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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.

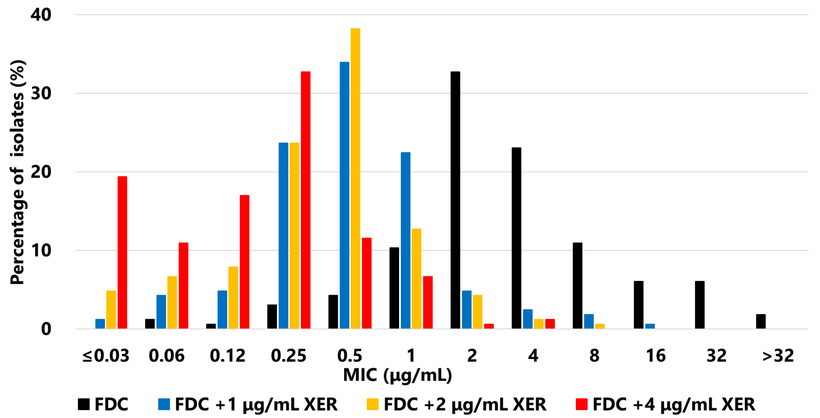
## MATERIALS AND METHODS

- 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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