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Ceftolozane-Tazobactam Activity against *Pseudomonas aeruginosa* Clinical Isolates from U.S. Hospitals: Report from the PACTS Antimicrobial Surveillance Program, 2012 to 2015

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ABSTRACT The activity of ceftolozane-tazobactam was compared to the activities of 7 antimicrobials against 3,851 *Pseudomonas aeruginosa* isolates collected from 32 U.S. hospitals in the Program to Assess Ceftolozane-Tazobactam Susceptibility from 2012 to 2015. Ceftolozane-tazobactam and comparator susceptibilities were determined using the CLSI broth microdilution method at a central monitoring laboratory. For ceftolozane-tazobactam, 97.0% of the isolates were susceptible. Susceptibilities of the other antibacterials tested were: amikacin, 96.9%; cefepime, 85.9%; ceftazidime, 85.1%; colistin, 99.2%; levofloxacin, 76.6%; meropenem, 81.8%; and piperacillin-tazobactam, 80.4%. Of the 699 (18.1%) meropenem-nonsusceptible *P. aeruginosa* isolates, 87.6% were susceptible to ceftolozane-tazobactam. Six hundred seven isolates (15.8%) were classified as multidrug resistant (MDR), and 363 (9.4%) were classified as extensively drug resistant (XDR). Only 1 isolate was considered pandrug resistant, which was resistant to all tested agents, including colistin. Of the 607 MDR isolates, 84.9% were ceftolozane-tazobactam susceptible, and 76.9% of XDR isolates were ceftolozane-tazobactam susceptible. *In vitro* activity against drug-resistant *P. aeruginosa* indicates ceftolozane-tazobactam may be an important agent in treating serious bacterial infections.

KEYWORDS *Pseudomonas aeruginosa*, ceftolozane-tazobactam, United States, susceptibility, MDR, XDR

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Pseudomonas aeruginosa remains an important cause of hospital-acquired infections in the United States and is frequently multidrug resistant (MDR) (1). Zilberberg and Shorr found that MDR *P. aeruginosa* was much more common in bloodstream infections (14.7%) and pneumonia (22.0%) than carbapenem-resistant *Enterobacteriaceae* from bloodstream infections (1.1%) and pneumonia (1.6%) (1), which makes treating serious *P. aeruginosa* infections more challenging. Furthermore, the delay of appropriate antimicrobial therapy has been associated with increased morbidity and mortality. Patients with MDR *P. aeruginosa* have a higher 30-day mortality than patients with non-MDR *P. aeruginosa* (2).

Frequently, MDR *P. aeruginosa* infections are resistant to carbapenems and other beta-lactams. *P. aeruginosa* resistance to beta-lactams is mediated through multiple mechanisms, including the acquisition of metallo-beta-lactamases, an increased production of chromosomal AmpC, an increased efflux, and changes in membrane permeability (3, 4).

Ceftolozane is a novel cephalosporin with enhanced activity against *P. aeruginosa* and is combined with the well-described beta-lactamase inhibitor tazobactam. Ceftolozane-tazobactam has been shown to be safe and effective in treating compli-

cated urinary tract infections and complicated intra-abdominal infections (in combination with metronidazole) caused by Gram-negative organisms, including *P. aeruginosa*. Ceftolozane-tazobactam (Zerbaxa; Merck & Co. Inc., Whitehouse Station, NJ) was approved for use by the U.S. Food and Drug Administration (FDA) in 2014 and by the European Medicines Agency in 2015. This combination has been shown to have good *in vitro* activity against MDR *P. aeruginosa* (5).

In this study, we described the activity of ceftolozane-tazobactam and comparators against 3,851 isolates of *P. aeruginosa* collected from 32 U.S. hospitals in the Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) from 2012 to 2015, including isolates that were categorized as MDR or extensively drug resistant (XDR) and isolates categorized as resistant to other beta-lactams and other beta-lactamase inhibitor combinations (6).

RESULTS

Colistin and ceftolozane-tazobactam were the most active agents against 3,851 *P. aeruginosa* isolates. Susceptibilities are shown in Table 1 and ranged from 99.2% for colistin (MIC_{50}/MIC_{90}, 1/2 μg/ml), 97.0% for ceftolozane-tazobactam (MIC_{50}/MIC_{90}, 0.5/2 μg/ml), and 96.9% for amikacin (MIC_{50}/MIC_{90}, 2/8 μg/ml) to 76.6% for levofloxacin (MIC_{50}/MIC_{90}, 0.5/$>$4 μg/ml), and 81.8% of isolates were susceptible to meropenem (MIC_{50}/MIC_{90}, 0.5/8 μg/ml).

When comparing susceptibilities of meropenem-nonsusceptible isolates, 87.6% of isolates were susceptible to ceftolozane-tazobactam (Table 1). The 2 most active agents against meropenem-nonsusceptible isolates were colistin (98.7%) and amikacin (90.3%). A total of 241 isolates (6.3%) were nonsusceptible to the 4 beta-lactam comparators tested in this study, cefepime, ceftazidime, meropenem, and piperacillin-tazobactam (Table 1). Of these multiple beta-lactam-nonsusceptible isolates, 68.0% were susceptible to ceftolozane-tazobactam. For other drug classes, 20.3% were susceptible to levofloxacin, 82.2% were susceptible to amikacin, and 98.8% were susceptible to colistin. For MDR isolates (Table 1), 84.0% were susceptible to ceftolozane-tazobactam. Only amikacin and colistin were more active with 87.0% and 98.5% susceptibilities, respectively.

Finally, for 363 XDR isolates (Table 1), ceftolozane-tazobactam was the most active beta-lactam with 76.9% susceptibility (MIC_{50}/MIC_{90}, 2/16 μg/ml). Only 7.2% of XDR isolates were susceptible to piperacillin-tazobactam, 6.3% were susceptible to levofloxacin, and 12.1% were susceptible to meropenem. The 2 most active agents against XDR *P. aeruginosa* were amikacin with 82.4% susceptibility and colistin with 98.1% susceptibility. The single pandrug-resistant strain was resistant to all agents tested, including colistin (data not shown).

Table 2 shows the ceftolozane-tazobactam MIC distribution of activity over the 4-year surveillance period. No increase in the MIC_{50} or MIC_{90} and little change in the MIC distributions were observed. The MIC_{90} remained below the susceptible breakpoint of $\leq$4.0 μg/ml for the 4-year period.

Ceftolozane-tazobactam susceptibility and MIC distributions in the 9 U.S. Census divisions were also examined (Table 3). Susceptibilities in all divisions were $>$94% and ranged from 99.6% in the West North Central division to 94.3% in the Pacific division. No trends were observed in the number of ceftolozane-tazobactam-resistant isolates in any division for the 4 years in the study period. The 12 resistant isolates in the Mid-Atlantic division were isolated across the 4-year period and were from 3 different institutions, suggesting that they were not epidemiologically related.

As mentioned, *P. aeruginosa* isolates were isolated from various culture sources, including blood, respiratory, and wound infections. The susceptibility rate to ceftolozane-tazobactam was $>$96% for all culture sources (data not shown). Susceptibility rates between isolates from intensive care unit (ICU) patients and non-ICU patients did not differ significantly for ceftolozane-tazobactam at $>$96% for both patient populations.

TABLE 1 Activity of ceftolozane-tazobactam and comparators against 3,851 *P. aeruginosa* isolates from the United States (2012 to 2015)

Antimicrobial agent	MIC (μg/ml)			Susceptibility[a] (%)		
	50%	90%	Range	S	I	R
All isolates (n =3,851)						
Ceftolozane-tazobactam	0.5	2	0.03 to >32	97.0	1.6	1.3
Amikacin	2	8	≤0.25 to >32	96.9	1.2	1.8
Cefepime	2	16	≤0.5 to >16	85.9	8.0	6.1
Ceftazidime	2	32	≤0.25 to >32	85.1	3.9	11.0
Colistin	1	2	≤0.5 to >8	99.2	0.7	0.1
Levofloxacin	0.5	>4	≤0.12 to >4	76.6	6.2	17.3
Meropenem	0.5	8	≤0.06 to >8	81.8	5.6	12.5
Piperacillin-tazobactam	4	>64	≤0.5 to >64	80.4	9.4	10.2
Meropenem-nonsusceptible isolates (n = 699)						
Ceftolozane-tazobactam	1	8	0.25 to >32	87.6	6.0	6.4
Amikacin	4	16	0.25 to >32	90.3	3.9	5.9
Cefepime	8	>16	1 to >16	50.5	24.7	22.7
Ceftazidime	8	>32	1 to >32	55.1	10.3	34.6
Colistin	1	2	≤0.5 to >8	98.7	1.0	0.3
Levofloxacin	>4	>4	≤0.12 to >4	33.5	12.3	54.2
Meropenem	8	>8	4 to >8	0.0	31.0	69.0
Piperacillin-tazobactam	32	>64	≤0.5 to >64	41.8	25.9	32.3
Nonsusceptible to cefepime, ceftazidime, meropenem, and piperacillin-tazobactam (n = 241)						
Ceftolozane-tazobactam	4	>32	0.5 to >32	68.0	16.2	15.8
Amikacin	8	>32	≤0.25 to >32	82.2	6.6	11.2
Cefepime	>16	>16	16 to >16	0.0	42.3	57.7
Ceftazidime	>32	>32	16 to >32	0.0	12.9	87.1
Colistin	1	2	≤0.5 to >8	98.8	0.8	0.4
Levofloxacin	>4	>4	≤0.12 to >4	20.3	13.3	66.4
Meropenem	>8	>8	4 to >8	0.0	16.6	83.4
Piperacillin-tazobactam	>64	>64	32 to >64	0.0	22.8	77.2
MDR (n = 607)						
Ceftolozane-tazobactam	2	8	0.25 to >32	84.0	7.7	8.2
Amikacin	8	32	≤0.25 to >32	97.0	4.9	8.1
Cefepime	16	>16	1 to >16	32.6	36.2	31.1
Ceftazidime	16	>32	0.5 to >32	33.8	16.3	49.9
Colistin	1	2	≤0.5 to >8	98.5	1.2	0.3
Levofloxacin	>4	>4	≤0.12 to >4	18.3	15.0	66.7
Meropenem	8	>8	≤0.06 to >8	23.1	17.0	60.0
Piperacillin-tazobactam	64	>64	0.5 to >64	19.8	33.6	46.6
XDR (n = 363)						
Ceftolozane-tazobactam	2	16	0.25 to >32	76.9	10.5	12.7
Amikacin	8	>32	≤0.25 to >32	82.4	6.3	11.3
Cefepime	16	>16	2 to >16	17.1	41.3	41.6
Ceftazidime	32	>32	1 to >32	23.7	14.9	61.4
Colistin	1	2	≤0.5 to >8	98.1	1.4	0.6
Levofloxacin	>4	>4	≤0.12 to >4	6.3	15.7	78.0
Meropenem	8	>8	0.12 to >8	12.1	16.3	71.6
Piperacillin-tazobactam	>64	>64	2 to >64	7.2	35.5	57.3

[a]According to the Clinical and Laboratory Standards Institute, 2016 (15). S, susceptible; I, intermediate; R, resistant.

DISCUSSION

Population-based surveys conducted in the United States have documented an increasing resistance among Gram-negative bacilli in a large proportion of medical facilities (7–9). Prominent among the resistant species are MDR strains of *P. aeruginosa* (7, 8). In the United States, *P. aeruginosa* is the second most frequent cause of ventilator-associated pneumonia and the third most frequent cause of catheter-associated urinary tract infection (8). The MDR nature of *P. aeruginosa* has been shown

TABLE 2 Ceftolozane-tazobactam MIC distribution for each year of the 4-year surveillance period

Year	No. of isolates at MIC (μg/ml) of:												Total no.	% susceptible	MIC (μg/ml)	
	0.03	0.06	0.12	0.25	0.5	1	2	4[a]	8	16	32	>32			50%	90%
2015	1	3	9	215	449	120	31	18	8	2	1	6	863	98.0	0.5	1
2014			8	51	491	229	62	35	18	3	4	8	909	96.4	0.5	2
2013	2	1	6	43	593	263	94	40	20	6	1	12	1,081	96.4	0.5	2
2012		2	2	39	546	256	73	55	17	3	1	4	998	97.5	0.5	2

[a]CLSI breakpoints: S, ≤4 μg/ml; I, 8 μg/ml; R, ≥16 μg/ml.

to reduce the likelihood of appropriate (active *in vitro*) initial antimicrobial therapy (10, 11). Delaying the initiation of appropriate antimicrobial therapy is well established as being associated with increased morbidity and mortality in patients with severe *P. aeruginosa* infections (2, 10). Clinical outcomes have not been shown to improve if the initial therapy is with an inactive agent against the infecting pathogen and later changed to an active agent, underscoring the importance of starting therapy with an active agent against the infecting pathogen (2, 10, 12). These findings support the need for a treatment option with a high degree of antipseudomonal activity in hospital settings where the risk of infection with *P. aeruginosa* is elevated (13).

The results in this study confirm and expand the previously reported activity of ceftolozane-tazobactam against *P. aeruginosa* isolates from the United States (5). Although colistin was more active, ceftolozane-tazobactam had activity similar to that of amikacin overall and was the most active beta-lactam tested. It maintained very good activity against meropenem-nonsusceptible isolates (87.6% susceptible) and isolates that were nonsusceptible to multiple beta-lactams (68.0% susceptible). More importantly, ceftolozane-tazobactam retained good activity against MDR (84.0% susceptible) and XDR (76.9% susceptible) *P. aeruginosa* isolates. Only 51 isolates were ceftolozane-tazobactam resistant, 96.1% were colistin susceptible, 60.8% were amikacin susceptible, and <12% were susceptible to the remaining comparators.

The *in vitro* activity of ceftolozane-tazobactam has remained excellent following FDA approval in 2014. No differences in susceptibility rates between culture sources or ICU versus non-ICU isolates were observed. While all U.S. Census divisions had very high rates of susceptibility to ceftolozane-tazobactam, some variations were observed between divisions that suggest continued surveillance of regional resistance rates is required.

In summary, these data for ceftolozane-tazobactam susceptibility based on a large number of recent U.S. *P. aeruginosa* isolates collected from 2012 to 2015 demonstrate that it is a potent antipseudomonal cephalosporin/beta-lactamase inhibitor combination. This potent activity supports the use of ceftolozane-tazobactam as an important therapy to be considered for early use in seriously ill patients with *P. aeruginosa* infections, including those with MDR and XDR infections.

TABLE 3 Ceftolozane-tazobactam MIC distributions and susceptibility in U.S. Census divisions for 2012 to 2015

U.S. Census region[a]	No. of isolates at MIC (μg/ml) of:												Total no.	% susceptible
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
1. New England	2	2	11	34	219	102	26	13	1	3	2	3	418	97.8
2. Mid-Atlantic		1	1	53	273	103	44	25	8			12	520	96.2
3. East North Central			2	62	311	132	32	24	12	2	1	2	580	97.1
4. West North Central				42	274	101	17	15		1		1	451	99.6
5. South Atlantic	1	1	3	66	330	134	43	33	17			1	629	97.1
6. East South Central		1		17	150	60	23	8	6			1	266	97.4
7. West South Central			1	36	236	87	30	16	4	5	1	4	420	96.7
8. Mountain			1	14	103	41	13	3	3		2		180	97.2
9. Pacific		1	6	24	183	108	32	11	12	3	1	6	387	94.3

[a]States in each U.S. Census Bureau division are: 1, Connecticut, Maine, Massachusetts, Rhode Island, and Vermont; 2, New Jersey, New York, and Pennsylvania; 3, Indiana, Illinois, Michigan, Ohio, and Wisconsin; 4, Iowa, Missouri, Nebraska, North Dakota, and South Dakota; 5, Delaware, DC, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia; 6, Alabama, Kentucky, Mississippi, and Tennessee; 7, Arkansas, Louisiana, Oklahoma, and Texas; 8, Arizona, Colorado, Idaho, New Mexico, Montana, Utah, Nevada, and Wyoming; 9, Alaska, California, Hawaii, Oregon, and Washington.

MATERIALS AND METHODS

A total of 3,851 nonduplicate *P. aeruginosa* isolates were collected prospectively from 32 medical centers in the United States. Participant centers submit clinical bacterial organisms (one per infection episode) that were consecutively collected by infection type according to a common protocol, which established the number of isolates for the target infection types and the period of time the isolates should be collected. Each institution contributed either 500 or 250 isolates per year with approximately 50 isolates per target infection type. Isolates were from patients with bloodstream infections (413 isolates [10.7%]), pneumonia (1,985 isolates [51.5%]), skin and skin structure infections (648 isolates [16.8%]) urinary tract infections (236 isolates [6.1%]), intra-abdominal infections (243 isolates [6.3%]), and other types of infections (326 isolates [8.5%]). Isolates were identified at each medical center and confirmed by the central laboratory (JMI Laboratories, North Liberty, IA) using a matrix-assisted laser desorption ionization–time of flight technology mass spectrometer (Bruker, Billerica, MA).

MICs for all antibiotics were determined using frozen broth microdilution panels according to Clinical and Laboratory Standards Institute (CLSI) standards (14). All MIC testing for ceftolozane-tazobactam and piperacillin-tazobactam used a fixed tazobactam concentration of 4 μg/ml. Quality control and interpretation of results were performed according to CLSI M100-S26 (15). All MIC results for ATCC quality control strains were within published ranges.

Isolates were considered meropenem nonsusceptible if their MIC was $\geq$4 μg/ml, ceftazidime or cefepime nonsusceptible if their MIC was $\geq$16 μg/ml, and piperacillin-tazobactam nonsusceptible if their MIC was $\geq$32 μg/ml. Isolates were classified as MDR (nonsusceptible to at least 1 agent in $\geq$3 antimicrobial categories), XDR (nonsusceptible to at least 1 agent in all but 2 or fewer antimicrobial categories), or pandrug resistant (nonsusceptible to all agents in all antimicrobial categories) based on CLSI criteria as described in Magiorakos et al. (6).

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