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SUSCEPTIBILITY

In Vitro Activity of Ceftolozane-Tazobactam, Imipenem-Relebactam, Ceftazidime-Avibactam, and Comparators against *Pseudomonas aeruginosa* Isolates Collected in United States Hospitals According to Results from the SMART Surveillance Program, 2018 to 2020

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ABSTRACT Ceftolozane-tazobactam (C/T), imipenem-relebactam (IMR), and ceftazidime-avibactam (CZA) were tested against 2,531 *P. aeruginosa* strains isolated from patients in the United States from 2018 to 2020 as part of the SMART (Study for Monitoring Antimicrobial Resistance Trends) surveillance program. MICs were determined by CLSI broth microdilution and interpreted using CLSI M100 (2021) breakpoints. Imipenem-, IMR-, or C/T-nonsusceptible isolates were screened for β-lactamase genes: 96.4% of all isolates and ≥70% of multidrug-resistant (MDR), pan-β-lactam-nonsusceptible, and difficult-to-treat resistance (DTR) isolates were C/T-susceptible; 52.2% of C/T-nonsusceptible isolates remained susceptible to IMR compared to 38.9% for CZA; and 1.7% of isolates tested were nonsusceptible to both C/T and IMR versus 2.2% of isolates with a C/T-nonsusceptible and CZA-resistant phenotype (a difference of 12 isolates). C/T and IMR modal MICs for pan-β-lactam-nonsusceptible isolates remained at or below their respective susceptible MIC breakpoints from 2018 to 2020, while the modal MIC for CZA increased 2-fold from 2018 to 2019 and exceeded the CZA-susceptible MIC breakpoint in both 2019 and 2020. Only six of 802 molecularly characterized isolates carried a metallo-β-lactamase, and two isolates carried a GES carbapenemase. Most *P. aeruginosa* isolates were C/T-susceptible, including many with MDR, pan-β-lactam-nonsusceptible, DTR, CZA-resistant, and IMR-nonsusceptible phenotypes. While C/T was the most active antipseudomonal agent, IMR demonstrated greater activity than CZA against isolates nonsusceptible to C/T.

KEYWORDS ceftolozane-tazobactam, imipenem-relebactam, ceftazidime-avibactam, *Pseudomonas aeruginosa*, United States, SMART, surveillance

Ceftolozane-tazobactam (C/T), imipenem-relebactam (IMR), and ceftazidime-avibactam (CZA) are preferred options in the treatment of patients with suspected or documented serious infections caused by non-carbapenemase-producing multidrug-resistant (MDR) and difficult-to-treat resistance (DTR) *P. aeruginosa* (1). *P. aeruginosa* isolates with MDR and DTR phenotypes are common in many countries, including the United States (2–6). Previous studies of clinical isolates of *P. aeruginosa* from patients in the United States have reported that C/T, IMR, and CZA have sustained their potent *in vitro* activities against *P. aeruginosa* over time (2–4, 7–11). Lower C/T, IMR, and CZA susceptibilities have been reported in regions outside North America in association

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TABLE 1 Percent susceptible to ceftolozane-tazobactam, imipenem-relebactam, ceftazidime-avibactam, and comparators among all *P. aeruginosa* isolates and subsets of MDR, pan-β-lactam-nonsusceptible, and DTR isolates[a]

Phenotype	No. (% of all isolates)	Antimicrobial agent, % susceptible										
		C/T	IMR	CZA	TZP	FEP	CAZ	MEM	IMI	ATM	AMK	LVX
All	2,531 (100)	96.4	91.5	94.4	77.0	81.6	79.9	78.3	66.0	69.9	97.0	66.8
MDR	319 (12.6)	75.9	58.9	63.3	8.8	12.2	16.6	19.7	16.3	3.8	84.0	18.5
Pan-β-lactam-NS	207 (8.2)	73.4	51.2	50.2	0	0	0	0	0	0	84.5	15.9
DTR	169 (6.7)	69.8	46.2	45.0	0	0	0	0	0	0	82.8	0

[a]C/T, ceftolozane-tazobactam; IMR, imipenem-relebactam; CZA, ceftazidime-avibactam; TZP, piperacillin-tazobactam; FEP, cefepime; CAZ, ceftazidime; MEM, meropenem; IMI, imipenem; ATM, aztreonam; AMK, amikacin; LVX, levofloxacin; NS, nonsusceptible; R, resistant; MDR, multidrug-resistant (resistant to ≥3 sentinel agents [AMK, ATM, FEP, colistin, IMI, LVX, and TZP]); pan-β-lactam-NS, nonsusceptible to all tested β-lactams (excluding C/T, IMR, and CZA); DTR, difficult-to-treat resistance (nonsusceptible to all tested β-lactams, excluding C/T, IMR, and CZA, and fluoroquinolones).

with higher numbers of isolates carrying metallo-β-lactamases (12). The current report provides an update on antimicrobial susceptibility testing results for *P. aeruginosa* isolates submitted to the SMART (Study for Monitoring Antimicrobial Resistance Trends) surveillance program from 2018 to 2020 by clinical laboratories in the United States. We focused our evaluation on the activity of C/T (FDA approved, 2014) and the newer β-lactam/non-β-lactam β-lactamase inhibitor combinations IMR (2019) and CZA (2015) over a time period (2018 to 2020) when the agents were available clinically for use in the United States.

RESULTS

A proportion of 96.4% of all isolates tested were susceptible to C/T compared to 94.4% CZA susceptible and 91.5% IMR-susceptible (Table 1). A proportion of 81.6% of *P. aeruginosa* isolates were susceptible to cefepime, while <80% of isolates were susceptible to the other β-lactams tested and to levofloxacin. Higher percentages of MDR, pan-β-lactam-nonsusceptible, and DTR isolates were susceptible to C/T than to CZA (by 13 to 25%) or to IMR (by 17 to 24%). A proportion of 52.2% of C/T-nonsusceptible isolates were susceptible to IMR compared to 38.9% susceptible for CZA (Table 2). The percent susceptible rate for C/T was 16% higher than that for CZA against IMR-nonsusceptible isolates and 16% higher than that for IMR against CZA-resistant isolates. C/T retained activity against 61.0% of CZA-resistant *P. aeruginosa*, whereas 38.9% of C/T-nonsusceptible isolates were CZA-susceptible. A proportion of 1.7% of isolates tested were nonsusceptible to both C/T and IMR compared to 2.2% of isolates with a C/T-nonsusceptible and CZA-resistant phenotype (a difference of 12 isolates).

Percentages of C/T-susceptible isolates were similar (95.5 to 98.2%) across four United States census regions (see Table S1 and Fig. S1 in the supplemental material). *In vitro* susceptibility to C/T was higher than that to IMR and CZA among all, MDR, pan-β-lactam-nonsusceptible, and DTR *P. aeruginosa* isolates collected in each of the four regions (Table S1, Fig. S1).

Figure 1A to D provides MIC distributions for C/T, IMR, and CZA for all isolates and isolates with specific antimicrobial-nonsusceptible and -resistant phenotypes. Shift or drift in MIC distributions and modal MICs suggest future changes in antimicrobial susceptibility overall or within specific phenotype subgroups. The C/T, IMR, and CZA modal MICs were 0.5, 0.5, and 2 μg/mL, respectively, for all isolates of *P. aeruginosa*. For MDR, pan-β-lactam-nonsusceptible, and DTR phenotypes, the modal MIC for C/T of 2 μg/mL was one doubling dilution below the susceptible MIC breakpoint, and the modal MIC for IMR (2 μg/mL) was at the susceptible IMR MIC breakpoint. The modal MIC for CZA was at its susceptible MIC breakpoint (8 μg/mL) for MDR isolates but was greater than its susceptible MIC breakpoint for both pan-β-lactam-nonsusceptible and DTR isolates (16 μg/mL). The CZA modal MIC for C/T-nonsusceptible isolates was >32 μg/mL (31.1% of isolates) compared to a modal MIC of 2 μg/mL (23.3%) for IMR (Fig. S2). Figure S2 also compares the cumulative percentage of C/T-nonsusceptible isolates inhibited by doubling-dilution increases in IMR and CZA. Of the 90 C/T-nonsusceptible isolates

TABLE 2 Cross-susceptibility to ceftolozane-tazobactam, imipenem-relebactam, and ceftazidime-avibactam among *P. aeruginosa* isolates with different phenotypes[a]

Phenotype	No. (% of all isolates)	Antimicrobial agent, % susceptible		
		C/T	IMR	CZA
C/T-NS	90 (3.6)	0	52.2	38.9
IMR-NS	214 (8.5)	79.9	0	64.0
CZA-R	141 (5.6)	61.0	45.4	0

[a]C/T, ceftolozane-tazobactam; IMR, imipenem-relebactam; CZA, ceftazidime-avibactam; NS, nonsusceptible; R, resistant.

identified in the study, 22 (24.4%) were IMR-susceptible and CZA-resistant, while 10 (11.1%) were IMR-nonsusceptible and CZA-susceptible.

To evaluate *in vitro* activity over time, MIC distributions of C/T, IMR, and CZA against pan-β-lactam-nonsusceptible isolates were compared over the 3-year study period (2018 to 2020) (Fig. 2). Notably, the modal MIC of CZA increased 2-fold from 2018 to 2019 (and remained 2-fold higher in 2020) and exceeded the CZA-susceptible MIC breakpoint in both 2019 and 2020. In comparison, C/T and IMR modal MICs remained at their respective susceptible MIC breakpoints (or one doubling dilution lower for C/T in 2019) from 2018 to 2020. No statistically significant differences in corresponding percent susceptibilities were noted over this 3-year time period ($P > 0.05$, Cochran-Armitage test).

A total of 802 isolates of *P. aeruginosa* were characterized molecularly based upon the

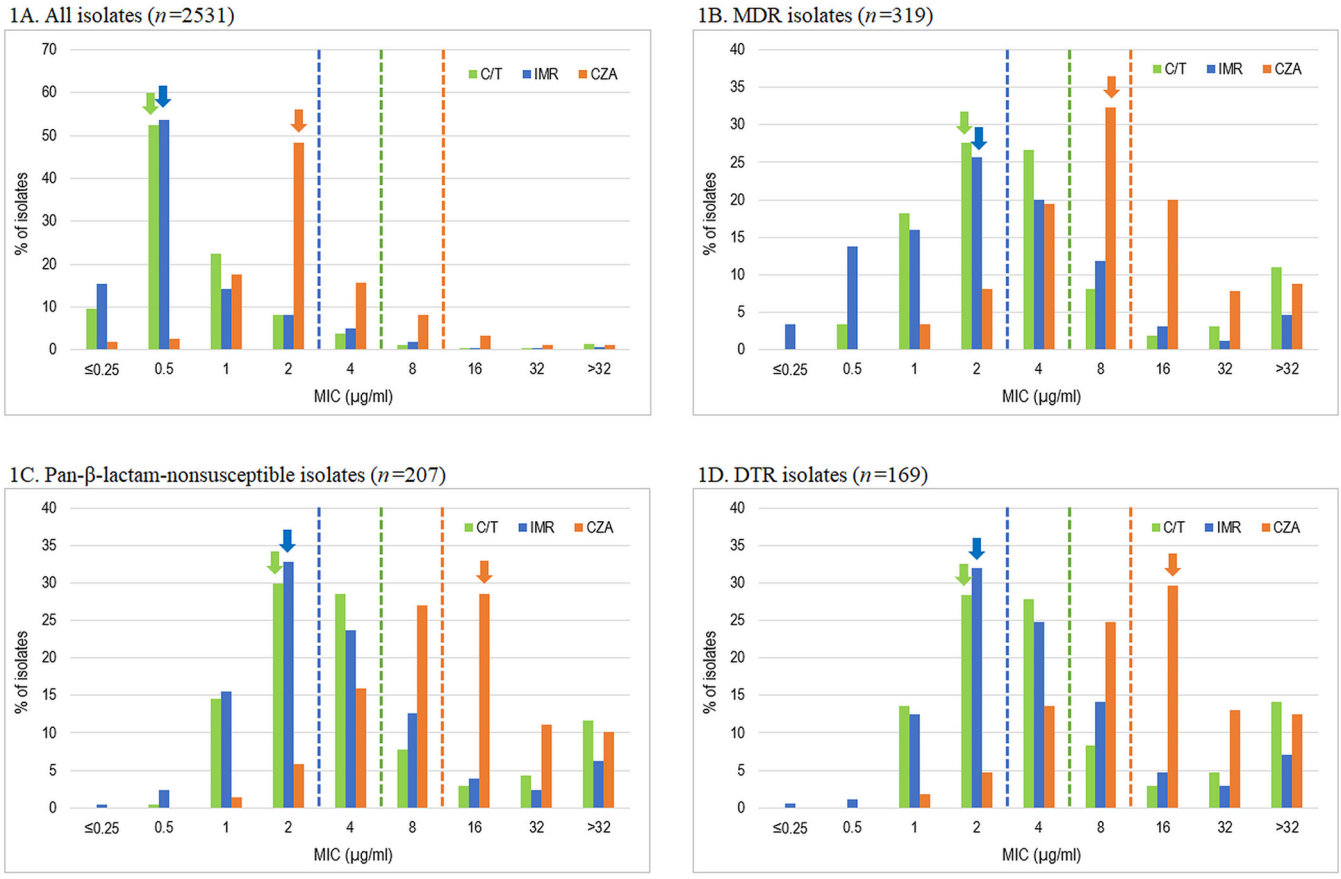

FIG 1 Distribution of ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-relebactam MIC values against all *P. aeruginosa* isolates and resistant subsets. C/T, ceftolozane-tazobactam; IMR, imipenem-relebactam; CZA, ceftazidime-avibactam; MDR, multidrug resistant (resistant to ≥3 sentinel agents [amikacin, aztreonam, cefepime, colistin, imipenem, levofloxacin, and piperacillin-tazobactam]); pan-β-lactam-nonsusceptible, nonsusceptible to all tested β-lactams (excluding C/T, IMR, and CZA); DTR, difficult-to-treat resistance (nonsusceptible to all tested β-lactams [excluding C/T, IMR, and CZA] and fluoroquinolones). Dashed lines indicate the respective susceptible breakpoints. Arrows indicate the mode of the respective MIC distributions.

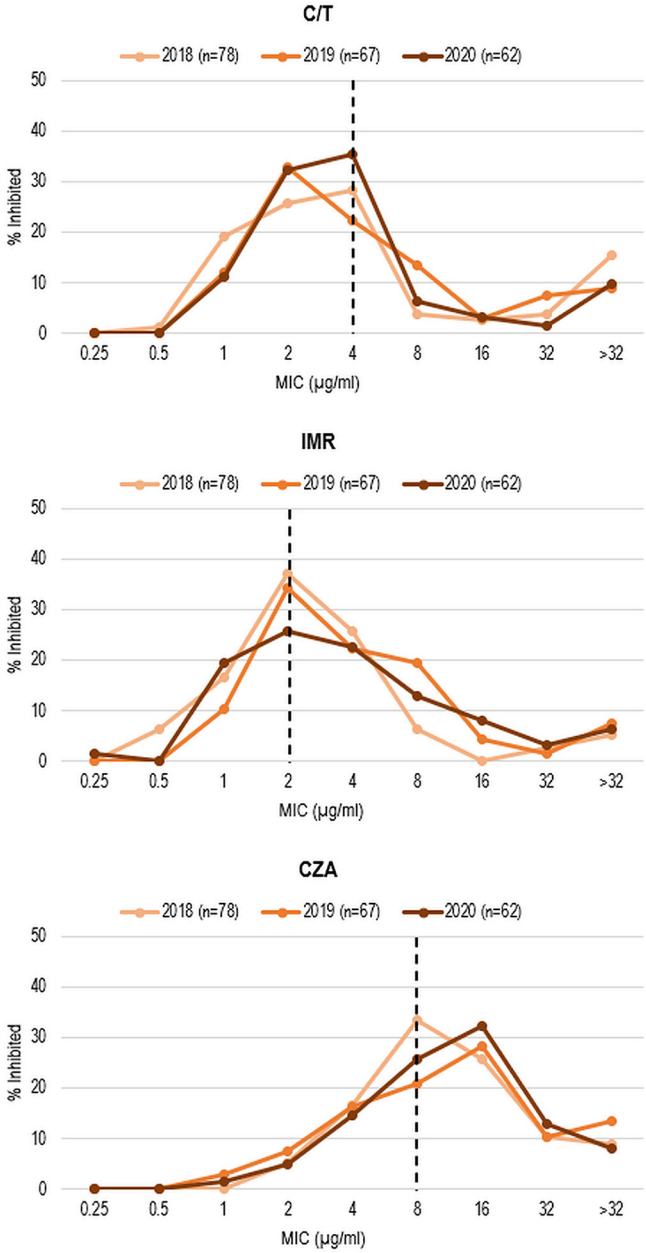

FIG 2 MIC distributions for ceftolozane-tazobactam, imipenem-relebactam, and ceftazidime-avibactam against pan-β-lactam-nonsusceptible *P. aeruginosa* isolates, by year. C/T, ceftolozane-tazobactam; IMR, imipenem-relebactam; CZA, ceftazidime-avibactam. CLSI susceptibility breakpoints are indicated by dashed lines.

selection criteria. In 792 isolates (98.8%), no acquired β-lactamases were detected; in all but one isolate, PDC (*Pseudomonas*-derived cephalosporinase) (AmpC) was detected. Carbapenemases were detected in only 9.9%, 4.1%, 5.9%, and 1.0% of molecularly characterized C/T-nonsusceptible (n = 81), IMR-nonsusceptible (n = 196), CZA-resistant (n = 119), and IMI-nonsusceptible (n = 781) isolates, respectively. Five isolates producing IMP-type metallo-β-lactamases (MBLs) were collected in the West (IMP-13, n = 2; IMP-15, n = 1), Midwest (IMP-13, n = 1), and South (IMP-75, n = 1) regions, and one isolate carrying a VIM-2 MBL was collected in the Midwest. All MBL-positive isolates tested as resistant to C/T, CZA, and IMR. Two isolates carrying GES-type carbapenemases were collected in the West (GES-20 [also carrying a GES-19 ESBL], n = 1; tested as resistant to C/T, CZA, and IMR) and

in the Northeast (GES-5; tested as resistant to IMR, intermediate to C/T, and susceptible to CZA). Two additional isolates carrying only ESBLs were collected in the Northeast (VEB-14, $n = 1$; tested as resistant to C/T and CZA and as intermediate to IMR) and in the Midwest (TEM-type, $n = 1$; tested as resistant to C/T and CZA and as susceptible to IMR) (data not shown).

DISCUSSION

In the current study, 96.4% of *P. aeruginosa* isolates collected from patients in United States hospitals in 2018 to 2020 were susceptible to C/T; >90% of isolates were also susceptible to amikacin (97.0% susceptible), CZA (94.4%), and IMR (91.5%), while other β-lactam agents and levofloxacin had percent susceptible rates of ≤82% (Table 1). In contrast to many regions in the world where carbapenemase rates among resistant *P. aeruginosa* isolates are higher (13, 14), almost all (98.8%) carbapenem-, IMR-, or C/T-nonsusceptible isolates of *P. aeruginosa* did not carry an acquired β-lactamase, including carbapenemases, confirming earlier reports of isolates from United States patients (14, 15).

MDR phenotypes are commonly observed among *P. aeruginosa* isolates in the United States, particularly among isolates from patients with lower respiratory tract infections (2–5). The MDR rate in the current study, 12.6%, was comparable to rates for *P. aeruginosa* isolates tested from U.S. patients in the cited studies. Among these MDR *P. aeruginosa* isolates, 75.9% of isolates were C/T-susceptible compared to 63.3% CZA-susceptible and 58.9% IMR-susceptible. DTR isolates of Gram-negative bacilli are associated with increased therapeutic failure and mortality, especially in severely ill patients (16, 17). In the current study, 6.7% of *P. aeruginosa* isolates were DTR; percent susceptible rates for DTR isolates exceeded 50% only for amikacin (82.8% susceptible) and C/T (69.8% susceptible).

We found subtle but notable differences in the overlap in nonsusceptibility and resistance to C/T, IMR, and CZA (Table 2). We noted among C/T-nonsusceptible isolates that a greater percentage of isolates were IMR-susceptible (52.2%) than CZA-susceptible (38.9%), among IMR-nonsusceptible isolates that C/T was more active (79.9% susceptible) than CZA (64.0%), among CZA-resistant isolates that C/T was more active (61.0%) than IMR (45.4%), and that the CZA modal MIC for C/T-nonsusceptible isolates was >32 μg/mL compared to 2 μg/mL for IMR. Previously, Fraile-Ribot et al. reported 50% (39/78) of C/T-resistant and 61% (51/84) of CZA-resistant isolates that were not carbapenemase producers to be IMR-susceptible (18), similar to results in the current study (Table 2). We also observed that C/T and IMR modal MICs for pan-β-lactam-nonsusceptible isolates remained at or below their respective susceptible MIC breakpoints from 2018 to 2020, while the modal MIC for CZA increased 2-fold from 2018 to 2019 and exceeded the CZA-susceptible MIC breakpoint in both 2019 and 2020 (Fig. 2), although the corresponding annual percent susceptible values for each agent did not change significantly.

In the current study, 98.3% of all isolates were C/T-susceptible and/or IMR-susceptible, compared to 97.8% of all isolates being C/T-susceptible and/or CZA-susceptible (a difference of 12 isolates). This difference, although slight (0.5% of isolates), suggests a greater propensity for nonoverlapping mechanisms of resistance between C/T and IMR than between C/T and CZA. These observations align with the reports of sporadic isolates of *P. aeruginosa* that developed cross-resistance to C/T, CZA, and/or cefiderocol during therapy due to amino acid substitutions, insertions, and/or deletions within the Ω-loop of AmpC (PDC) or adjacent AmpR regions (R1 and R2) (sometimes in combination with the ESBLs PER-1, GES-2, and OXA-15) but that maintain susceptibility to or result in lower MICs for IMR and/or piperacillin-tazobactam (18–23).

Ceftolozane is a poor inducer of AmpC (PDC) production (24, 25). In addition, it is only slowly hydrolyzed, if at all, by most AmpC β-lactamases (24, 25). Tazobactam is also a poor inducer of AmpC production; however, tazobactam becomes a poor inhibitor in the presence of high levels of AmpC (24–26). OprD loss, derepression/hyperproduction of AmpC, and MexAB/OprM efflux are not associated with C/T resistance (15).

In comparison, CZA resistance mechanisms in *P. aeruginosa* may also be related to AmpC derepression and increased expression of RND (resistance-nodulation-division) efflux pumps (e.g., MexAB-OprM).

A single study of 46 isolates of CZA-resistant *P. aeruginosa* collected from United States hospitals in 2015 suggested that a complex combination of MexAB-OprM overexpression and mutations in efflux regulators, penicillin-binding proteins (PBPs), and chaperone proteins was responsible for resistance; AmpC Ω-loop mutations were rarely associated with CZA resistance in this set of isolates (27). However, several other studies have shown that mutations in the Ω-loop broaden the AmpC binding pocket to permit cephalosporins with bulkier R2 side chains (such as the 2-methyl-3-aminopyrazolium of ceftolozane) to enter, resulting in increased catalysis of both ceftazidime and ceftolozane (28, 29). Mutations in the Ω-loop also reduce the affinity of the AmpC binding pocket for avibactam (28). These AmpC structural modifications are also hypothesized to enable carbapenems to rotate their bulky 6α-hydroxyethyl side chain within the AmpC binding pocket to prevent hydrolysis (30). Imipenem is not effluxed by the MexAB/OprM efflux pump or affected significantly by AmpC overexpression but is affected by OprD porin loss with concomitant AmpC hyperexpression (31). These properties suggest that IMR is an option for rescue therapy in cases of pseudomonal infection where C/T and CZA resistance arises during therapy.

Based on *in vitro* testing of current (2018 to 2020) clinical isolates of *P. aeruginosa* collected in the United States, C/T remains highly active and provides an important treatment option for patients with infections caused by antimicrobial-nonsusceptible and -resistant *P. aeruginosa*. C/T was the most active antipseudomonal β-lactam/β-lactamase inhibitor combination tested, and IMR demonstrated greater activity than CZA against C/T-nonsusceptible isolates.

MATERIALS AND METHODS

Bacterial isolates. Twenty-four medical laboratories in 16 states in the United States collected 14,177 isolates of Gram-negative bacilli from 2018 to 2020 as part of the SMART surveillance program; 2,351 (16.6%) of these isolates were *P. aeruginosa*. Bloodstream (n = 237, 9.4% of isolates), intra-abdominal (n = 255, 10.1%), lower respiratory tract (n = 1,781, 70.4%), and urinary tract (n = 258, 10.2%) infection specimens accounted for the *P. aeruginosa* collected. All isolates were sent to IHMA (Schaumburg, IL), where organism identity was confirmed using matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Billerica, MA).

Antimicrobial susceptibility testing. The CLSI broth microdilution method was used to determine MICs (32, 33) at IHMA on in-house-prepared panels. Avibactam was obtained from Advanced ChemBlocks, Inc. (Burlingame, CA); ceftolozane, imipenem, and relebactam from Merck & Co., Inc. (Kenilworth, NJ); and tazobactam from USP. Other antimicrobial agents were purchased from commercial sources. Cefiderocol is not an agent currently tested by the SMART surveillance program and meropenem-vaborbactam was not tested in 2018, but vaborbactam was not expected to improve the activity of meropenem against *P. aeruginosa* (34).

MICs were interpreted using 2021 CLSI breakpoints (32). MDR isolates were resistant to three or more of the following seven sentinel antimicrobial agents: amikacin, aztreonam, cefepime, colistin, imipenem, levofloxacin, and piperacillin-tazobactam. Pan-β-lactam-nonsusceptible isolates were nonsusceptible (intermediate or resistant MICs) to all traditional β-lactams tested (aztreonam, ceftazidime, cefepime, piperacillin-tazobactam, imipenem, and meropenem); this definition excluded C/T, IMR, and CZA. DTR isolates were nonsusceptible to all tested traditional β-lactams (excluding C/T, IMR, and CZA) and fluoroquinolones (ciprofloxacin [tested only in 2018] and levofloxacin) (16).

Screening for β-lactamase genes. Isolates testing as nonsusceptible to imipenem (MIC of $\geq$4 μg/mL), IMR (MIC of $\geq$4 μg/mL), or C/T (MIC of $\geq$8 μg/mL) were screened for the presence of genes encoding ESBLs, acquired AmpC β-lactamases, PDC (*Pseudomonas*-derived cephalosporinase), serine carbapenemases, and metallo-β-lactamases using published multiplex PCR assays and sequencing (Sanger) as previously described (35, 36). For *P. aeruginosa* collected in 2020 only, C/T-nonsusceptible, imipenem-nonsusceptible, and IMR-nonsusceptible isolates were characterized by short-read whole-genome sequencing (2 $\times$ 150 bp reads; Illumina HiSeq) and analyzed using CLC Genomics Workbench (Qiagen) (37). Of 885 isolates that met the molecular testing criteria, 82 randomly selected isolates collected in 2020 were not characterized. One isolate collected in 2018 that met the molecular testing criteria was also not characterized.

Data availability. Data are available on request.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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The sponsor participated in the development of the overall study design, but collection and testing of isolates, data analysis, and manuscript preparation were independently performed by IHMA.

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