

P-1198

Inner Zones of Inhibition in Disk Diffusion Testing of Cefiderocol Best Reflect Activity Against *Acinetobacter baumannii*

IDWeek 2025
Atlanta, GA
October 19–22, 2025

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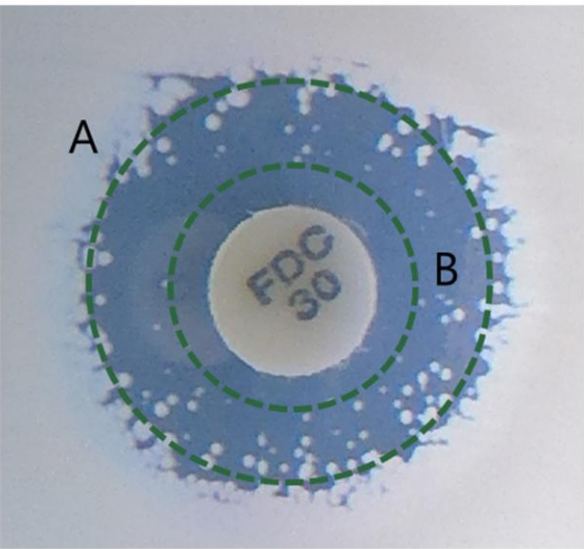


BACKGROUND

- Cefiderocol (FDC) is a siderophore-conjugated cephalosporin with activity against aerobic Gram-negative bacteria, including multidrug-resistant isolates.
- The disk diffusion (DD) method for FDC was approved by the Clinical and Laboratory Standards Institute (CLSI), but appearance of colonies within the zone of growth inhibition of *Acinetobacter baumannii*, whilst non-reproducible, can complicate endpoint reading (Figure 1).

Figure 1: Example of *A. baumannii* isolates showing colonies within zone of growth inhibition

Zone of Inhibition
Inner: 9 mm
Outer: 17 mm



A: Predominant inhibition zone (outer inhibition zone)
B: Inner zone of inhibition taking colonies within zone of inhibition into account

OBJECTIVE

- To investigate if reading outer zone of growth inhibition, which is more reproducible, can be used as endpoint reading.

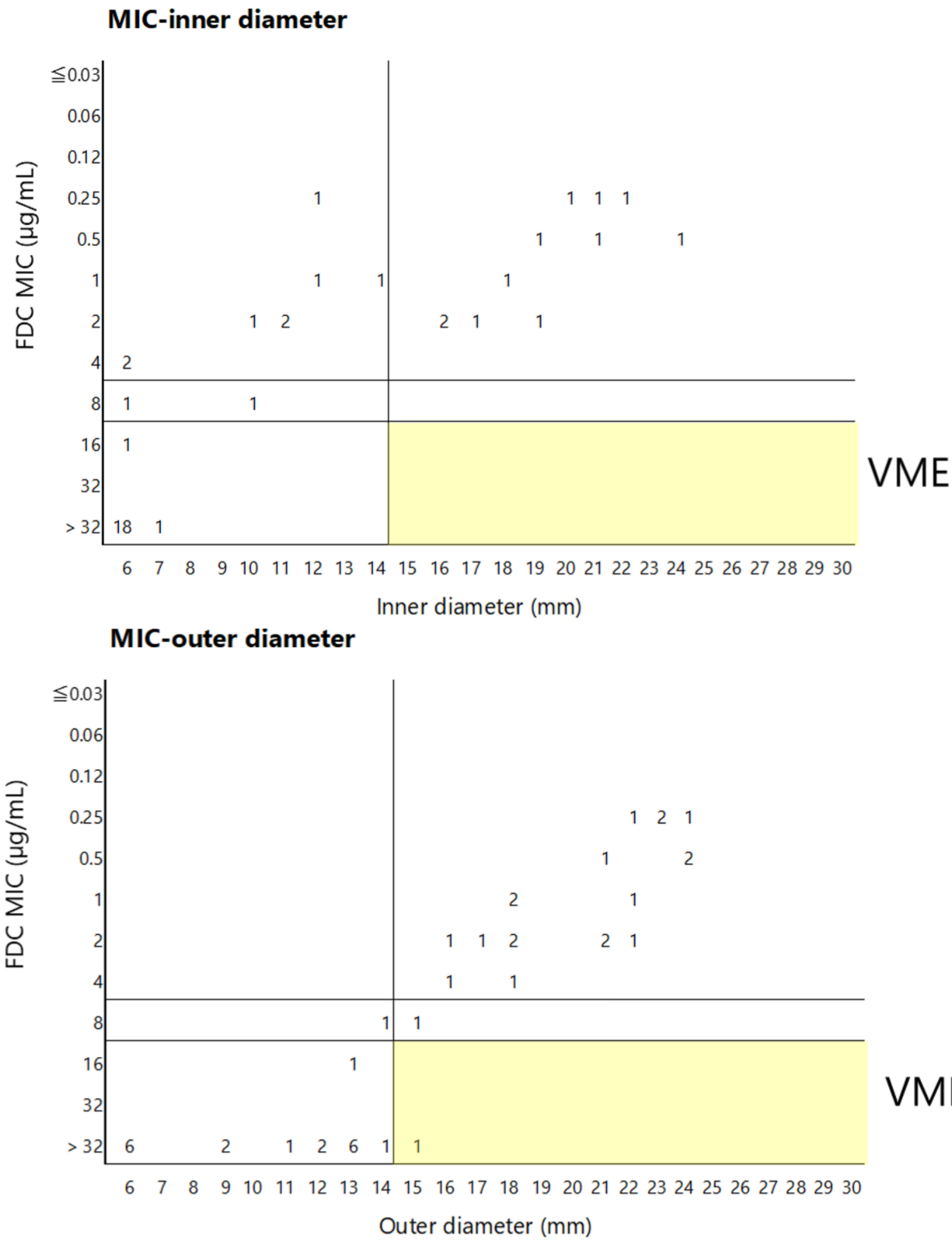
MATERIALS AND METHODS

- 41 *A. baumannii* strains were used for this study. Of these 41 strains, 17 showed colonies in the disk inhibition zone.
- MIC measurements in iron-depleted cation-adjusted Mueller–Hinton broth (Becton Dickinson BBL) and DD testing using Mueller–Hinton agar (Becton Dickinson) and FDC disk (Mast Group) were performed and interpreted according to CLSI protocols and guidance in 2024. The VME (very major error) was defined as a “resistant” result by the reference method (broth dilution method) but a “susceptible” result by the direct antimicrobial susceptibility testing method (DD test) for a particular drug-bug combination.
- In vivo efficacy was evaluated in a neutropenic murine thigh infection model using human-simulated regimen dosing of FDC.^{1, 2, 3}

RESULTS

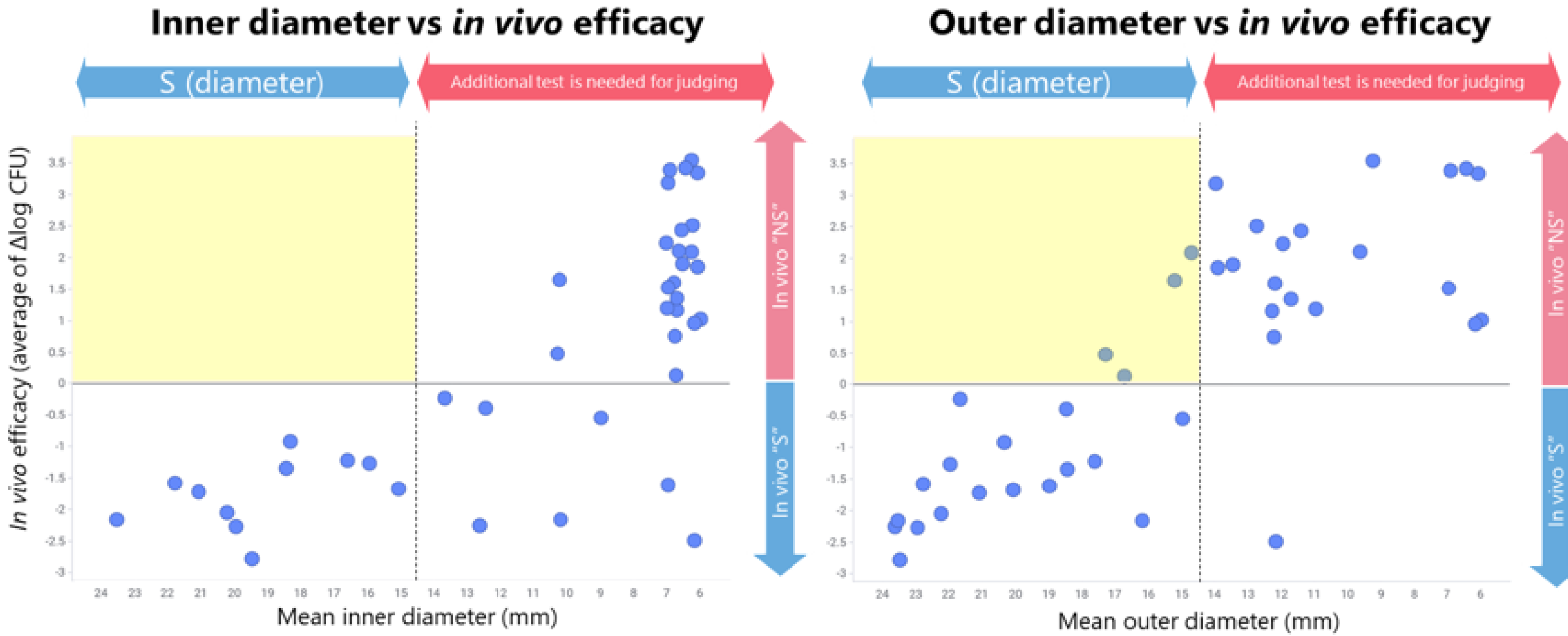
- In correlation analysis between DD zone of growth inhibition and FDC MIC, inner diameters and MIC showed no very major error (VME), while outer diameters and MIC showed 2% (1/41) VME (Figure 2).
- In correlation analysis between DD zone of growth inhibition and *in vivo* efficacy, all strains judged susceptible by inner diameter read-out showed a reduction in bacterial burden *in vivo*, whereas 19% (4/41) of strains judged susceptible by outer diameter read-out showed an increase in bacterial burden *in vivo* (Figure 3).

Figure 2: Correlation between inhibition zone diameters obtained by DD and MIC of FDC determined with broth microdilution



Modal MIC (n=9-30) and mean diameter (n=9) were plotted.

Figure 3: Correlation between mean inhibition zone diameters of DD tests and *in vivo* efficacy



“S” indicates susceptible. Mean zone diameter was calculated by using 9 diameter data for each strain. Yellow shading indicates areas where the DD mean diameter was determined to be “S” but *in vivo* efficacy was not demonstrated, which is similar to the VME category.

CONCLUSIONS

- Using the inner diameter as endpoint for zone of growth inhibition showed a better correlation with MIC and efficacy *in vivo*, providing rationale for using inner diameters in assessing *A. baumannii* susceptibility to FDC using DD.

References

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- Gill CM, *et al.*, *JAC Antimicrob Resist.* 2022;4(3):dlac047.
- Gill CM, *et al.*, *J Antimicrob Chemother.* 2023;78(4):983-990.

Conflict of interest statement

Funding: This research was sponsored by Shionogi & Co., Ltd.
Conflict of interest: all members are employees of Shionogi & Co., Ltd. and its affiliates.



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