LETTERS TO THE EDITOR

Is There a Carbapenem MIC Cutoff Value That Distinguishes Carbapenemase-Producing and Non-Carbapenemase-Producing Carbapenem Non-Susceptible *Pseudomonas* and *Acinetobacter* Isolates?

To the Editor—The critical threat of carbapenemase-producing (CP) *Enterobacteriaceae* has garnered significant attention.[1] However, the hazards posed by CP *Pseudomonas aeruginosa* and CP *Acinetobacter baumannii* have been underestimated.[2] The transmission of mobile genetic elements containing carbapenemase-encoding genes is not species specific. Early and accurate detection of CP *P. aeruginosa* and CP *A. baumannii* is necessary to prevent the propagation of carbapenemases across all gram-negative organisms in healthcare settings.

Both *P. aeruginosa* and *A. baumannii* pose challenges for carbapenemase detection, but for different reasons. Although accurate and cost-effective phenotypic assays are available to detect CP *P. aeruginosa*, carbapenem nonsusceptibility among *P. aeruginosa* isolates in the United States are predominantly mediated by non-carbapenemase (non-CP) mediated mechanisms (eg, the loss of OprD porin expression and/or upregulation of MexAB-OprM efflux pumps).[2,3] Clinical microbiology laboratories may not see the resources needed to identify carbapenemase detection in carbapenem-nonsusceptible *P. aeruginosa* as a "high return on investment." Although carbapenemase production is the primary resistance mechanism among carbapenem nonsusceptible *A. baumannii* in the United States, commonly employed methods for carbapenemase detection in *Enterobacteriaceae* and *P. aeruginosa* are limited in their ability to detect carbapenemases in *A. baumannii*.[3] We sought to determine whether a carbapenem minimum inhibitory concentration (MIC) cutoff value exists to accurately distinguish CP and non-CP *P. aeruginosa* and *A. baumannii*. Identification of such a cutoff value could overcome challenges posed by phenotypic carbapenemase detection methods for these 2 species while eliminating the need to place all people with carbapenem-nonsusceptible isolates on contact precautions.[4]

We included 199 carbapenem-nonsusceptible *P. aeruginosa* and *A. baumannii* isolates: 111 were obtained from the Centers for Disease Control and Prevention and Food and Drug Administration Antimicrobial Resistance Isolate Bank (CDC-FDA) and 88 consecutive clinical isolates were obtained from the Johns Hopkins Hospital (JHH). CDC-FDA isolates had been previously molecularly characterized to identify β-lactamase genes using whole-genome sequencing and/or polymerase chain reaction (PCR). The Phoenix Automated System (Becton Dickinson Diagnostics, Sparks, MD) was used for antimicrobial susceptibility testing (AST) for the JHH isolates and carbapenem AST results were confirmed using the ETEST method (bioMérieux, Marcy-l'Étoile, France). Carbapenem nonsusceptibility was defined as meropenem or imipenem MIC of ≥4 mcg/mL. The β-lactamase genes in the JHH isolates were identified using the Check-MDR CT103XL kit microarray-based assay (Check-Points, Wageningen, Netherlands).

Receiver operating characteristic (ROC) curves were generated using various carbapenem MICs to determine the optimal MIC for the detection of CP isolates. The discriminatory power was evaluated using the area under the ROC curve (AUC), with an AUC value of 0.5 indicating no discriminative ability and an AUC value >0.8 indicating good-to-excellent prediction. Sensitivities and specificities were calculated at various carbapenem MIC values. It was determined a priori that sensitivities would be more relevant than specificities in establishing MIC cutoff values. It was more important to have sensitivity approaching 100% so that all or most CP-*Pseudomonas* and *Acinetobacter* could be detected, at the expense of specificity. Analyses were performed using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria).

Of 118 *P. aeruginosa* isolates, 23 (19%) were CP producers. Ambler Class B carbapenemases were identified in 74% of the CP *P. aeruginosa* isolates; the carbapenemase gene most frequently detected was bla_{VIM}. Of 81 *A. baumannii* isolates, 50 (62%) were CP producers. With the exception of 3 isolates that produced NDM-1, all *A. baumannii* isolates produced at least 1 acquired OXA-type carbapenemase.

We explored the possibility of an AUC that maximized both sensitivity and specificity for the detection of CP and non-CP *P. aeruginosa* and *A. baumannii*. The meropenem ROC curves were relatively poor at distinguishing CP and non-CP *P. aeruginosa* and *A. baumannii*, with AUCs of 0.66 (95% confidence interval [CI], 0.57–0.75) and 0.55 (95% CI, 0.49–0.62), respectively. For imipenem, the AUC of the ROC curve was 0.86 (95% CI, 0.74–0.97) for *P. aeruginosa*. An imipenem MIC of 64 mcg/mL had the greatest overall sensitivity and specificity (82% and 97%, respectively) for distinguishing CP and non-CP *P. aeruginosa*. However, an imipenem MIC value of 64 mcg/mL would fail to detect an unacceptably large portion of CP *P. aeruginosa*. The imipenem ROC curve was poor at distinguishing CP and non-CP *A. baumannii* (AUC, 0.61; 95% CI, 0.51–0.72).

We refocused our efforts to identify the meropenem and imipenem MIC values that maximized sensitivity, at the sake of specificity, of CP nonfermenters (Table 1). A meropenem MIC of 8 mcg/mL yielded a sensitivity of 98% for CP *P. aeruginosa*. An imipenem MIC of 8 mcg/mL detected 100% of CP *Pseudomonas*. For *Acinetobacter*, a meropenem MIC of 8 mcg/mL detected 100% of CP *Acinetobacter* and an imipenem of 8 mcg/mL detected 98% of CP *Acinetobacter*.

Our findings suggest that a meropenem or imipenem MIC cutoff value of 8 mcg/mL could detect ≥98% of CP *P. aeruginosa* and CP *A. baumannii*. The specificities associated with these

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TABLE 1. Sensitivities and Specificities Distinguishing Carbapenemase-Producing and Non-carbapenemase-Producing Carbapenem Non-susceptible *Pseudomonas* and *Acinetobacter* Isolates

Carbapenemase-Producing *Pseudomonas aeruginosa*			Carbapenemase-Producing *Acinetobacter baumannii*		
Minimum Inhibitory Concentrations	Sensitivity, %	Specificity, %	Minimum Inhibitory Concentrations	Sensitivity, %	Specificity, %
Meropenem ≥2 mcg/mL	100	10	Meropenem ≥2 mcg/mL	100	0
Meropenem ≥4 mcg/mL	100	19	Meropenem ≥4 mcg/mL	100	7
Meropenem ≥8 mcg/mL	98	24	Meropenem ≥8 mcg/mL	100	10
Meropenem ≥16 mcg/mL	83	48	Meropenem ≥16 mcg/mL	98	13
Imipenem ≥2 mcg/mL	100	6	Imipenem ≥2 mcg/mL	98	3
Imipenem ≥4 mcg/mL	100	13	Imipenem ≥4 mcg/mL	98	7
Imipenem ≥8 mcg/mL	100	17	Imipenem ≥8 mcg/mL	98	13
Imipenem ≥16 mcg/mL	96	22	Imipenem ≥16 mcg/mL	96	16

values, however, would be poor. We prioritized sensitivity over specificity because failing to recognize the presence of carbapenemase-producing organisms in healthcare settings could have unfortunate infection control implications. An MIC cutoff value above the carbapenem susceptibility breakpoint would reduce the proportion of patients placed on contact precautions.

Mobile genetic elements containing carbapenemase genes can spread rapidly in healthcare settings, between both glucose-fermenting (e.g., *Enterobacteriaceae*) and non-fermenting organisms.[1,2] Identifying carbapenem cutoff values highly sensitive for detecting carbapenemase production can support enhanced infection control practices for patients harboring CP organisms, potentially averting outbreaks.

The isolates provided by the CDC-FDA bank purposefully contain an overrepresentation of carbapenemase producers to allow for diverse resistance mechanisms to be evaluated. The inclusion of the CDC-FDA isolates improved the accuracy of our sensitivity estimates; however, the prevalence of CP isolates in our cohort should not be extrapolated to general US prevalence estimates. Because only US isolates were included in our cohort, our results may not be generalizable to carbapenem-nonsusceptible isolates from other parts of the world.

Our findings suggest that meropenem or imipenem MIC cutoff values of 8 mcg/mL have sensitivities approaching 100% for the detection of CP *P. aeruginosa* and CP *A. baumannii*. Carbapenem susceptibility patterns and resistance mechanisms for nonfermenters are anticipated to change over time, and appropriate MIC cutoff values need to be reviewed periodically to remain accurate.

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Pranita D. Tamma, MD, MHS;[1]
Ruibin Wang, MHS;[2]
Shawna Lewis, BA;[3]
Belita N.A. Opene, BA;[3]
Patricia J. Simner, PhD[3]

Affiliations: 1. Division of Infectious Diseases Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland; 2. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; 3. Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

Address correspondence to Pranita D. Tamma, MD, MHS, Division of Infectious Diseases, Department of Pediatrics, Johns Hopkins University School of Medicine, 200 North Wolfe Street, Suite 3149, Baltimore, MD 21287 (ptamma1@jhmi.edu).

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Cessation of Contact Precautions for Extended-Spectrum Beta-Lactamase (ESBL)–Producing *Escherichia coli* Seems to be Safe in a Nonepidemic Setting

To the Editor—According to a prospective multicenter cohort study, when the proportion of patients in contact isolation increases, compliance with contact isolation precautions