

P-1186 Pharmacodynamic Assessment of Combination of Cefiderocol with Xeruborbactam in Murine Thigh Infection Model

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BACKGROUND

- Cefiderocol (FDC) is a siderophore-conjugated cephalosporin with potent activity against Gram-negative bacteria including carbapenem-resistant strains. FDC resistance has been observed with some isolates producing NDM- or PER/VEB-type β -lactamases together with mutations in iron transporters and/or PBP3 (Santerre Henriksen A, *et al.* Microbiol Spectr. 2024;12(4):e0383623, Santerre Henriksen A, *et al.* Microbiol Spectr. 2024;12(8):e0418123).
- Xeruborbactam (XER) is a novel β -lactamase inhibitor that inhibits both serine- and metallo-type β -lactamases. XER can enhance the potency of FDC against FDC-non-susceptible Enterobacterales (ENT) and *Acinetobacter baumannii* complex (ABC) isolates producing various serine- and metallo-type β -lactamases.

OBJECTIVE

- To evaluate the impact of XER on the efficacy of FDC in a murine thigh infection model.

MATERIALS AND METHODS

- A panel of 19 challenge clinical isolates (6 ENT, 6 *Pseudomonas aeruginosa* (PA) and 7 ABC) with elevated FDC MIC values (1 to >32 $\mu\text{g/mL}$) were used. The β -lactamase content for each isolate was determined by PCR or whole genome sequencing (**Table 1**).
- MICs of FDC were determined according to the 2024 CLSI guidance using iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB) prepared with Chelex resin and BD-BBL Mueller – Hinton broth powder. MICs of FDC in combination with 4 $\mu\text{g/mL}$ of XER were also determined using ID-CAMHB.
- Neutropenic and infected mice were administered a single subcutaneous dose of FDC/XER at 100/20 mg/kg. Blood samples (N=3 per timepoint) were collected at various times. The plasma concentrations of FDC and XER were determined using the LC-MS/MS method.
- Neutropenic mice were infected by intramuscular injection of bacterial suspension into the thigh (10^5 to 10^7 CFU/thigh). Infected mice were dosed subcutaneously with FDC 100 mg/kg q2h, with or without XER 20 mg/kg q2h, for 24 hours starting at 2 hours after inoculation. The dosing schedule in mice simulates the human PK profile of FDC and XER (i.e., FDC dosing [with or without XER] achieved 97.1% and 81.4% of time above MIC for the free drug ($fT > \text{MIC}$) for MICs of 4 and 8 $\mu\text{g/mL}$, respectively) (**Table 2**). XER alone (20 mg/kg q2h) was also evaluated correspondingly, and XER dosage regimen was tentatively set based on the $f\text{AUC}$ achieved in humans at 250 mg TID (**Table 3**). Viable bacterial cells were counted in the thighs at 2 and 26 hours after inoculation and the changes between pre- and post-treatment were determined.

Table 1: Susceptibility and β -Lactamase Content of Strains Used in the Studies

Species	Strain No.	β -lactamase content	MIC ($\mu\text{g/mL}$)	
			FDC alone	FDC/XER
<i>K. pneumoniae</i>	1142926	TEM-1, SHV-11, CTX-M-15, OXA-1	2	0.25
<i>K. pneumoniae</i>	1584026	TEM-1, SHV-11, CTX-M-15, OXA-48	4	1
<i>K. pneumoniae</i>	1217638	TEM-1, OXA-9, SHV-12, KPC-2	8	2
<i>K. pneumoniae</i>	1319427	TEM-1, SHV-1, OXA-427, OXA-9	16	0.5
<i>E. coli</i>	1919981	EC-15, TEM-1, CTX-M-15, NDM-5, OXA-1	>32	0.5
<i>E. coli</i>	581487	EC-15, TEM-1, SHV-12, NDM-1, CMY-59, OXA-9	>32	2
<i>A. baumannii</i>	1946458	ADC-52, ADC-199, CARB-16, OXA-23, OXA-91	>32	0.06
<i>A. baumannii</i>	1752060	ADC-215, OXA-65, OXA-24	32	1
<i>A. baumannii</i>	561320	ADC-25, TEM-1, PER-1, OXA-23, OXA-66	>32	0.12
<i>A. baumannii</i>	1121190	ADC-11, PER-1, OXA-23, OXA-66	>32	0.5
<i>A. baumannii</i>	1559552	ADC-33 like, OXA-172	>32	8
<i>A. baumannii</i>	2018684	ADC-175, GES-22, OXA-66, OXA-72	>32	16
<i>A. baumannii</i>	1933372	ADC-175, GES-22, OXA-66, OXA-72	>32	16
<i>P. aeruginosa</i>	1422297	PDC-35, OXA-14, OXA-488	1	0.25
<i>P. aeruginosa</i>	1276161	PDC-135, PER-1, OXA-2, OXA-74, OXA-488	4	0.5
<i>P. aeruginosa</i>	1217570	PDC-8, OXA-396	4	4
<i>P. aeruginosa</i>	1468828	PDC-3, OXA-1288	8	4
<i>P. aeruginosa</i>	1439533	PDC-8, OXA-494	8	0.5
<i>P. aeruginosa</i>	2097647	PDC-30, OXA-395	16	4

Table 2: Comparison of %24h $fT > \text{MIC}$ of FDC in Mice and Humans

Species	Dosage Regimen	%24h $fT > \text{MIC}$					
		1	2	4	8	16	32
Human	FDC 2 g q8h	100	100	100	100	65.6	15.6
Mouse	FDC/XER 100/20 mg/kg q2h	100	100	97.1	81.4	64.9	46.6

%24h $fT > \text{MIC}$ of FDC in humans was calculated using FDC Ph3 (CREDIBLE-CR) data.
For the calculation of %24h $fT > \text{MIC}$ of FDC in mice, a protein binding value of 39.6% (measured with FDC alone) was used.

Table 3: Comparison of XER $f\text{AUC}$ and %24h $fT > \text{XER Conc.}$ $\mu\text{g/mL}$ in Mice and Humans

Species	Dosage Regimen	XER $f\text{AUC}_{0-24}$ (hr $\cdot\mu\text{g/mL}$)	%24h $fT > \text{XER Conc.}$ $\mu\text{g/mL}$		
			1	2	4
Human	XER 250 mg q8h*	135	100	100	100
Mouse	FDC/XER 100/20 mg/kg q2h	66.1	73.6	54.0	29.0

*The data was calculated using Ph1 (QPEX-200) data.
For the calculation of the PK profile in mice, a protein binding value of 81.6% (measured with XER alone) was used.

Conflict of interest statement

Funding: This research was sponsored by Shionogi & Co., Ltd. and Qpex Biopharma Inc.
Conflict of interest: EM, MI, SK, TH, DG and YY are employees of Shionogi & Co., Ltd. or Qpex Biopharma Inc.

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Figure 1: Efficacy of FDC with or without XER against Enterobacterales

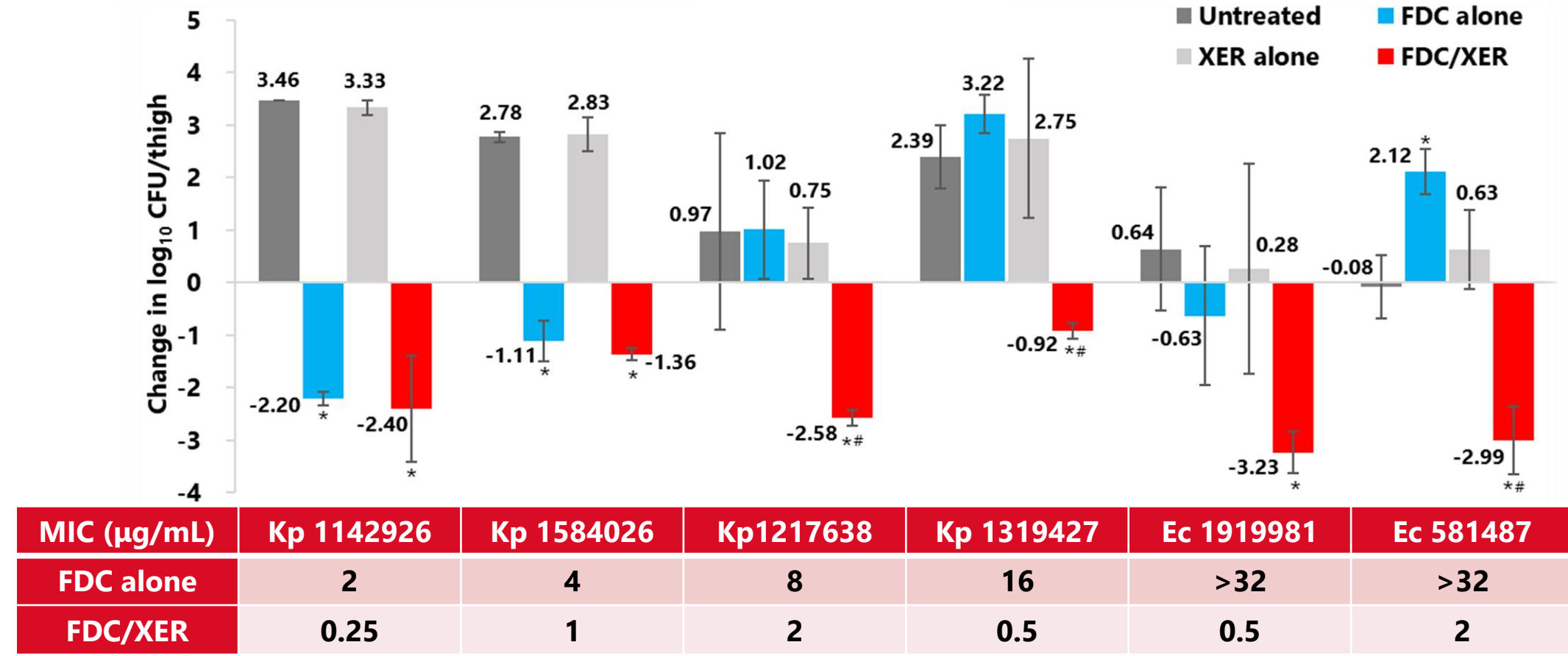


Figure 2: Efficacy of FDC with or without XER against *A. baumannii* complex

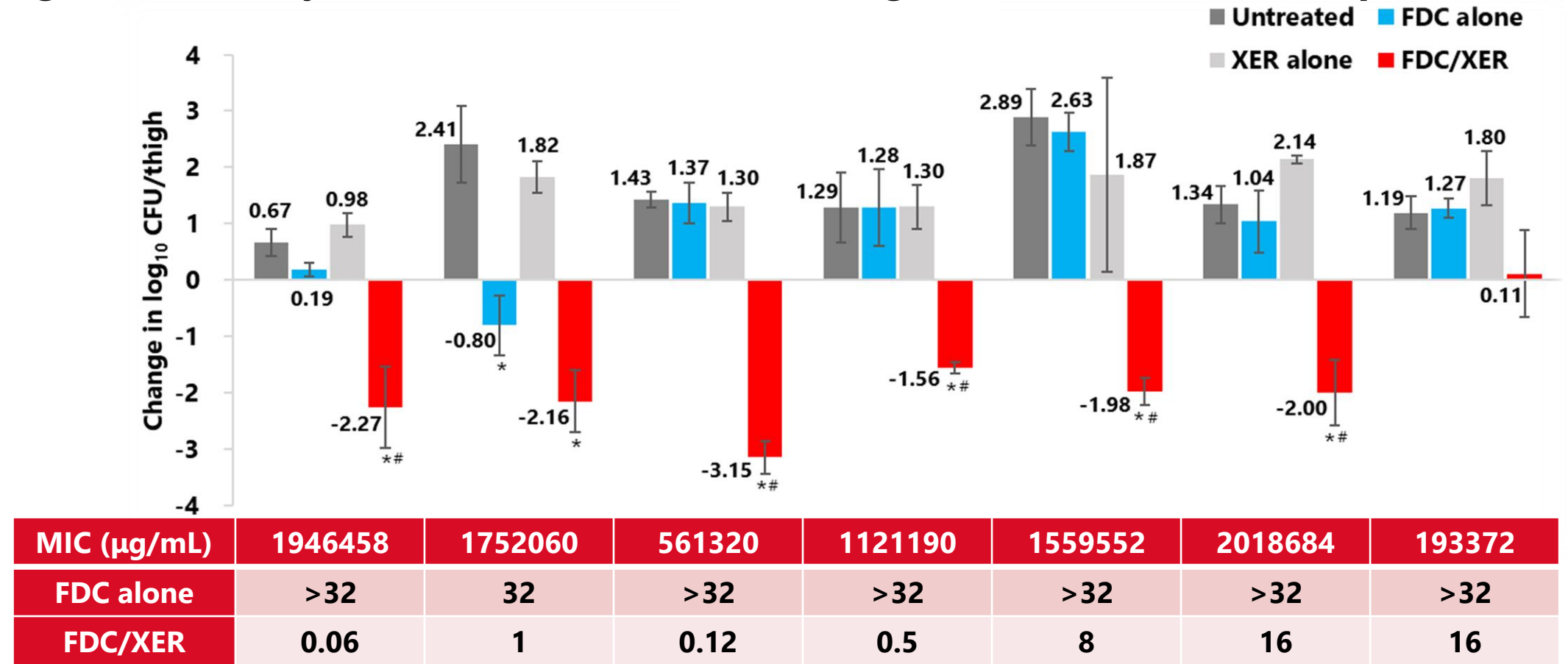


Figure 3: Efficacy of FDC with or without XER against *P. aeruginosa*

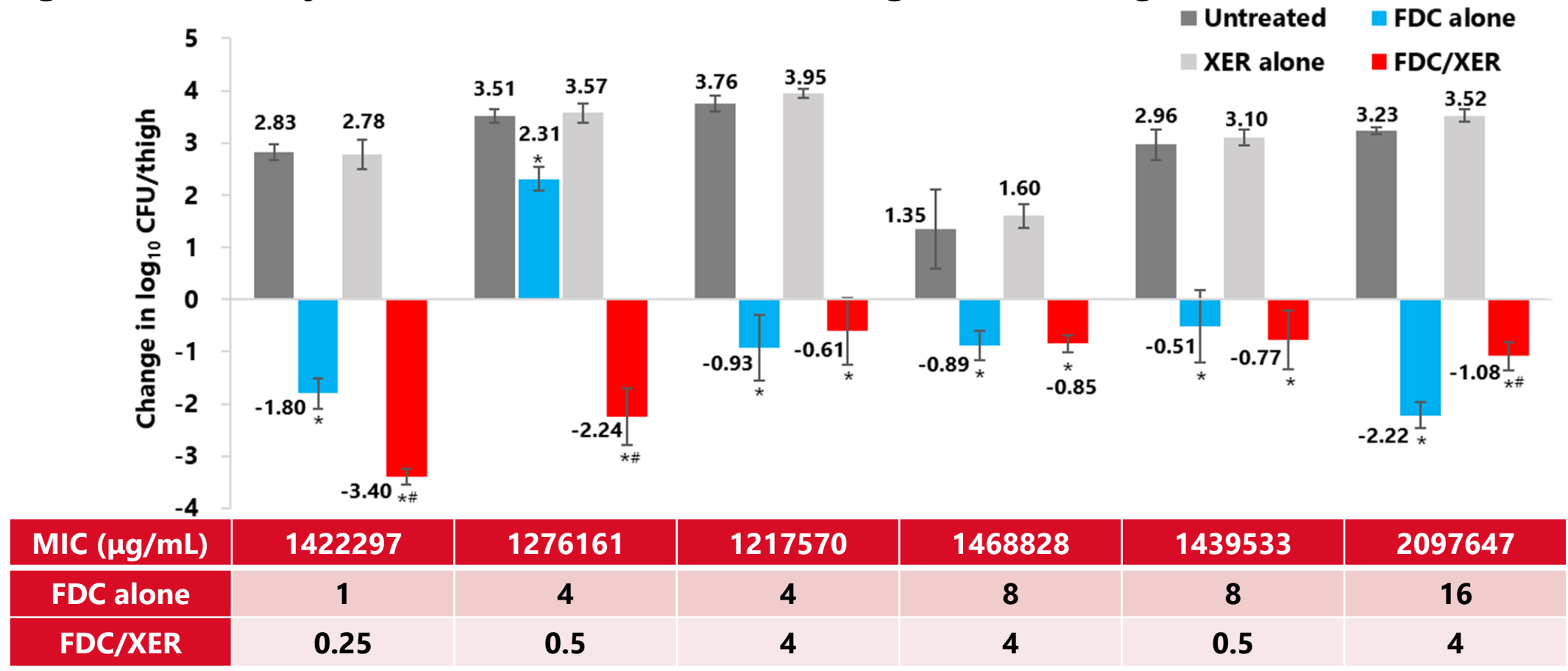


Figure1–3:

Statistical significance was determined using Dunnett's multiple comparison test (* $P < 0.01$; the treatment groups vs the untreated groups [26 hours after inoculation]). Additionally, statistical significance was determined using t-test (# $P < 0.01$; the FDC/XER treatment groups vs the FDC alone treatment groups).

RESULTS

- Against the 6 ENT isolates, treatment with FDC resulted in ≥ 1 $\log_{10}$ reduction for the 2 isolates with MIC values ≤ 4 $\mu\text{g/mL}$, but not for the 4 isolates with MIC values >4 $\mu\text{g/mL}$. The addition of XER increased FDC efficacy against all 4 FDC-non-susceptible isolates. (**Figure 1**).
- Against the 7 ABC isolates, treatment with FDC resulted in no or static effect for the 6 isolates with MICs >32 $\mu\text{g/mL}$ but demonstrated 0.8 $\log_{10}$ reduction for 1 isolate with a MIC of 32 $\mu\text{g/mL}$. The addition of XER was able to restore the efficacy of FDC against all tested isolates and resulted in ≥ 1 $\log_{10}$ reduction for the 6 isolates with FDC/XER MICs ranging from 0.06 to 16 $\mu\text{g/mL}$. FDC/XER was not effective against 1 isolate with a FDC/XER MIC of 16 $\mu\text{g/mL}$ (**Figure 2**).
- Against the 6 PA isolates, treatment with FDC resulted in ≥ 1 $\log_{10}$ reduction for 2 isolates and demonstrated 0.5–0.9 $\log_{10}$ reduction for 3 isolates, irrespective of MIC (1–16 $\mu\text{g/mL}$). On the other hand, treatment with FDC resulted in no effect for 1 isolate with an MIC of 4 $\mu\text{g/mL}$. The addition of XER caused a significant increase in efficacy of FDC against 2 isolates (1422297 and 1276161), but not against the remaining 4 isolates (**Figure 3**).

CONCLUSIONS

- The addition of XER to FDC significantly increased the efficacy of FDC in a murine thigh infection model for ENT and ABC that showed elevated MIC values (>4 $\mu\text{g/mL}$) for FDC.