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The Impact of Xeruborbactam on *in vitro* Activity of Cefiderocol against a Challenge Panel of Enterobacterales Enriched with Isolates with Increased Cefiderocol MICs

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BACKGROUND

- Cefiderocol (FDC) is a siderophore cephalosporin with potent activity against resistant gram-negative bacteria. According to SIDERO-WT 2014 to 2019 surveillance studies that involved testing of over 30,000 Enterobacterales (ENT) isolates collected in North America and Europe, 99.8% were susceptible (S) to FDC (by CLSI breakpoint) (MIC_{90}=1 µg/mL). Against meropenem non-susceptible (non-S) ENT, 96.5% were susceptible to FDC (MIC_{90}=4 µg/mL).
- Resistance to FDC in ENT does not appear frequently, but when it occurs it appears to be multifactorial and requiring production of certain serine (SBL) or metallo β-lactamases (MBL) (J Glob Antimicrob Resist. 2020 22:738-741).
- Xeruborbactam (XER) is a novel β-lactamase inhibitor that inhibits numerous SBL and MBL. Previous study demonstrated that XER enhanced potency of multiple β-lactam antibiotics against meropenem non-susceptible Enterobacterales that produced various SBL and MBL β-lactamases (Antimicrob Agents Chemother. 2023 67(11):e0044023).

OBJECTIVE

- Evaluate the impact of XER on the activity of FDC against a challenge panel of ENT highly enriched in isolates with elevated FDC minimum inhibitory concentration (MIC) values.

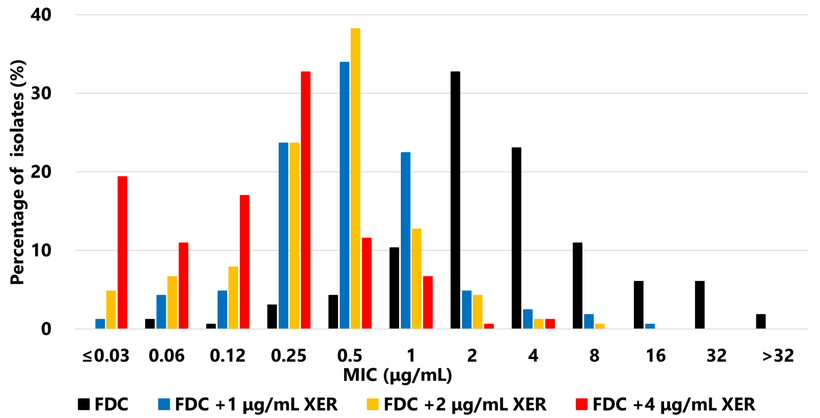
MATERIALS AND METHODS

- A challenge panel of 165 ENT isolates was selected from SIDERO-WT and clinical isolates. The panel contained 139 carbapenem resistant isolates. 79 (47.9%) and 41 (24.8%) of isolates had FDC MIC values >2 µg/mL and >4 µg/mL (non-S by EUCAST/CLSI breakpoint), respectively.
- The β-lactamase profile for each isolate was determined by PCR or whole genome sequencing.
- MICs were determined for FDC alone, in combination with 1, 2 and 4 µg/mL of XER according to CLSI guidelines for FDC using iron-depleted cation-adjusted Mueller-Hinton broth (CAMHB). XER alone was also tested using iron-depleted CAMHB. The other antimicrobials were tested using CAMHB.

RESULTS

- MIC_{50}/MIC_{90} of FDC alone and XER alone against the challenge panel were 2/16 and 16/>16 µg/mL, respectively. Dose-dependent shifts to lower FDC MICs were observed in the presence of increasing concentrations of XER for the challenge panel and individual subsets (Figure 1, Table 1).
- For isolates non-S to FDC (MIC >4 µg/mL), 4 µg/mL of XER reduced the FDC MIC_{90} from 32 to 1 µg/mL and the MIC_{50} from 16 to 0.25 µg/mL.
- FDC-XER (at fixed 4 µg/mL XER) showed the highest activity against this challenge panel compared to other agents tested (Table 2).

Figure 1: MIC distribution of cefiderocol alone and with xeruborbactam against challenge panel enriched in cefiderocol-non-susceptible isolates (N=165)



FDC: cefiderocol, XER: xeruborbactam

Table 1: $MIC_{50/90}$ (µg/mL) of cefiderocol alone and with xeruborbactam against challenge panel enriched in cefiderocol-non-susceptible isolates

	Total (N = 165)	FDC MIC>4 (N=41)	MBL (N = 67)
FDC	2 / 16	16 / 32	4 / 32
FDC +1 µg/mL XER	0.5 / 1	1 / 4	0.5 / 2
FDC +2 µg/mL XER	0.5 / 1	0.5 / 2	0.5 / 1
FDC +4 µg/mL XER	0.25 / 0.5	0.25 / 1	0.12 / 0.5
XER	16 / >16	16 / >16	16 / >16

FDC: cefiderocol, XER: xeruborbactam; MBL: metallo-β-lactamase
Of the 41 isolates with FDC MIC>4, 28 had NDM-type MBL.

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Table 2: $MIC_{50/90}$ (µg/mL) of antimicrobials against challenge panel enriched in cefiderocol-non-susceptible isolates

	Total (N = 165)	FDC MIC>4 (N=55)	MBL (N = 67)	KPC (N = 60)	OXA-48 (N = 11)	Carbapenemase negative (N=27)
FDC-XER	0.12 / 1	0.5 / 2	0.25 / 1	0.12 / 0.5	0.5 / 1	0.06 / 0.5
MVB	4 / >64	64 / >64	64 / >64	0.5 / 4	8 / 16	0.12 / >64
I-R	4 / 64	32 / 64	32 / >64	1 / 4	4 / 4	1 / 16
CZA	4 / >64	>64 / >64	>64 / >64	2 / 8	2 / 8	1 / >64
C/T	>64 / >64	>64 / >64	>64 / >64	>64 / >64	>64 / >64	4 / >64
ATM-AVI	0.25 / 2	0.25 / 8	0.25 / 1	0.25 / 1	0.25 / 16	0.25 / 16
CST	2 / 32	1 / 32	1 / 32	2 / 32	2 / 16	2 / 16
TGC	1 / 4	1 / 4	1 / 4	1 / 2	1 / 2	1 / 2

FDC: cefiderocol, XER: xeruborbactam, MVB: meropenem-vaborbactam, I-R: imipenem-relebactam,
CZA: ceftazidime-avibactam, C/T: ceftolozane-tazobactam, ATM: aztreonam, AVI: avibactam, CST: colistin,
TGC: tigecycline, MBL: metallo-β-lactamase
All β-lactamase inhibitors except for vaborbactam were used at fixed 4 µg/mL, and only vaborbactam was used at fixed 8 µg/mL.
Of the 55 isolates with FDC MIC>4, 37 had NDM-type MBL.
Of the 67 MBL isolates, 58 had NDM-type MBL and the other 9 had VIM-1.

CONCLUSIONS

- XER strongly improved FDC activity against rarely encountered isolates of ENT with increased FDC MIC and showed the highest activity compared to other agents tested.
- FDC-XER is a promising combination with good activity against highly resistant ENT isolates that warrants further development

＜**Conflict of interest statement**＞
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