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Carbapenem-Nonsusceptible *Pseudomonas aeruginosa* Isolates from Intensive Care Units in the United States: a Potential Role for New β-Lactam Combination Agents

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ABSTRACT *Pseudomonas aeruginosa*, a frequent pathogen in the intensive care unit (ICU), has the propensity to develop antibiotic resistance. In particular, carbapenem-nonsusceptible (NS) *P. aeruginosa* poses tremendous challenges, and new antibiotics will be needed to treat this phenotype. Here we determine carbapenem nonsusceptibility rates for contemporary *P. aeruginosa* isolates from U.S. ICUs and *in vitro* activities of new β-lactam combination agents. Between July 2017 and June 2018, consecutive nonduplicate *P. aeruginosa* isolates from blood and respiratory tract sources were recovered from patients admitted to the ICUs of 36 geographically diverse U.S. hospitals. Antimicrobial susceptibility to the following antipseudomonal agents was tested: ceftazidime, imipenem, meropenem, ceftazidime-avibactam, and imipenem-relebactam (an investigational β-lactam/β-lactamase inhibitor). MICs and susceptibility rates were measured using Clinical and Laboratory Standards Institute reference broth microdilution methodology. Among the 538 consecutive ICU *P. aeruginosa* isolates collected, carbapenem nonsusceptibility was observed for 35% of the isolates and was more common among respiratory tract versus bloodstream specimens. Susceptibility rates, MIC_{50} values, and MIC_{90} values were as follows: ceftazidime-avibactam, 92.8%, 2 μg/ml, and 8 μg/ml; imipenem-relebactam, 91.5%, 0.25 μg/ml, and 2 μg/ml; ceftazidime, 77.1%, 4 μg/ml, and 64 μg/ml; meropenem, 72.7%, 1 μg/ml, and 16 μg/ml; imipenem, 67.1%, 2 μg/ml, and 16 μg/ml. Most (>75%) of the carbapenem-NS isolates were susceptible to ceftazidime-avibactam and imipenem-relebactam. In these U.S. hospital ICUs, carbapenem-NS *P. aeruginosa* isolates from respiratory sources were frequently observed. Novel β-lactam combination agents appear to retain active *in vitro* susceptibility profiles against these isolates and may play a role in the treatment of infections caused by carbapenem-NS *P. aeruginosa* strains.

KEYWORDS Gram-negative resistance, bloodstream, ceftazidime-avibactam, imipenem-relebactam, respiratory, surveillance

Pseudomonas aeruginosa is a Gram-negative pathogen that frequently causes infections in critically ill patients. In the intensive care unit (ICU), *P. aeruginosa* is a common cause of ventilator-associated pneumonia (VAP) and central-line-associated bloodstream infections (CLABSIs) (1–3). In addition to its burdensome prevalence, *P. aeruginosa* harbors a multitude of resistance mechanisms, including β-lactamase production, efflux pump upregulation, and porin loss, which can render several antimicrobials ineffective (4, 5). The development of antimicrobial resistance is of particular importance in the ICU because antibiotic utilization among critically ill patients is high, resulting in significant antimicrobial-selective pressure; furthermore, critically ill patients should gain the most benefit from effective antibiotic therapy (6–8).

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Whereas group 2 carbapenem antibiotics (i.e., imipenem, meropenem, and doripenem) have historically been reserved as agents of last resort for *P. aeruginosa* strains that are resistant to first-line broad-spectrum antibiotics, carbapenem nonsusceptibility (defined here as testing intermediate or resistant to at least one group 2 carbapenem) is becoming more frequent. The treatment of infections caused by carbapenem-nonsusceptible (NS) *P. aeruginosa* strains poses several challenges for ICU providers, as therapeutic options are limited and often are associated with toxicity (e.g., fluoroquinolone-, aminoglycoside-, or colistin-based therapy) (9, 10). Escalating rates of antibiotic resistance contribute to patient morbidity and death, especially among those in the ICU setting (11–13). A study evaluating the impact of multidrug-resistant (MDR) and carbapenem-resistant *P. aeruginosa* strains demonstrated a significant increase in mortality rates (adjusted odds ratio, 5.26; $P = 0.033$) during a strain outbreak (13). In response to poor patient outcomes and a growing economic burden, the Centers for Disease Control and Prevention (CDC) designated MDR *P. aeruginosa* a serious bacterial threat to our public health (14). Although a number of novel approaches to treating MDR *P. aeruginosa* are in development, the most well established is to combine a novel β-lactamase inhibitor with an older antipseudomonal β-lactam agent, thereby returning microbiological activity to the backbone β-lactam. Ceftazidime-avibactam is the most recently approved β-lactam combination agent that utilizes this strategy for *P. aeruginosa*. Imipenem-relebactam is another β-lactam combination antibiotic in development for serious *P. aeruginosa* infections, including VAP.

It will be important to understand the potential role of newer antimicrobials against carbapenem-NS *P. aeruginosa*. Here we determined carbapenem nonsusceptibility in a contemporary collection of ICU-derived *P. aeruginosa* isolates from across the United States and assessed the *in vitro* activity of two β-lactam combination agents.

(These results were presented in part at the Society of Critical Care Medicine 48th Critical Care Congress, San Diego, CA, 17 to 20 February 2019 [15].)

MATERIALS AND METHODS

Participating ICUs. The ICUs of 36 geographically diverse medical centers across the United States were selected to participate in this study. All sites received local institutional review board approval or waiver to participate. Sites reported the age and sex of the patient, the collection source, and the type of ICU.

Bacterial isolates. Consecutive clinical *P. aeruginosa* isolates were collected prospectively, between July 2017 and June 2018, from blood and lower respiratory tract sources among ICU patients ≥18 years of age. *P. aeruginosa* was identified by the microbiology laboratory of each participating hospital via conventional automated identification methods, including the Vitek system (bioMérieux), the BD Phoenix automated microbiology system (Becton Dickinson), the MicroScan system (Beckman Coulter), and matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Vitek MS Healthcare, bioMérieux). Any subsequent *P. aeruginosa* isolate collected from the same patient during the isolate collection period, regardless of the susceptibility profile, body source, or specimen type, was defined as duplicate according to the Clinical and Laboratory Standards Institute (CLSI) criteria and was excluded (16). Isolates collected from urine, wound/skin, cerebrospinal fluid, or any other source that was not blood or the lower respiratory tract were excluded. For this study, respiratory tract sources included expectorated or induced sputum, tracheal aspirates, Lukens trap secretions, bronchoalveolar lavage fluid, and protected specimen bushes of the lower respiratory tract. After local identification, isolates were transferred to Trypticase soy agar (TSA) slants (Becton Dickinson, Sparks, MD), refrigerated for no longer than 1 month, and shipped to the Center for Anti-Infective Research and Development (CAIRD) (Hartford, CT) for susceptibility testing. Within the CAIRD, isolates were immediately subcultured onto TSA with 5% sheep blood plates (Becton Dickinson) and stored in skim milk at −80°C until susceptibility testing was conducted. Any isolates suspected of another identification were confirmed to be *P. aeruginosa* via MALDI-TOF MS (MALDI Biotyper; Bruker Scientific LLC, Billerica MA).

Antimicrobial susceptibility. Susceptibility to ceftazidime (≤64 μg/ml), imipenem (≤64 μg/ml), meropenem (≤64 μg/ml), ceftazidime (≤64 μg/ml)-avibactam (fixed 4 μg/ml), and imipenem (≤32 μg/ml)-relebactam (fixed 4 μg/ml) was determined by broth microdilution a single time using the 2-fold dilution technique, in accordance with CLSI guidelines (16). Antibiotics were obtained as laboratory-grade powders from their respective manufacturers. MICs for ceftazidime, ceftazidime-avibactam, imipenem, and meropenem were interpreted using current CLSI breakpoints (16). Since no CLSI or U.S. Food and Drug Administration (FDA) breakpoints are available for imipenem-relebactam and the dosage of the imipenem component is the same as for imipenem-cilastatin (Primaxin; Merck & Co., Inc., Kenilworth, NJ), imipenem breakpoints were provisionally applied (susceptible, ≤2 μg/ml; resistant, ≥8 μg/ml); this methodology has been applied in other studies (17). *Klebsiella pneumoniae* ATCC 700603, *K. pneumoniae* BAA-2814, and *P. aeruginosa* ATCC 27853 were used as quality control strains for testing, as defined by

TABLE 1 Antimicrobial susceptibility of *P. aeruginosa* isolates by ICU origin (2017 to 2018)

ICU type and antimicrobial agent	Susceptibility status (%)			MIC determination (μg/ml)		
	Susceptible	Intermediate	Resistant	MIC_{50}	MIC_{90}	MIC range
All isolates ($n = 538$)						
Ceftazidime	77.1	4.5	18.4	4	64	0.125 to >64
Ceftazidime-avibactam	92.8	—[b]	7.2	2	8	0.125 to >64
Imipenem	67.1	5.2	27.7	2	16	0.125 to >64
Imipenem-relebactam	91.5	5.5	3	0.25	2	0.03 to >32
Meropenem	72.7	4.8	22.5	1	16	0.06 to >64
Medical ICU ($n = 266$)						
Ceftazidime	75.2	5.6	19.2	4	64	0.125 to >64
Ceftazidime-avibactam	92.5	—	7.5	2	8	0.125 to >64
Imipenem	65	6.4	28.6	2	16	0.25 to 32
Imipenem-relebactam	91.7	7.2	1.1	0.25	2	0.06 to 8
Meropenem	69.9	6	24.1	1	16	0.06 to 64
Surgical ICU ($n = 64$)						
Ceftazidime	79.7	3.1	17.2	4	32	0.5 to >64
Ceftazidime-avibactam	95.3	—	4.7	2	8	0.125 to >64
Imipenem	60.9	6.3	32.8	2	32	0.125 to >64
Imipenem-relebactam	92.2	3.1	4.7	0.25	2	0.03 to >32
Meropenem	68.8	4.7	26.6	1	32	0.06 to >64
Mixed ICU ($n = 154$)[a]						
Ceftazidime	77.9	3.9	18.2	4	64	1 to >64
Ceftazidime-avibactam	90.9	—	9.1	2	8	0.5 to >64
Imipenem	70.8	2.6	26.6	2	32	0.125 to >64
Imipenem-relebactam	89.6	4.5	5.8	0.25	4	0.03 to >32
Meropenem	75.3	3.2	21.4	0.5	16	0.06 to >64

[a]Primarily medical-surgical ICUs.
[b]—, CLSI intermediate breakpoint currently not available.

the CLSI (16). In addition, to assess the appropriate concentration of relebactam in microdilution trays, *P. aeruginosa* CDC isolate 0516, harboring a *K. pneumoniae* carbapenemase 2 (KPC-2) enzyme, was used as a quality control (range, 0.5/4 to 2/4 μg/ml) (18).

Analyses. *P. aeruginosa* isolates were classified as carbapenem NS if they were intermediate or resistant to at least one of the group 2 carbapenems (imipenem and meropenem) tested. Isolate susceptibility was analyzed by type of ICU (medical, surgical, or mixed medical and surgical), source (respiratory versus bloodstream), and carbapenem-NS and ceftazidime-NS (i.e., ceftazidime intermediate or resistant) phenotypes. Descriptive statistics were analyzed using Sigma Plot 14 (Systat Software Inc., San Jose, CA). Differences in carbapenem nonsusceptibility were assessed among (i) respiratory and bloodstream isolates and (ii) medical ICU, surgical ICU, and mixed (medical-surgical) ICU isolates using the χ^2 test. Student's *t* test was utilized to determine an association between age and carbapenem nonsusceptibility. In each instance, a two-tailed test was carried out and a prespecified alpha value of 0.05 was used.

RESULTS

During the 2017–2018 surveillance period, 538 nonduplicate *P. aeruginosa* isolates collected from an equal number of patients were submitted for testing. The mean patient age was 58 years (standard deviation, 19 years), and 60.2% of the patients ($n = 324$) were male. Most isolates ($n = 433$ [81%]) were recovered from a respiratory tract source. Forty-nine percent of isolates ($n = 266$) were obtained from a medical ICU, 12% ($n = 64$) from a surgical ICU, and 29% ($n = 154$) from a mixed ICU setting.

Carbapenem nonsusceptibility was observed for 189 isolates (35%). Most carbapenem-NS isolates were from a respiratory source (89%), compared with bloodstream isolates (11% [$P = 0.024$]). Carbapenem nonsusceptibility rates did not vary by age ($P = 0.241$) or type of ICU ($P = 0.274$).

The susceptibility rates, MIC_{50} values, MIC_{90} values, and ranges of MIC values for ceftazidime, imipenem, meropenem, ceftazidime-avibactam, and imipenem-relebactam are summarized in Table 1. Among all isolates tested, ceftazidime-avibactam and imipenem-relebactam were the most active agents (>90%). Susceptibility to ceftazidime (77.1%) was greater than that of meropenem (72.7%) and that of imipenem

TABLE 2 *In vitro* activity of carbapenems and comparator antimicrobial agents against *P. aeruginosa* isolates from ICUs (2017 to 2018)

Specimen source or susceptibility and antimicrobial agent	Susceptibility status (%)			MIC determination (μg/ml)		
	Susceptible	Intermediate	Resistant	MIC_{50}	MIC_{90}	MIC range
Respiratory tract (n = 433)						
Ceftazidime	74.6	4.1	21.3	4	64	0.125 to >64
Ceftazidime-avibactam	91.7	—[a]	8.3	2	8	0.125 to >64
Imipenem	63.3	5.3	31.4	2	32	0.125 to >64
Imipenem-relebactam	90.1	6.5	3.4	0.25	2	0.03 to >32
Meropenem	69.1	5.5	25.4	1	16	0.06 to >64
Bloodstream (n = 104)						
Ceftazidime	87.5	5.8	6.7	2	64	0.5 to 64
Ceftazidime-avibactam	97.1	—	2.9	2	8	0.5 to 32
Imipenem	82.7	4.8	12.5	2	16	0.25 to >64
Imipenem-relebactam	97.1	1.9	1	0.25	1	0.125 to >32
Meropenem	87.5	1.9	10.6	0.5	8	0.06 to >64
Carbapenem-NS (n = 189)						
Ceftazidime	58.2	8.5	33.3	8	64	0.5 to >64
Ceftazidime-avibactam	84.7	—	15.3	4	16	0.5 to >64
Imipenem	6.4	14.8	78.8	16	32	1 to >64
Imipenem-relebactam	75.7	15.9	8.4	1	4	0.06 to >32
Meropenem	22.2	13.8	64	8	32	0.125 to >64
Ceftazidime-NS (n = 123)						
Ceftazidime	0	19.5	80.5	64	128	16 to >64
Ceftazidime-avibactam	71.5	—	28.5	8	32	1 to >64
Imipenem	40.6	4.9	54.5	8	32	0.5 to >64
Imipenem-relebactam	77.3	14.6	8.1	1	4	0.125 to >32
Meropenem	41.5	5.6	52.9	8	32	0.06 to >64

[a]—, CLSI intermediate breakpoint currently not available.

(67.1%). When susceptibilities were compared by ICU type, ceftazidime-avibactam and imipenem-relebactam inhibited 90% to 95% of isolates from medical ICUs and surgical ICUs, while 60% to 70% of isolates were inhibited by meropenem and imipenem (Table 1).

Table 2 depicts the *in vitro* activity of tested antibiotics against all respiratory and blood isolates, as well as against carbapenem-NS and ceftazidime-NS *P. aeruginosa* isolates. Among all isolates, those collected from a respiratory source demonstrated consistently lower antimicrobial susceptibility rates, compared with bloodstream isolates. Among carbapenem-NS isolates (n = 189), 84.7% and 75.7% of isolates were susceptible to ceftazidime-avibactam and imipenem-relebactam, respectively. For the ceftazidime-NS isolates (n = 123), imipenem-relebactam was the most active agent, with 77.3% susceptibility (Table 2).

Relebactam restored susceptibility in 74% of isolates that tested NS to imipenem (n = 177), while avibactam restored susceptibility in 71.5% of isolates that tested NS to ceftazidime (n = 123). A total of 39 ceftazidime-avibactam-NS isolates and 46 imipenem-relebactam-NS isolates were identified in this study. Imipenem-relebactam susceptibility among isolates with a ceftazidime-avibactam-NS phenotype was 53.9%, while ceftazidime-avibactam susceptibility among isolates with an imipenem-relebactam-NS phenotype was 60.9%.

DISCUSSION

P. aeruginosa has emerged as one of the leading causes of nosocomial infections in the ICU, especially among patients undergoing invasive procedures or receiving mechanical ventilation (2). Due to a remarkable ability to develop resistance to a variety of antimicrobial agents, the management of *P. aeruginosa* infections poses a serious therapeutic challenge, supporting the need for alternative and novel therapeutic options with potent antipseudomonal activity in the ICU, where the risk of infection with *P. aeruginosa* is elevated (10, 19, 20).

Our findings corroborate and expand on previously reported antimicrobial resistance rates for *P. aeruginosa* isolates across ICUs in the United States, although higher resistance rates were observed in some instances in this study. In a surveillance study evaluating *Enterobacterales*, *P. aeruginosa*, and *Acinetobacter* sp. isolates from various infection sources, carbapenem nonsusceptibility was highest among *Acinetobacter* sp. isolates, followed by *P. aeruginosa* isolates (21). Notably, the authors reported a significant *P. aeruginosa* carbapenem nonsusceptibility burden, i.e., *P. aeruginosa* accounted for the most frequent observations (58%) of the carbapenem-NS phenotype among all Gram-negative isolates examined (21). Among *P. aeruginosa* strains from ICU patients in particular, the carbapenem nonsusceptibility rate was 19.2%, compared with a rate of 35% observed in the current study (21). The lower resistance rate observed may be due to those authors' composite assessment of isolates from respiratory tract, bloodstream, urine, and skin/wound infections, compared with our assessment of respiratory tract and bloodstream isolates only. This finding highlights the significance of culture source in the interpretation of resistance patterns, as noted in several other studies (22, 23).

To expand on differences in susceptibilities according to source, we compared our results to the most recent data from the CDC National Healthcare Safety Network, which provides antimicrobial resistance data for health care-associated infections, including CLABSIs and VAP, that occurred in 2011 to 2014 (2). While we observed resistance rates among bloodstream isolates similar to those from the CDC report, higher carbapenem nonsusceptibility rates (31% and 37% for meropenem and imipenem, respectively) were observed among ICU respiratory isolates, compared with 28.4% among VAP isolates reported by Weiner and colleagues (2). Notwithstanding differences in patient populations, it is important to note that this finding may in fact reflect a more contemporary assessment of resistance rates (i.e., 2012 versus 2018). Indeed, from 1993 to 2002, *P. aeruginosa* isolates from the Intensive Care Unit Surveillance Study demonstrated nationwide increases in antimicrobial resistance to several drugs, including imipenem (24).

It is generally accepted that the prevalence of resistance among isolates from patients in ICUs is higher than that among isolates from patients in general wards (25, 26). However, because the critically ill patient population varies widely, even within a single ICU, differences in antimicrobial susceptibility rates across ICUs are not as delineated (27–29). In our study, the rates of susceptibility to the agents tested were similar among the different types of ICUs. Similarly, in a study evaluating 1,723 *P. aeruginosa* isolates, no differences in the prevalence of imipenem resistance was observed between isolates from the medical ICU and isolates from the surgical ICU (30).

One interesting observation was the higher overall activity of ceftazidime against these *P. aeruginosa* isolates, compared with the carbapenems. These data, which are in agreement with other studies, demonstrate that ceftazidime may be a viable empirical therapeutic option in hospitals, including those in which carbapenem-NS *P. aeruginosa* is endemic (17, 31, 32). More than one-half (58%) of carbapenem-NS isolates were found to be susceptible to ceftazidime. This is noteworthy, illustrating that resistance to carbapenems (an antimicrobial class typically reserved as a last-line option for life-threatening infections) does not necessarily confer resistance to all other β-lactams. This distinction is due to the impact of different resistance mechanisms on individual β-lactams. For example, most ceftazidime-NS *P. aeruginosa* isolates hyperproduce chromosomal AmpC and MexAB-OprM and MexX-OprM efflux pumps, while the carbapenem-resistant isolates studied are typically deficient in the carbapenem cell membrane surface porin OprD (4, 33). Hyperproduction of AmpC confers resistance to most β-lactams; however, cefepime and the carbapenems are typically stable to hydrolysis (34). Antimicrobial susceptibility trends such as these emphasize the importance of using local antibiogram and surveillance study data as a resource for clinical decision-making and infection control interventions.

Historically, antimicrobial options for MDR Gram-negative bacteria were limited (9, 10). Fortunately, the unmet need for safe and reliable therapies for these pathogens has

seen the development and approval of several β-lactam combination agents (i.e., ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam). Although not included in this study, ceftolozane-tazobactam has consistently demonstrated potent *in vitro* activity against *P. aeruginosa* that is similar to if not greater than that of ceftazidime-avibactam in large surveillance studies (22, 32, 35). Importantly, the addition of tazobactam does little to enhance the activity of ceftolozane against *P. aeruginosa*. Similarly, the addition of vaborbactam to meropenem does not enhance the activity of meropenem alone against *P. aeruginosa* (36). As a result, these agents were not included in this analysis. Currently in clinical development is relebactam, a novel, non-β-lactam, bicyclic diazabicyclooctane β-lactamase inhibitor to be paired with imipenem for the treatment of complicated intra-abdominal infections, complicated urinary tract infections, hospital-acquired pneumonia, and infections specifically caused by MDR pathogens, including *P. aeruginosa*. Imipenem-relebactam has *in vitro* activity against class A β-lactamases such as KPC and class C β-lactamases, including AmpC cephalosporinases (37). In a study by Mushtaq et al, avibactam reversed AmpC-mediated ceftazidime resistance in *P. aeruginosa*, reducing MICs for fully derepressed mutants (38). With regard to imipenem-relebactam, several studies suggest that improved activity over imipenem involves the ability of relebactam to restore imipenem activity against the combined resistance mechanisms of OprD downregulation and AmpC overexpression (33, 39).

In the current study, 91.5% of *P. aeruginosa* isolates were susceptible to imipenem-relebactam (MIC_{50}, 0.5 μg/ml; MIC_{90}, 2 μg/ml), with relebactam restoring *in vitro* activity to 74% of imipenem-NS isolates. A similar observation was made by Karlowsky and colleagues, with imipenem-relebactam susceptibility rates being reported as 94.4% for all *P. aeruginosa* isolates and 78% for imipenem-NS isolates (17). Imipenem-relebactam was the most active agent against the 123 ceftazidime-NS isolates identified in this study, while we observed ceftazidime-avibactam to be the more active agent against carbapenem-NS isolates in this cohort of isolates. It should be noted, however, that 15.9% of the carbapenem-NS isolates tested intermediate to imipenem-relebactam using the breakpoints applied, whereas ceftazidime-avibactam currently has no CLSI intermediate category.

Our findings should be interpreted with the knowledge that CLSI or FDA MIC breakpoints for imipenem-relebactam have yet to be determined. It is also important to appreciate that the activity of ceftazidime-avibactam and imipenem-relebactam may reflect the particular resistance mechanisms of the *P. aeruginosa* isolates evaluated in this study. One limitation of this study was the lack of genotypic testing for the included isolates. Neither ceftazidime-avibactam nor imipenem-relebactam has activity against class B metallo-β-lactamases (e.g., VIM, IMP, and NDM), although metallo-β-lactamase-producing *P. aeruginosa* isolates are relatively uncommon in the United States (31, 40, 41). As previously mentioned, carbapenem resistance in *P. aeruginosa* is commonly the result of a combination of production of the chromosomally encoded AmpC β-lactamase, downregulation of the porin protein OprD, and overexpression of MexA-MexB-OprM efflux pumps (4, 5, 42). Results from previous studies suggest that most ceftazidime-avibactam and imipenem-relebactam resistance among *P. aeruginosa* is multifactorial and related to increased AmpC expression and downregulation of OprD (32, 43, 44). While we acknowledge the value of genotypic testing to provide further understanding of observed resistance mechanisms, it is worth noting that results from previous investigations indicate that the interplay of enzymatic and mutation-driven resistance mechanisms in *P. aeruginosa* is complex, with the correlation of gene expression to a phenotypic profile sometimes proving a challenge. In a study by Castanheira et al. comparing the genotypic profiles of ceftazidime-avibactam-resistant isolates ($n = 47$) and ceftazidime-avibactam-susceptible isolates ($n = 60$), the relative expression of MexCD-OprJ was greater in the ceftazidime-avibactam-resistant group, while overexpression of AmpC, MexXY-OprM, Pa5542, and PoxB was more common among ceftazidime-avibactam-susceptible isolates. OprD loss and MexAB-OprM expression were similar in the two groups (45).

Conclusion. The results of this study support and expand on results from other investigations by providing a contemporary susceptibility assessment of *P. aeruginosa* strains isolated from ICU patients across the United States. The high levels of decreased susceptibility to carbapenems, particularly among respiratory isolates, are concerning and further limit the use of these drugs for empirical monotherapy. While ceftazidime alone continues to demonstrate moderate *in vitro* activity, the introduction of novel β-lactam combination agents represents new therapeutic alternatives for the treatment of *P. aeruginosa* infections, especially those with a carbapenem-NS phenotype.

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