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Cefepime Pharmacodynamics Against *Pseudomonas aeruginosa* Evaluated in a Chemostat Infection Model: Do Generalized Cephalosporin Targets Translate?

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Background

- **Cefepime-taniborbactam** is a β-lactam/β-lactamase inhibitor combination that demonstrated safety and efficacy in the treatment of complicated urinary tract infections.[1]
- **Taniborbactam** restores activity to cefepime via inhibition of serine- and metallo-β-lactamases produced by cefepime-resistant strains of Enterobacterales and *Pseudomonas aeruginosa*.[2]
- **Cefepime** is administered currently to treat infections caused by susceptible strains of *P. aeruginosa*; however nonclinical pharmacokinetic-pharmacodynamic (PK/PD) data are scarce for this bug-drug combination.
- An in vitro **chemostat infection model (CSIM)** was used to assess the translatability of broadly established cephalosporin **PK/PD targets** to support development of the cefepime-taniborbactam combination.

Methods

Bacterial strain characterization

- *P. aeruginosa* strains with no known acquired β-lactamases (N=6) were obtained from the CDC & FDA Antimicrobial Resistance (AR) Isolate Bank, except for the reference strain, *P. aeruginosa* PAO1; Enterobacterales strains (N=2) were acquired from the AR Bank and American Type Culture Collection (ATCC).
- Minimum inhibitory concentrations were determined by reference broth microdilution (**BMD MIC**)[3] or in a higher volume assay that simulated chemostat infection model conditions (**CS MIC**, *example shown in schematic*).
- In all MIC assays and CSIM experiments that included taniborbactam, the concentration of taniborbactam was fixed at 4 µg/mL.

*CS MIC is 2 µg/mL in 125 mL cation-adjusted Mueller Hinton broth

Chemostat infection model (CSIM)

- Overnight cultures of study strains were subcultured and diluted in chemostat flasks containing growth media (cation-adjusted Mueller Hinton broth, 125 mL) to achieve the target inoculum density of 2–8 x 10^5 CFU/mL.
- Programmable syringe pumps were used to infuse a range of escalating doses (1 dose level per CSIM) over 10 seconds every 8 hours.
- The desired elimination rate (meropenem half-life= 1 h; cefepime half-life= 2 h) was achieved by infusion of non-drug supplemented media; volume was maintained by removal of waste from the chemostat flask at an equal rate.
- At initiation of treatment (0 h), 24 h, and an intermediate time point, ~1 mL was removed for pharmacokinetic analysis and/or quantification of colony forming units (CFU) by serial dilution and plating (easySpiral Dilute, Interscience, Woburn, MA).
- A meropenem dose-ranging study versus *Klebsiella pneumoniae* ATCC 700603 was conducted to highlight the importance of the CS MIC.
- In all cefepime dose-ranging studies, CSIM media was supplemented with taniborbactam (4 µg/mL) to reduce potential confounding due to differential induction of chromosomal *Pseudomonas*-derived cephalosporinases (PDC) among study strains.
- Qualification was performed with *Escherichia coli* AR-0019 to confirm that results in this CSIM aligned with in vivo cefepime PK/PD reported by others.[4,5]

Pharmacokinetic/pharmacodynamic analysis

- Cefepime concentrations in each chemostat flask were determined by a qualified UPLC-MS/MS method and fit to a one-compartment model with bolus input and first-order output (Phoenix WinNonlin 8.4, Certara USA, Inc.).
- Simulated percentages of time concentrations exceeded the MIC (T > CS MIC or T > BMD MIC) and corresponding $\Delta CFU_{0\text{-}24}$ among all strains were fit to sigmoid inhibitory effect models (WinNonlin) according to the equation:

$$E = E_0 - \left[I_{max}(C^\gamma)/\left(C^\gamma + IC_{50}^\gamma\right)\right]$$

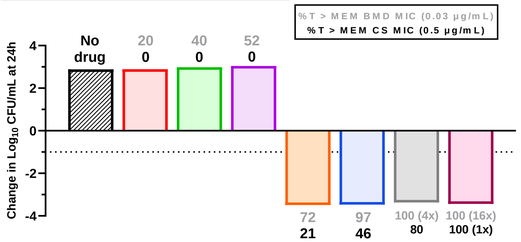
Results: *P. aeruginosa* Strain Characterization

Strain	Known resistance mechanisms	MIC (µg/mL) FEP BMD	FEP CS	FTB BMD	FTB CS
PAO1	OXA-50, PDC-1	2	8	2	4
AR-0233	OXA-494, PDC-15, *mexA*, *mexE*, *mexX*	8	8	8	8
AR-0238	OXA-50, PDC-3, *mexA*, *mexE*	4	8	4	8
AR-0258	OXA-488, PDC-37, *mexA*, *mexE*, *mexX*	4	16	4	8
AR-0264	OXA-494, PDC-407, *mexA*, *mexE*	2	8	1	8
AR-0244	OXA-488, PDC-37, *mexA*, *mexE*, *mexX*	16	16	16	16

BMD, broth microdilution; CS, chemostat; FEP, cefepime; FTB, cefepime-taniborbactam

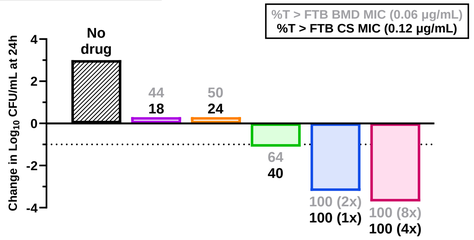
Results: Chemostat Qualification Studies

Meropenem vs. *K. pneumoniae* ATCC 700603



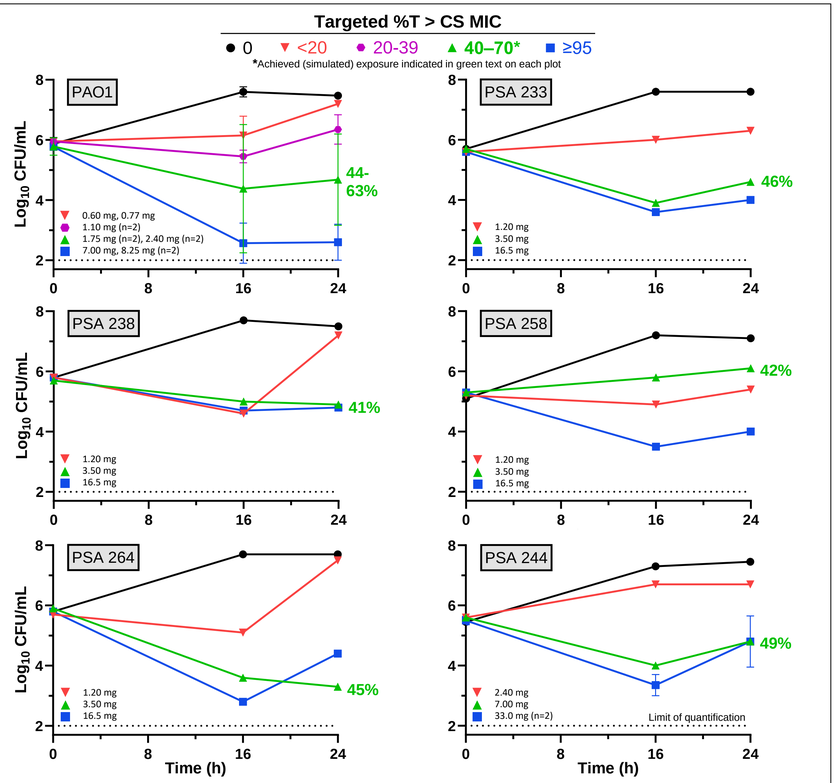
Meropenem demonstrates in vivo efficacy against Enterobacterales strains when unbound (free) plasma exposures achieve **≥ 20%** T > MIC.[6] In this CSIM when examining meropenem pharmacodynamics against *K. pneumoniae*, reductions in bacterial burden were observed at doses targeting **≥ 21% T > CS MIC** while those up to 52% T > BMD MIC allowed growth. These results highlight the importance of the CS MIC, which may trend higher due to increased drug requirements in a larger volume assay.

Cefepime vs. *E. coli* AR-0019



Reductions in bacterial burdens in vivo (neutropenic murine thigh infection model) have been observed consistently against Enterobacterales strains when unbound (free) cefepime plasma exposures achieve **≥ 40%** T > MIC.[4,5] In this CSIM when examining cefepime pharmacodynamics against *E. coli*, reductions were observed at doses achieving **≥ 40% T > CS MIC** or ≥ 64% T > BMD MIC.

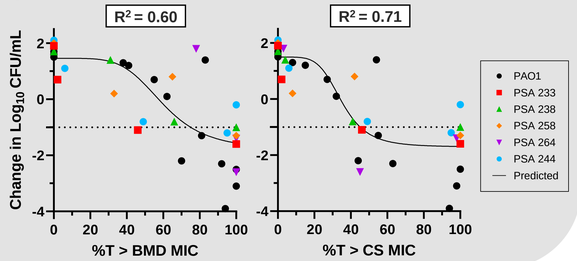
Results: Cefepime Dose-ranging Studies in Chemostat Infection Models (*P. aeruginosa*)



Composite pharmacodynamic models indexed to BMD MIC versus CS MIC

Among all *P. aeruginosa* strains evaluated in the CSIM, change in bacterial burden from 0 to 24 h was **better described by %T > CS MIC** versus %T > BMD MIC.

Additional studies are needed to understand the wide range of activity observed at exposures approaching 100% T > MIC.

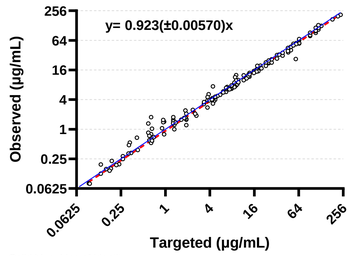


Results: Pharmacokinetic Analysis

Targeted cefepime pharmacokinetics in chemostat models

Dose (mg)	24-hour %T > MIC for an MIC of: 1	2	4	8	16	32	64	$C_{max,0\text{-}24}$	$C_{min,0\text{-}24}$	$AUC_{0\text{-}24}$
0.60	58	33	8	0	0	0	0	5	0.3	40
0.77	68	42	17	0	0	0	0	6	0.4	52
1.10	80	55	30	5	0	0	0	9	0.6	74
1.20	83	58	33	8	0	0	0	10	0.6	81
1.75	97	71	46	22	0	0	0	15	0.9	118
2.40	100	83	58	33	8	0	0	20	1.2	162
3.50	100	97	71	46	22	0	0	29	1.8	236
7.00	100	100	97	71	46	22	0	58	3.6	472
8.25	100	100	100	78	53	28	0	69	4.3	556
16.5	100	100	100	100	78	53	0	138	8.5	1112
33.0	100	100	100	100	100	78	0	275	17.1	2225

Targeted cefepime concentrations were achieved in chemostat models



Solid blue: Line of identity
Dashed red: Best-fit line (simple linear regression) ± standard error on slope

Conclusions

- **In a chemostat infection model, efficacious cefepime exposures against *P. aeruginosa* were similar to those established for Enterobacterales when indexed to MIC values relevant to the chemostat environment (CS MIC).**
- **Differences between MIC values by reference testing methods and the CS MIC should be considered when performing in vitro PK/PD profiling of discovery-phase antibacterials to prevent underestimation of therapeutic potential.**
- **Further investigation into the impact of MIC shifts (BMD → CS MIC) is warranted in additional species and antimicrobial agents.**

References

1. Wagenlehner FM, Gasink LB, McGovern PC, et al. *N Engl J Med*. 2024;390(7):611-622.
2. Karlowsky JA, Hackel MA, Wise MG, et al. *Antimicrob Agents Chemother (AAC)*. 2023;67(1):e01281-22.
3. Clinical and Laboratory Standards Institute. M07, 11th edition (2018).
4. Andes D and Craig W. *Clin Microbiol Infect*. 2005;(s6):10-17. doi:10.1111/j.1469-0691.2005.01265.x
5. Maglio D, Ong C, Banevicius MA, Geng Q, Nightingale CH, Nicolau DP. *AAC*. 2004;48(6):1941-1947.
6. Andes D and Craig W. *Int J Antimicrob Agents*. 2002;19:261-8.

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