AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

LETTER TO THE EDITOR

Reporting Considerations for Cefepime-Susceptible and -Susceptible-Dose Dependent Results for Carbapenemase-Producing *Enterobacterales*

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KEYWORDS antimicrobial susceptibility testing, *Enterobacterales*, *Enterobacteriaceae*, breakpoints, carbapenemases, cefepime

The rise of carbapenemase-producing carbapenem-resistant *Enterobacterales* (CP-CRE) presents an urgent public health threat and has created challenges for clinicians and clinical microbiology laboratories (1). Whereas most carbapenemases hydrolyze third- and fourth-generation cephalosporins (exceptions include OXA-48 or SME in the absence of other β-lactamases), many institutions in the United States have observed CP-CRE isolates (mostly KPC producers) with cefepime MICs that fall into the susceptible (S) or susceptible-dose dependent (SDD) interpretive categories (2, 3). Cefepime, even when susceptible, has not been included as a treatment recommendation for CP-CRE (4–7). To assess the potential risk posed by the selection of cefepime for CP-CRE isolates, we sought to determine the relative frequency that these isolates are encountered by clinical laboratories.

To address the former question, cefepime antimicrobial susceptibility testing (AST) was performed on CRE isolates (i.e., isolates that were not susceptible to ertapenem and/or meropenem on testing) collected from two institutions and interpreted using obsolete (M100-S23 [8]) and current (M100-S30 [9]) Clinical and Laboratory Standards Institute (CLSI) breakpoints (BPs). Site 1 (Barnes-Jewish Hospital, St. Louis, MO) tested CP-CRE isolates possessing bla_{KPC} by disk diffusion (cefepime 30 μg; $n = 149$) according to CLSI guidelines. The presence of bla_{KPC} was detected by laboratory-developed real-time PCR or by Cepheid Xpert Carba-R assay (Sunnyvale, CA). Site 2 (Johns Hopkins Hospital, Baltimore, MD) tested both CP-CRE ($n = 298$) and non-CP-CRE (i.e., carbapenem resistance mediated by non-carbapenemase-mediated mechanisms; $n = 329$) isolates by the BD Phoenix automated susceptibility system (Sparks, MD). Carbapenemase production was detected by a modified carbapenem inactivation method (9), and specific carbapenemase genes were identified via whole-genome sequencing. Isolates were collected for 7 years at site 1 and 32 months at site 2.

Using current CLSI BPs, CP-CRE isolates were designated S/SDD at a rate of 14.1% (21/149) by disk diffusion and 23.1% (69/298) by BD Phoenix automated system (Table 1). Interpretation using obsolete BPs resulted in more isolates categorized as S/intermediate, i.e., 55% (82/149) and 31.2% (93/298) by disk diffusion or BD Phoenix, respectively (Table 1). Non-KPC CP-CRE isolates tested S/SDD by BD Phoenix at a lower rate than KPC-producing CP-CRE isolates, i.e., 11.2% (10/89) and 28.2% (59/209; $P = 0.001$), respectively. Isolates were not tested by both sites, so observed differences in rates may be due to the testing method or local epidemiology. Independent of the AST method applied, this illustrates a concerning number of cases where cefepime may be selected for therapy despite uncertainty of its efficacy against these isolates. Furthermore, this possibility is exacerbated when

Citation Fissel JA, Yarbrough ML, Tekle T, Burnham C-AD, Simner PJ. 2020. Reporting considerations for cefepime-susceptible and -susceptible-dose dependent results for carbapenemase-producing *Enterobacterales*. J Clin Microbiol 58:e01271-20. https://doi.org/10.1128/JCM.01271-20.

Editor Nathan A. Ledeboer, Medical College of Wisconsin

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Accepted manuscript posted online 8 July 2020
Published 24 August 2020

TABLE 1 Cefepime antimicrobial susceptibility testing results of carbapenem-resistant *Enterobacterales* interpreted using obsolete and current CLSI breakpoints

	Frequency by CLSI breakpoint (% [*n*]) according to[a]:					
	M100-S23, obsolete			M100-S30, current		
Enterobacterales	S	I	R	S	SDD	R
Site 1[b] (zone diameter breakpoint [mm])	≥18	15–17	≤14	≥25	19–24	≤18
KPC-producing CRE (*n* = 149)	20.8 (31)	34.2 (51)	45.0 (67)	1.3 (2)	12.8 (19)	85.9 (128)
Site 2[c] (MIC breakpoint [μg/ml])	≤8	16	≥32	≤2	4–8	≥16
CP-CRE (*n* = 298)	23.1 (69)	8.1 (24)	68.8 (205)	8.7 (26)	14.4 (43)	76.9 (229)
KPC-producing CP-CRE (*n* = 209)	28.2 (59)	11.0 (23)	60.8 (127)	9.1 (19)	19.1 (40)	71.8 (150)
Non-KPC-producing CP-CRE[d] (*n* = 89)	11.2 (10)	1.1 (1)	87.6 (78)	7.8 (7)	3.4 (3)	88.8 (79)
Non-CP-CRE (*n* = 329)	34.3 (113)	15.5 (51)	50.2 (165)	14.6 (48)	19.7 (65)	65.7 (216)

[a]S, susceptible; SDD, susceptible-dose dependent; I, intermediate; R, resistant; CRE, carbapenem-resistant *Enterobacterales*; CP-CRE, carbapenemase-producing CRE; non-CP-CRE, non-carbapenemase-producing CRE; CLSI, Clinical and Laboratory Standards Institute.
[b]Cefepime results determined by disk diffusion (previously published).
[c]Cefepime results determined by BD Phoenix automated susceptibility system.
[d]Non-KPC CP-CRE: NDM, 7; NDM + OXA-48, 48; OXA-48, 7; SME, 2; unknown, 25.

obsolete BPs are applied, highlighting patient safety concerns for laboratories that continue to use them (10).

The data were presented at the CLSI AST Subcommittee Meetings in June 2019 and January 2020 to provide guidance to laboratories on how to approach reporting for cefepime and CP-CRE. Different options for reporting were considered, including (i) suppressing cefepime S/SDD results and not reporting them at all, (ii) forcing cefepime S/SDD results to resistant, or (iii) continuing to report cefepime as tested. The CLSI AST subcommittee decided that the best way to approach this concern was to continue to report cefepime as tested, adding a comment after confirmation of the results. The scenario will be added to Appendix H (Using Molecular Assays for Resistance Detection) of CLSI document M100, where discrepant results between phenotypic AST and molecular detection of antimicrobial resistance are addressed (9). A new section will be added to cover the broader scenario when susceptibility (S/SDD) to third- and/or fourth-generation cephalosporins but intermediate or resistant results to at least one tested carbapenem are encountered for isolates in which a carbapenemase gene target or phenotypic carbapenemase production is detected. The suggested resolution is to repeat both molecular and phenotypic tests (AST and/or phenotypic carbapenemase test). If this discrepancy persists in an isolate, cefepime AST should be confirmed by a reference method, and conflicting genotypic and phenotypic testing results should be reported as tested. A comment should also be appended advising caution because there is currently insufficient clinical and laboratory evidence to conclude whether cephalosporin therapy of carbapenemase-carrying strains testing as S/SDD will be effective (11–15). These changes will be updated in the forthcoming CLSI M100 standard in 2021 (11).

For some laboratories, the recommended CLSI approach may not be feasible for routine clinical testing due to the frequency of these results (i.e., high rate of KPC-producing CRE) or the delay of cefepime results after confirmation. Furthermore, comments added to AST results may be difficult to incorporate into electronic health records and may be easily overlooked by the end users. Ultimately, laboratories should adopt the current BPs and discuss with appropriate stakeholders (i.e., antimicrobial stewardship) how these results should be reported for patient care at their respective institutions.

ACKNOWLEDGMENTS

P.J.S. has received grants and personal fees from Accelerate Diagnostics, OpGen, Inc., and BD Diagnostics; grants from bioMerieux, Inc., Affinity Biosensors, and Hardy Diagnostics; and personal fees from Roche Diagnostics and Shionogi, Inc. C.-A.D.B. receives research support from bioMérieux, BioFire, Cepheid, and Luminex and con-

sulting fees from Bio-Rad Laboratories and Thermo Fisher. M.L.Y. has a research relationship with Arkray and is a scientific advisor for Roche.

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