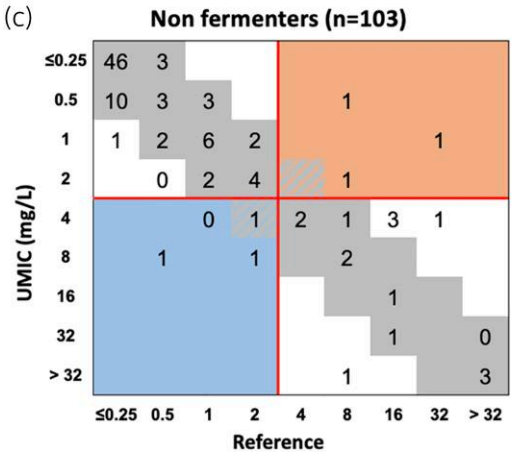
Day-to-day, site-to-site and operator-to-operator reproducibility was 97.6%, run-to-run reproducibility was 95.5%, and lot-to-lot reproducibility was 100%, respectively. During the within-run repeatability study none of the strains showed deviations of more than one dilution step in the same run. Thus, repeatability was 100% for each test strain. All parameters fulfilled the ≥95% requirement as outlined in ISO 20776-2:2021.[23] Overall, it could be shown that there is good performance of the UMIC® Cefiderocol in conjunction with iron-depleted CAMHB irrespective of whether the test is run on different times of the day, on different days, on different sites by different operators, or with different lots.



EA	90.8%
CA	90.1%
bias	-14.5%
R	30.4%
S	69.6%



EA	91.7%
CA	87.8%
bias	-25.0%
R	37.8%
S	62.2%



EA	89.3%
CA	94.2%
bias	3.9%
R	17.5%
S	82.5%

Figure 1. MICs of cefiderocol using UMIC® Cefiderocol compared with the BMD reference method. (a) Comparison of MICs obtained for Gram-negative bacilli. (b) Comparison of MICs obtained for Enterobacterales. (c) Comparison of MICs obtained for non-fermenters. MICs corresponding to essential agreement (EA) are in grey, major error (ME) in blue and very major error (VME) in orange. Hatching on the grey boxes within the orange (VME) and blue (ME) boxes corresponds to MICs that are also in the EA. R, resistant; S, susceptible. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Clinical performance

Our global collection of Gram-negative bacteria included 283 isolates with cefiderocol MICs ranging from ≤0.03 mg/L to >32 mg/L. Among them, 30.4% tested resistant to cefiderocol (MIC ≥ 4 mg/L) using the reference BMD method (Figure 1a). The UMIC® Cefiderocol exhibited 90.8% EA (95% CI: 86.9%–93.7%) with a bias of −14.5% compared with the reference method. Thus, the UMIC® Cefiderocol can be considered as a valid method for the

determination of cefiderocol MIC. In more detail, the CA was 90.1% (95% CI: 86.1%–93.1%) with 22.1% (95% CI: 14.6%–31.9%) VME and 4.6% (95% CI: 2.4%–8.5%) ME. Most of the VME (11/19) and ME (6/9) corresponded to isolates with MICs within the EA (±2-fold dilution). Considering only isolates with a difference to the reference method of more than two 2-fold dilutions, the UMIC® Cefiderocol led to 9.3% (95% CI: 4.8%–17.3%) VME (five Enterobacterales and three non-fermenters) and 1.5% (95% CI: 0.5%–4.4%) ME (Figure 1).

Focusing on Enterobacterales ($n=180$), the UMIC® Cefiderocol exhibited 91.7% EA (95% CI: 86.7%–94.9%) with a bias of −25.0% compared with the reference method. Thus, the UMIC® Cefiderocol can be considered as a valid method for the determination of cefiderocol MIC in Enterobacterales according to the ISO 20776-2:2021 parameters, even if a tendency to undercall MIC values was observed. The overall CA was of 87.8% (95% CI: 82.2%–91.8%), being lower for *E. coli* (52/60, 86.7%; 95% CI: 75.8%–93.1%) and *Klebsiella pneumoniae* (37/45, 82.2%; 95% CI: 68.7%–88.7%) and higher for *Enterobacter cloacae* complex (29/30, 96.7%; 95% CI: 83.3%–99.4%) (Figure S1). The VME and ME were overall 23.5% (95% CI: 15.0%–34.9%) and 5.4% (95% CI: 2.5%–11.2%), respectively, falling to 7.4% (95% CI: 3.2%–16.1%) and 0.9% (95% CI: 0.2%–4.9%) when VME and ME within the EA were excluded (Figure 1b). More detailed data are available for *E. coli*, *K. pneumoniae* and *E. cloacae* in Figure S1.

Focusing on non-fermenters ($n=103$), the UMIC® Cefiderocol exhibited 89.3% EA (95% CI: 81.9%–93.9%) (not significantly different from 90.0%, Student *t*-test) with a bias of −3.9% compared with the reference method. Thus, the UMIC® Cefiderocol can be considered as a valid method for the determination of cefiderocol MIC in non-fermenters. The CA was of 94.2% (95% CI: 87.9%–93.3%) with CA of 98.0% (95% CI: 89.3%–99.6%) for *P. aeruginosa*, 90.9% (95% CI: 78.8%–96.4%) for *A. baumannii* and 90.0% (95% CI: 59.6%–98.2%) for *S. maltophilia*. The VME and ME were of 16.7% (95% CI: 5.8%–39.2%) and 3.5% (95% CI: 1.2%–9.9%), respectively, remaining at 16.7% (95% CI: 5.8%–39.2%) and 2.4% (95% CI: 0.7%–8.2%) when excluding VME and VME within the EA (Figure 1c). In more detail, the EA obtained for *P. aeruginosa* and *A. baumannii* was of 93.9% (95% CI: 83.5%–97.9%) and 84.1% (95% CI: 70.6%–92.1%), with bias of +12.2% and −11.4%, respectively (Figure S2). As previously described, all *S. maltophilia* isolates remained susceptible to cefiderocol, with MIC ranging from ≤0.03 mg/L to 0.125 mg/L with the BMD reference method.[9] Only 1 of the 10 tested isolates was tested outside of the EA and considered as ME (0.5 mg/L reference method versus 8 mg/L with UMIC® Cefiderocol).

Altogether, the UMIC® Cefiderocol, a ready-to-use strip containing dried cefiderocol (ranging from ≤0.03 mg/L to >32 mg/L), in combination with the ready-to-use iron-depleted CAMHB broth vials, is a reliable tool for testing MIC values of GNB, with EA ≥90% and −30%≤ bias ≤+30%, as compared with a frozen reference panel that was prepared and stored according to EN ISO 20776-1:2019[22] and CLSI document M07.[14] Of note, in all cases, when the EA was not over the acceptable 90%, the 90% were included in the 95% CI. In these cases, more strains might be further tested to definitively validate the UMIC® Cefiderocol on these bacterial species. CA values, which are no longer used to evaluate a susceptibility testing device, remain a crucial parameter in respect to the clinical use of such diagnostic tests. Our results suggest lower CAs with *E. coli* and *K. pneumoniae* compared with *E. cloacae*, and for Enterobacterales compared with non-fermenters. It has previously been reported that NDM production leads to a significant increase of cefiderocol MICs that are close to the clinical breakpoint of 2 mg/L.[18] Accordingly, just one 2-fold dilution difference between the two compared tests might have a huge impact on the CA with no difference in terms of EA. Because NDM producers are more prevalent in Enterobacterales (particularly *E. coli* and *K. pneumoniae*), it might explain the lower CA observed for *E. coli* and *K. pneumoniae*, at least partially. This must be further evaluated on a larger collection of strains that do or do not produce NDM. Finally, on a subset of 60 isolates that have been evaluated using two different frozen reference methods, 91.7% of EA, bias of −13.3% and only 88.3% of CA was obtained (Figure S3).[9] Again, this was mostly due to a high proportion of NDM producers that possess MICs close to the unique clinical breakpoint of 2 mg/L. These results support the need to introduce an area of technical uncertaintyfor the determination of cefiderocol MIC as is already the case with zone inhibition diameters.

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Transparency declarations

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Supplementary data

Figures S1 to S3 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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