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Reproducibility of Cefiderocol-Xeruborbactam in Cation Adjusted Mueller Hinton Broth (CAMHB) and Iron Depleted (ID) CAMHB Using Two Reading Endpoints

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Introduction

- Production of β-lactamases is the main β-lactam resistance mechanism among Gram-negative species and to overcome this resistance mechanism, β-lactam agents can be combined with β-lactamase inhibitors.
- Xeruborbactam is a novel boronic acid β-lactamase inhibitor that restores the cefiderocol activity against isolates producing β-lactamases, including Ambler classes A, B, C, and D.
- Cefiderocol susceptibility testing using the reference broth microdilution method (BMD) is performed in iron-depleted (ID) Cation Adjusted Mueller Hinton broth (CAMHB) and read at significant reduction (SR) of growth.
- We investigated the reproducibility of the reference BMD when testing cefiderocol-xeruborbactam in CAMHB and IDCAMHB and reading SR and 100% inhibition endpoints.

Materials and Methods

- Cefiderocol-xeruborbactam was tested by BMD against 212 Gram-negative clinical isolates that included 90 *Acinetobacter baumannii-calcoaceticus* complex, 57 *Pseudomonas aeruginosa*, and 65 Enterobacterales.
- Susceptibility testing was performed by the CLSI reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) M07 (2024) and M100 (2026) documents.
- Quality control (QC) was performed according to the CLSI M100 (2026) criteria using recently approved cefiderocol-xeruborbactam QC ranges.
- Isolates were tested in 6 to 16 replicates using four media manufacturers/lots of CAMHB and IDCAMHB prepared with these same manufacturers/lots and results were read by the same technicians.
- Cefiderocol-xeruborbactam was tested in triplicate against a subset of 50 isolates using the same four CAMHB manufacturers/lots and read by 10 technicians with different experience levels.
- Endpoints were determined as significant reduction (SR) in growth as defined by CLSI for cefiderocol and 100% growth inhibition.
- Results were compared to the modal MIC for the same testing conditions/reading endpoint to determine percentage essential agreement at ±1 dilution.

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Results

- The overall CAMHB essential agreement for on-scale values was 91.5% and 92.8% when reading at 100% growth inhibition and SR endpoints, respectively (Figure 1).
- The essential agreements for IDCAMHB when read at 100% growth inhibition and SR endpoints were 91.8% and 92.0%, respectively (Figure 1).
- The essential agreements varied among media manufacturers/lots, and they were lower for Oxoid CAMHB for the 100% endpoint (89.7% vs ≥91.5%; Figure 2).
- The Difco media displayed lower essential agreement values in IDCAMHB: 90.3% and 90.5% for 100% endpoint and SR, respectively, when compared to 91.5% to 93.2% for other media (Figure 2).
- The lowest essential agreements by species/groups were observed with *A. baumannii-calcoaceticus* complex isolates that ranged from 88.8% for IDCAMHB SR to 92.4% for CAMHB SR (Figure 3).
 - These values were ≥93.4% for *P. aeruginosa* and ≥91.2% for Enterobacterales (Figure 3).
- The essential agreement for the results for a subset of 50 isolates read by 10 readers was considerably higher for 100% growth inhibition (97.1%) compared to SR (91.6%) endpoint regardless of the reader's experience level (Figure 4).

Conclusions

- This robust evaluation of the reproducibility of cefiderocol-xeruborbactam BMD testing demonstrates that CAMHB and 100% growth inhibition endpoint reading had similar reproducibility compared to IDCAMHB SR, the recommended reading condition for cefiderocol BMD.
- Importantly, CAMHB and 100% growth inhibition endpoint reading displayed greater reproducibility compared to CAMHB and SR reading when results were determined by different readers.
- The BMD method of cefiderocol-xeruborbactam in CAMHB and 100% growth inhibition endpoint reading provides a more reliable and convenient method for testing this combination.

References

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Figure 1. Reproducibility of MIC results for cefiderocol-xeruborbactam compared to the modal MIC for 5,534 test results when testing 212 Gram-negative isolates

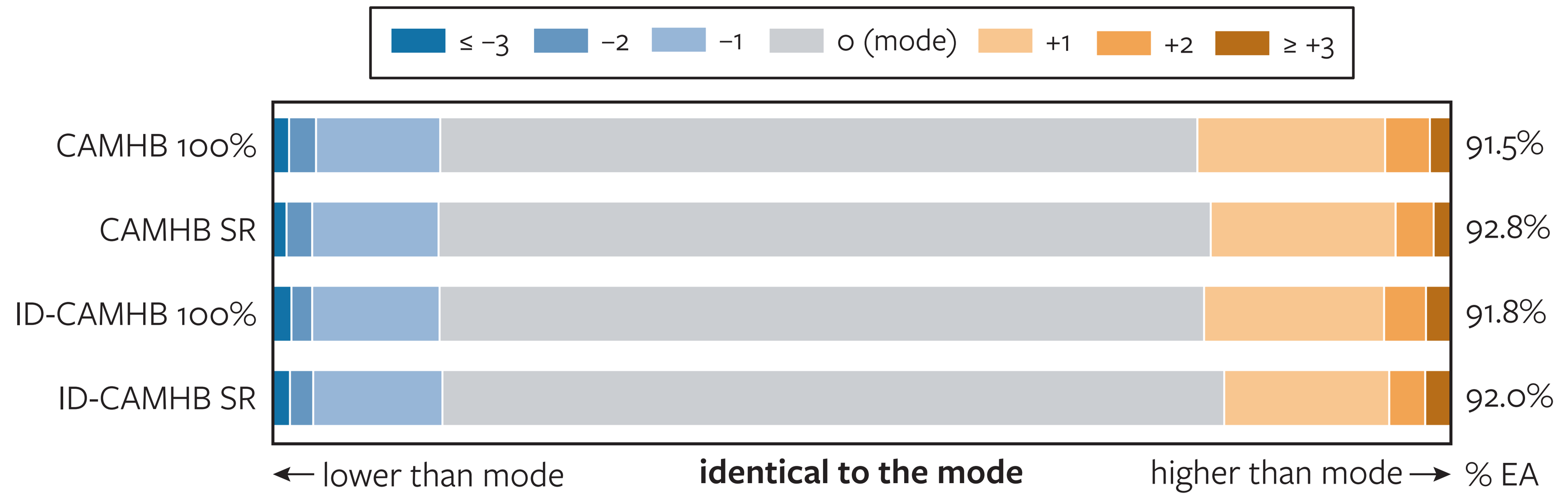
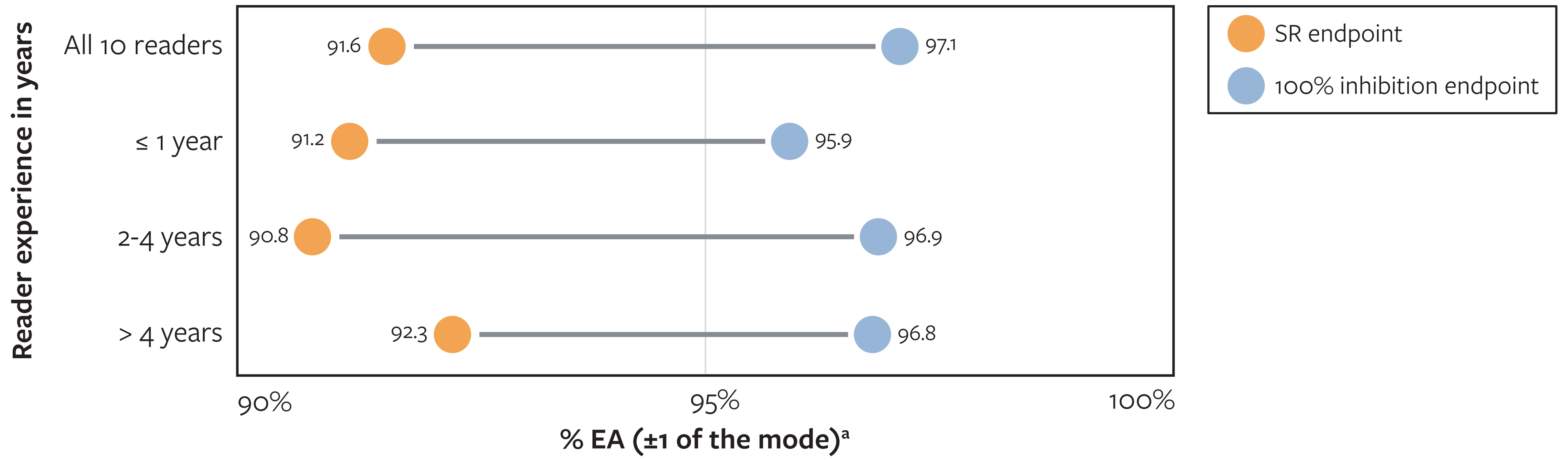
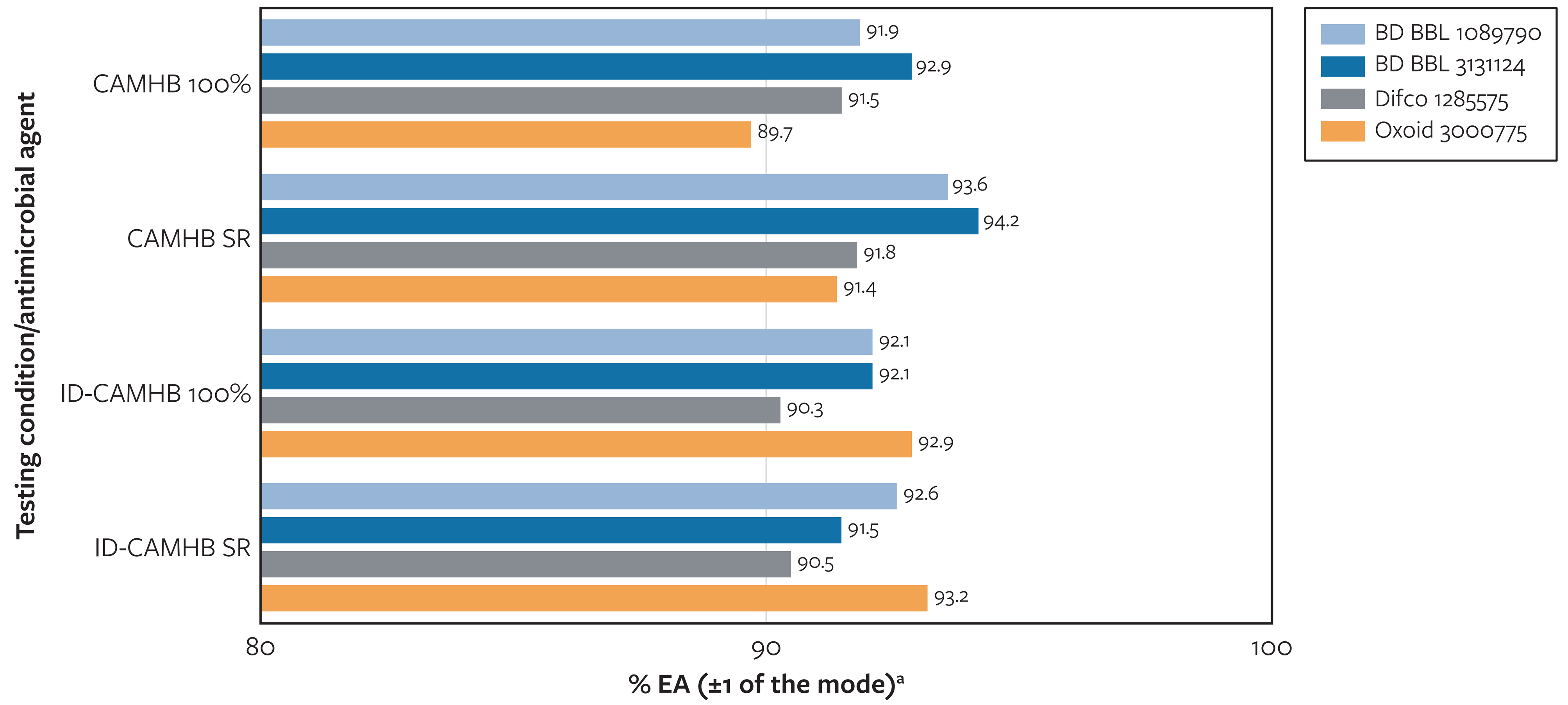

≤ −3
−2
−1
0 (mode)
+1
+2
≥ +3
CAMHB 100%
CAMHB SR
ID-CAMHB 100%
ID-CAMHB SR
91.5%
92.8%
91.8%
92.0%
lower than mode
identical to the mode
higher than mode
% EA

Figure 4. Essential agreement of MIC results for cefiderocol-xeruborbactam compared to the modal MIC for 50 Gram-negative isolates stratified by experience of the reader


Reader experience in years
All 10 readers
≤ 1 year
2-4 years
> 4 years
91.6
97.1
91.2
95.9
90.8
96.9
92.3
96.8
90%
95%
100%
% EA (±1 of the mode)a
SR endpoint
100% inhibition endpoint

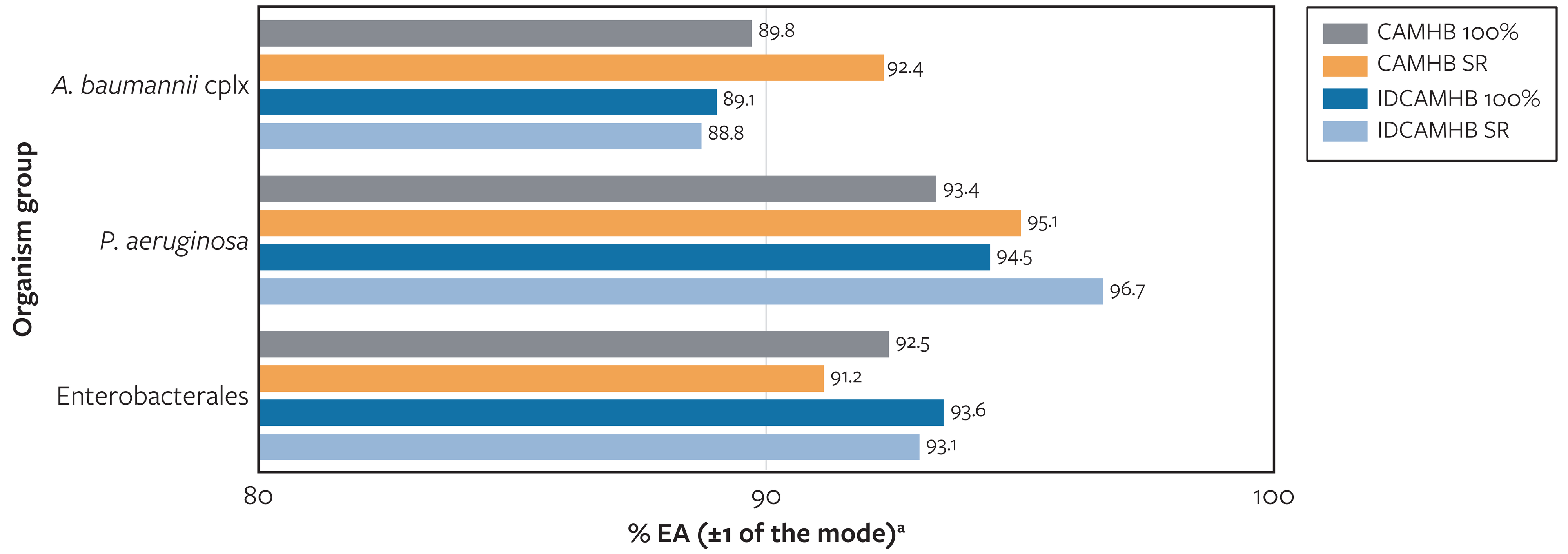
a % EA for single reader was calculated only for on-scale values.

Figure 2. Essential agreement of MIC results for cefiderocol-xeruborbactam compared to the modal MIC for 212 Gram-negative isolates stratified by media lot/manufacturer


Testing condition/antimicrobial agent
CAMHB 100%
91.9
92.9
91.5
89.7
CAMHB SR
93.6
94.2
91.8
91.4
ID-CAMHB 100%
92.1
92.1
90.3
92.9
ID-CAMHB SR
92.6
91.5
90.5
93.2
80
90
100
% EA (±1 of the mode)a
BD BBL 1089790
BD BBL 3131124
Difco 1285575
Oxoid 3000775

a % EA for single reader was calculated only for on-scale values.

Figure 3. Essential agreement of MIC results for cefiderocol-xeruborbactam compared to the modal MIC for 212 Gram-negative isolates stratified by bacterial species/group


Organism group
A. baumannii cplx
89.8
92.4
89.1
88.8
P. aeruginosa
93.4
95.1
94.5
96.7
Enterobacterales
92.5
91.2
93.6
93.1
80
90
100
% EA (±1 of the mode)a
CAMHB 100%
CAMHB SR
IDCAMHB 100%
IDCAMHB SR

a % EA for single reader was calculated only for on-scale values.

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