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Correlation Analysis of Cefiderocol *In vitro* Activity and *In vivo* Efficacy against *Acinetobacter baumannii* Strains with Difficult-to-Read MIC Endpoints

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BACKGROUND

- Cefiderocol (FDC) is a siderophore-conjugated cephalosporin with broad activity against Gram-negative bacteria, including *Acinetobacter baumannii*.
- For some isolates, determining the minimum inhibitory concentration (MIC) endpoint for FDC can be difficult due to the trailing growth phenomenon. Recently more specific guidance on how to determine the MIC when trailing occurs has been incorporated in the CLSI M100 document, to enhance MIC reproducibility.

OBJECTIVE

- To corroborate the CLSI updated reading guidance, we determined MICs of *A. baumannii* strains that show difficult to determine MIC endpoints due to trailing according to the updated CLSI guidance and analyzed correlations between MICs and *in vivo* efficacy.

MATERIALS AND METHODS

- MICs were determined according to the 2024 CLSI guidance using iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB) from BD-BBL for 43 *A. baumannii* isolates, including 13 strains that show severe trailing (Figure 1). MIC values were interpreted according to CLSI breakpoints 2024 (susceptible ≤4 µg/mL, intermediate 8 µg/mL, resistant ≥16 µg/mL).
- All strains had been evaluated *in vivo* in the murine thigh infection model using humanized pharmacokinetic exposure of FDC[1, 2, 3] (Figure 2).

RESULTS

- FDC MIC range of tested *A. baumannii* strains was 0.12 to >32 µg/mL. Among 19 strains that showed a reduction in bacterial load after treatment with FDC in the murine thigh infection model, 94.7% (18/19 strains) were categorized as FDC susceptible. Among 24 strains that showed increase in bacterial load after treatment with FDC *in vivo*, 87.5% (21/24 strains) were categorized as FDC non-susceptible. The agreement between MIC and *in vivo* efficacy was 90.7% (39/43) (Table 1a), and were in line with results earlier obtained using the previous reading guidelines.
- As for the 13 strains that showed severe trailing, the agreement between MIC and *in vivo* efficacy was 84.6% (11/13). The updated CLSI reading guidance did not impact the overall agreement that was obtained earlier using the previous CLSI reading guidance (Table 1b).

Figure 1: Reading MIC endpoints for difficult-to-read strains in 96-well MIC test plate

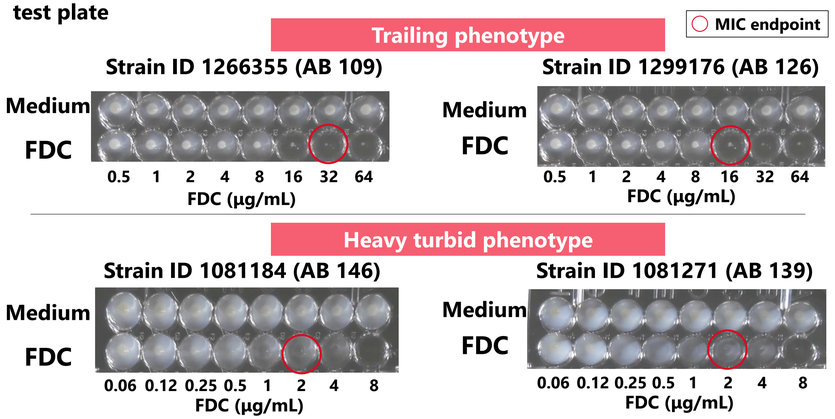
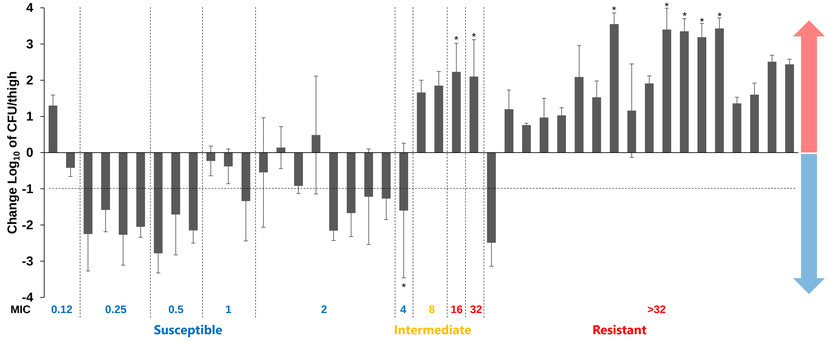


Figure 2: *In vivo* bacterial increase or decrease from start of treatment with cefiderocol against *Acinetobacter baumannii* in the neutropenic murine thigh infection model using humanized pharmacokinetic exposure of cefiderocol



In vivo bacterial decrease: reduction in bacterial count at 24 or 72 hours after start of cefiderocol treatment (mean of change <0 $\log_{10}$ colony forming unit [CFU] /thigh); *In vivo* bacterial increase: increase in bacterial count at 24 or 72 hours after initial treatment with cefiderocol (mean of change ≥0 $\log_{10}$ CFU/thigh). *bacterial count at 72 hours after start of cefiderocol treatment. MIC values shown blue, orange, and red indicate susceptible, intermediate, and resistant, respectively, according to CLSI guideline 2024.

Table 1a: Agreements between MIC and *in vivo* efficacy in murine thigh infection model

	In vivo bacterial decrease		*In vivo* bacterial increase		Agreement of *in vivo* responses with *in vitro* S/NS
Reading guidance	MIC ≤4 µg/mL (S)	MIC ≥8 µg/mL (NS)	MIC ≤4 µg/mL (S)	MIC ≥8 µg/mL (NS)	
CLSI 2024 reading guidance	18/19 (94.7%)	1/19 (5.3%)	3/24 (12.5%)	21/24 (87.5%)	39/43 (90.7%)
Previous CLSI reading guidance	17/19 (89.5%)	2/19 (10.5%)	4/24 (16.7%)	20/24 (83.3%)	37/43 (86.0%)

Table 1b: Agreements between MIC and *in vivo* efficacy in murine thigh infection model for 13 strains that showed severe trailing

	In vivo bacterial decrease		*In vivo* bacterial increase		Agreement of *in vivo* responses with *in vitro* S/NS
Reading guidance	MIC ≤4 µg/mL (S)	MIC ≥8 µg/mL (NS)	MIC ≤4 µg/mL (S)	MIC ≥8 µg/mL (NS)	
CLSI 2024 reading guidance	6/7 (85.7%)	1/7 (14.3%)	1/6 (16.7%)	5/6 (83.3%)	11/13 (84.6%)
Previous CLSI reading guidance	6/7 (85.7%)	1/7 (14.3%)	2/6 (33.3%)	4/6 (66.7%)	10/13 (76.9%)

Susceptible (S), Non-susceptible (NS), breakpoints as published by CLSI (2024). *In vivo* bacterial decrease: reduction in bacterial count at 24 or 72 hours after start of cefiderocol treatment (mean of change <0 $\log_{10}$ CFU /thigh); *In vivo* bacterial increase: increase in bacterial count at 24 or 72 hours after initial treatment with cefiderocol (mean of change ≥0 $\log_{10}$ CFU/thigh). MICs were interpreted by both CLSI 2024 reading guidance and the previous CLSI reading guidance. CLSI 2024 reading guidance: more quantitative comments that indicate the positive control well (the form of a button of >2 mm or heavy turbidity) and the endpoint well (the first well in which the reduction of growth corresponds to a button of <1 mm or is replaced by the presence of light haze/faint turbidity), including example photos, were added to the previous CLSI reading guidance.

CONCLUSIONS

- Correlation analysis between MIC and *in vivo* efficacy in thigh infection model confirms the validity of MIC endpoint determinations described in CLSI M100 document, including for strains that show severe trailing.

References
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3. Gill CM, *et al, J Antimicrob Chemother.* 2023;78(4):983-990)

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