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Cefiderocol-Xeruborbactam Antimicrobial Susceptibility Testing Does Not Require Iron-Depleted Media

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INTRODUCTION

- Cefiderocol is a siderophore cephalosporin with enhanced bacterial uptake under iron-limited conditions and stability against hydrolysis by both serine- and metallo-β-lactamases (SBLs/MBLs), supporting its potent activity against β-lactamase-producing strains.
- Minimum inhibitory concentration (MIC) testing in iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB) with MIC endpoint, defined as significant growth reduction, is the reference method for cefiderocol susceptibility testing because it best predicts clinical performance; however, it is labor-intensive and generally limited to reference laboratories.
- Xeruborbactam is a dual SBL/MBL inhibitor that potentiates the activity of cefiderocol against cefiderocol-resistant isolates. The combination is in clinical development.
- This study compared cefiderocol-xeruborbactam activity in ID-CAMHB versus standard CAMHB to inform optimal susceptibility testing methodology.

METHODS

- Among isolates collected through the global SENTRY Antimicrobial Surveillance Program in 2024, 416 Enterobacterales (including 101 New Delhi MBL [NDM]-producing isolates), 627 *Acinetobacter baumannii* isolates (including 29 NDM-producing and 24 *Pseudomonas* extended resistance [PER]-producing isolates), and 602 *Pseudomonas aeruginosa* isolates (including 24 NDM-producing isolates) met the selection criteria of meropenem MICs ≥2 µg/mL or cefiderocol MICs ≥4 µg/mL (in standard CAMHB), and were selected for testing.
- MICs of cefiderocol alone and in combination with a fixed 4 µg/mL concentration of xeruborbactam were determined by broth microdilution using either ID-CAMHB in accordance with Clinical and Laboratory Standards Institute (CLSI) reference methodology for cefiderocol, or standard CAMHB.
- MIC endpoint for cefiderocol and cefiderocol-xeruborbactam in ID-CAMHB was based on CLSI guidelines and corresponded to 80% or significant reduction of growth. MIC endpoint for cefiderocol and cefiderocol-xeruborbactam in CAMHB corresponded to complete inhibition of growth.
- To enable direct comparisons, CLSI cefiderocol susceptible, intermediate, and resistant breakpoints established in ID-CAMHB (≤4, 8, and ≥16 µg/mL, respectively) were applied to cefiderocol and cefiderocol-xeruborbactam under both testing conditions.

RESULTS

- Xeruborbactam enhanced the potency of cefiderocol against all groups of organisms in both test media (**Figure 1**).
- Cefiderocol-xeruborbactam MIC_{90} values were low in both ID-CAMHB and CAMHB, ranging from 0.25 to 0.5 µg/mL and from 0.5 to 2 µg/mL, respectively (**Table 1**).
- For cefiderocol-xeruborbactam, the percentage of isolates with cefiderocol-xeruborbactam MIC ≤4 µg/mL were high in both ID-CAMHB and CAMHB, ranging from 99% to 100% and from 96.3% to 100%, respectively; for cefiderocol alone, it was in 88–97.2% and 73.8–96.8% in ID-CAMHB and CAMHB, respectively (**Table 1**).
- Cefiderocol-xeruborbactam exhibited higher potency in ID-CAMHB than in CAMHB; consequently, testing in CAMHB modestly underestimated numerical cefiderocol-xeruborbactam potency relative to ID-CAMHB (**Figure 2**).
- However, there was high interpretive concordance between the two susceptibility testing methods for cefiderocol-xeruborbactam (**Table 2**).

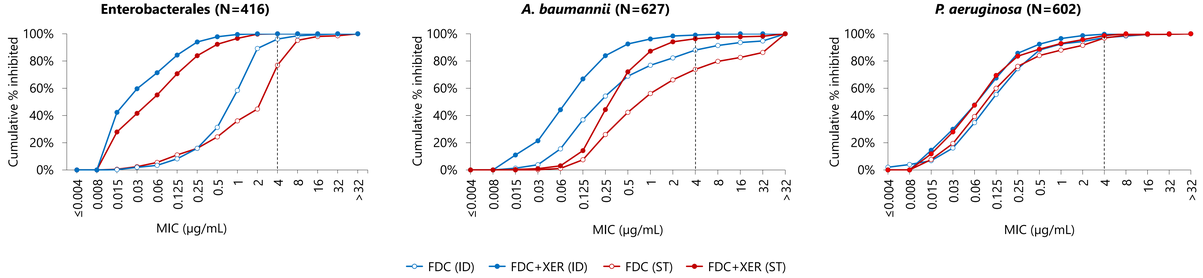
Table 1. Antibacterial activity of cefiderocol and cefiderocol-xeruborbactam determined in ID-CAMHB and CAMHB

	ID-CAMHB		CAMHB	
	FDC	FDC+XER	FDC	FDC+XER
Enterobacterales (N=416)				
MIC_{50}[a]	1	0.03	4	0.06
MIC_{90}[a]	4	0.25	8	0.5
% inhibited at ≤4 µg/mL[b]	96.2%	100%	76.9%	100%
***A. baumannii* (N=627)**				
MIC_{50}[a]	0.25	0.125	1	0.5
MIC_{90}[a]	8	0.5	>32	2
% inhibited at ≤4 µg/mL[b]	88.0%	99.0%	73.8%	96.3%
***P. aeruginosa* (N=602)**				
MIC_{50}[a]	0.125	0.125	0.125	0.125
MIC_{90}[a]	1	0.5	2	1
% inhibited at ≤4 µg/mL[b]	97.2%	99.7%	96.8%	98.7%

[a]MIC endpoint for FDC and FDC+XER in ID-CAMHB was based on CLSI guidelines and corresponded to significant reduction of growth. MIC endpoint for FDC and FDC+XER in CAMHB corresponded to complete inhibition of growth.
[b]The CLSI susceptible breakpoint for FDC in ID-CAMHB is 4 µg/mL, which was also applied to the other agents/test conditions to enable direct comparison.

CAMHB, cation-adjusted Mueller–Hinton broth; CLSI, Clinical and Laboratory Standards Institute; FDC, cefiderocol; ID, iron depleted; MIC, minimum inhibitory concentration; XER, xeruborbactam.

Figure 1. Cefiderocol and cefiderocol-xeruborbactam MIC distributions in ID-CAMHB and standard CAMHB



Dashed vertical line corresponds to susceptibility breakpoint of cefiderocol alone.
CAMHB, cation-adjusted Mueller–Hinton broth; FDC, cefiderocol; ID, iron-depleted CAMHB; MIC, minimum inhibitory concentration; ST, standard CAMHB; XER, xeruborbactam.

Figure 2. Correlation of cefiderocol-xeruborbactam MICs determined in ID-CAMHB versus standard CAMHB

A. Enterobacterales (N=416)

FDC+XER MIC (µg/mL) in ID-CAMHB \ FDC+XER MIC (µg/mL) in CAMHB	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
>32													
32													
16													
8													
4						1		1					
2					2	2	1	1					
1		1	3	3	1	1	5	2					
0.5		5	5	8	9	2	6	5					
0.25	4	13	11	9	8	3	3	3					
0.12	7	10	9	9	7	6	1						
0.06	19	9	9	11	12	11		1					
0.03	86	19	19	25	15	10	2						
≤0016													

B. *A. baumannii* (N=627)

FDC+XER MIC (µg/mL) in ID-CAMHB \ FDC+XER MIC (µg/mL) in CAMHB	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
>32													
32													
16													1
8						1		1		3			
4									1			**2**	**1**
2						2	4	3	3				**2**
1					1	5	8	6	1				**2**
0.5				1	4	19	17	6	3			**1**	**3**
0.25				2	32	40	18	7	5	**3**			
0.12			2	11	38	56	27	7	1				
0.06		1		14	72	33	14	5		**2**			**2**
0.03			2	20	26	10	3	4					
≤0016	2	3	9	22	16	8	4	4			**1**		

C. *P. aeruginosa* (N=602)

FDC+XER MIC (µg/mL) in ID-CAMHB \ FDC+XER MIC (µg/mL) in CAMHB	≤0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
>32													
32										1			
16										1			
8													
4							1		4	1			
2						1	4	1	6	**1**			
1					3	3	8	6	2	**3**			
0.5		4	5	6	14	6	3		2				
0.25		4	15	34	35	7	6	6	3				
0.12	6	19	33	29	18	9	2	1	1	**1**			
0.06	6	19	28	41	11	1		1					
0.03	21	27	24	15	2	3	1						
≤0016	38	24	13	7	2	1		2					

Numbers in red indicate strains with underestimated susceptibility when testing is performed in standard broth.
Green shading denotes the essential agreement zone, defined as MIC values that agree within ±1 log_2 (two-fold) dilution between the two comparator conditions.
Bold lines indicate CLSI susceptibility breakpoints for cefiderocol (susceptible ≤4 µg/mL; intermediate 8 µg/mL; resistant ≥16 µg/mL).
CAMHB, cation-adjusted Mueller–Hinton broth; FDC, cefiderocol; ID, iron depleted; MIC, minimum inhibitory concentration; XER, xeruborbactam.

Table 2. Interpretive concordance of cefiderocol and cefiderocol-xeruborbactam susceptibility results between ID-CAMHB and CAMHB

	% CA under both testing conditions[a]	
	Cefiderocol	Cefiderocol-xeruborbactam
Enterobacterales	79.3	100
A. baumannii	80.7	96.7
P. aeruginosa	96.4	98.7

[a]In the absence of established cefiderocol-xeruborbactam breakpoints, CLSI cefiderocol breakpoints determined in ID-CAMHB (susceptible ≤4 µg/mL; intermediate 8 µg/mL; resistant ≥16 µg/mL) were applied to both cefiderocol alone and cefiderocol-xeruborbactam for comparative calculation of % CA between media types.

CA, categorical agreement; CAMHB, cation-adjusted Mueller–Hinton broth; CLSI, Clinical and Laboratory Standards Institute; ID, iron depleted.

CONCLUSIONS

- The similarly high potency of cefiderocol-xeruborbactam in ID-CAMHB and CAMHB, together with high interpretive concordance between the two methods, supports the use of CAMHB and standard MIC reading criteria (100% growth inhibition) for cefiderocol-xeruborbactam susceptibility testing.
- Both the CLSI and European Committee on Antimicrobial Susceptibility Testing have approved the use of standard CAMHB and complete growth inhibition as the MIC endpoint for cefiderocol-xeruborbactam susceptibility testing.

Disclosures
OL is an employee of Qpex. MC, none. TH, YY are employees of Shionogi.

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