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In Vitro Activity of Ceftolozane-Tazobactam and Other Antimicrobial Agents against *Burkholderia cepacia* Complex and *Burkholderia gladioli*

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ABSTRACT We tested the activities of ceftolozane-tazobactam and 13 other antimicrobial agents against 221 strains of *Burkholderia cepacia* complex and *Burkholderia gladioli*. Most strains (82%) were cultured from persons with cystic fibrosis, and most (85%) were recovered since 2011. The ceftolozane-tazobactam MIC was ≤8 μg/ml for 77% of the strains. However, the MIC range was broad (≤0.5 to >64 μg/ml; $MIC_{50/90}$, 2/32 μg/ml). Significant differences in susceptibility to some antimicrobial agents were observed between species.

KEYWORDS *Burkholderia*, ceftolozane, cystic fibrosis

The 20 species in the *Burkholderia cepacia* complex (Bcc) and the closely related species *Burkholderia gladioli* are Gram-negative nonfermenting bacilli that cause opportunistic infections in susceptible hosts, particularly persons with cystic fibrosis (CF) or chronic granulomatous disease. Respiratory tract infection with *Burkholderia cenocepacia*, *Burkholderia multivorans* (both members of the Bcc), or *B. gladioli* accounts for the majority of *Burkholderia* infections in CF patients (1). Infection is often refractory to therapy, as most *Burkholderia* strains are resistant to available antimicrobial agents. Thus, there is a need to explore the utility of newer antimicrobials for their activity against *Burkholderia* species.

Ceftolozane-tazobactam is a combination cephalosporin-beta lactamase inhibitor approved by the Food and Drug Administration in 2014 for treatment of complicated intra-abdominal and complicated urinary tract infections. It has been shown to have good activity against antimicrobial-resistant Gram-negative pathogens, including *Enterobacteriaceae* and *Pseudomonas aeruginosa* (2–5). Studies evaluating ceftolozane-tazobactam activity against bacteria recovered from patients with CF have been limited (2, 6), and we are aware of no studies that specifically focused on activity against *Burkholderia* species. Further, no data have been published regarding differences in susceptibilities to ceftolozane-tazobactam between species within the Bcc.

We tested the activities of ceftolozane-tazobactam and 13 comparator antimicrobial agents against 221 Bcc and *B. gladioli* isolates from the strain collection of the *Burkholderia cepacia* Research Laboratory and Repository at the University of Michigan. All strains had been identified to the species level using genetically based methods previously described (7), and all were distinct by genotyping analyses (8). The strains were recovered from 221 patients receiving care in 122 medical centers in 91 cities in 41 U.S. states and Toronto, Ontario, Canada. Most strains (82%) were recovered from respiratory specimens from CF patients. All were recovered between 2005 and 2016, with the majority (85%) being isolated between 2011 and 2016. The distribution of *Burkholderia* species included in this set reflected that found in CF patients; *B. cenoce-*

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TABLE 1 Activities of ceftolozane-tazobactam and comparator agents against *Burkholderia* strains

Species or group (n^a)	Antibiotic(s)	MICs (μg/ml)		
		Range	MIC_{50}	MIC_{90}
Burkholderia, all isolates (221)	Ceftolozane-tazobactam	≤0.25 to >64	2	32
	Amikacin	≤16 to >64	64	>64
	Aztreonam	≤4 to >32	16	>32
	Ceftazidime	≤0.5 to >64	4	16
	Chloramphenicol	≤8 to >32	16	32
	Ciprofloxacin	≤2 to >8	≤2	>8
	Doripenem	≤1 to >8	4	8
	Levofloxacin	≤1 to >8	≤1	>8
	Meropenem	≤1 to >16	2	8
	Minocycline	≤1 to >16	2	8
	Piperacillin-tazobactam	≤4 to >128	≤4	128
	Tigecycline	≤2 to 16	≤2	8
	Tobramycin	≤2 to >16	>16	>16
	Trimethoprim-sulfamethoxazole	≤1 to >8	≤1	2
Burkholderia multivorans (50)	Ceftolozane-tazobactam	0.5 to >64	1	>64
	Amikacin	≤16 to >64	64	>64
	Aztreonam	≤4 to >32	≤4	>32
	Ceftazidime	1 to >64	2	64
	Chloramphenicol	≤8 to >32	≤8	32
	Ciprofloxacin	≤2 to >8	≤2	>8
	Doripenem	≤1 to >8	4	8
	Levofloxacin	≤1 to >8	≤1	>8
	Meropenem	≤1 to >16	4	>16
	Minocycline	≤1 to 16	<1	4
	Piperacillin-tazobactam	≤4 to >128	≤4	>128
	Tigecycline	≤2 to 16	≤2	8
	Tobramycin	≤2 to >16	>16	>16
	Trimethoprim-sulfamethoxazole	≤1 to 8	≤1	2
Burkholderia cenocepacia (42)	Ceftolozane-tazobactam	≤0.25 to >64	1	32
	Amikacin	≤16 to >64	>64	>64
	Aztreonam	≤4 to >32	16	>32
	Ceftazidime	1 to >64	4	16
	Chloramphenicol	≤8 to >32	16	>32
	Ciprofloxacin	≤2 to >8	≤2	>8
	Doripenem	≤1 to >8	4	>8
	Levofloxacin	≤1 to >8	2	>8
	Meropenem	≤1 to 16	2	8
	Minocycline	≤1 to >16	2	16
	Piperacillin-tazobactam	≤4 to >128	8	128
	Tigecycline	≤2 to 16	≤2	16
	Tobramycin	8 to >16	>16	>16
	Trimethoprim-sulfamethoxazole	≤1 to 8	≤1	4
Burkholderia vietnamiensis (22)	Ceftolozane-tazobactam	≤0.25 to 32	1	4
	Amikacin	≤16 to >64	≤16	>64
	Aztreonam	≤4 to >32	≤4	16
	Ceftazidime	1 to 16	2	4
	Chloramphenicol	≤8 to >32	16	>32
	Ciprofloxacin	≤2 to >8	≤2	4
	Doripenem	≤1 to 8	≤1	4
	Levofloxacin	≤1 to >8	2	8
	Meropenem	≤1 to 4	≤1	4
	Minocycline	≤1 to 8	2	4
	Piperacillin-tazobactam	≤4 to 128	≤4	16
	Tigecycline	≤2 to >16	≤2	4
	Tobramycin	≤2 to >16	8	>16
	Trimethoprim-sulfamethoxazole	≤1 to >8	≤1	8
Burkholderia cepacia (22)	Ceftolozane-tazobactam	0.5 to 4	1	4
	Amikacin	32 to >64	32	>64
	Aztreonam	8 to >32	16	>32
	Ceftazidime	2 to 16	4	8

(Continued on following page)

TABLE 1 (Continued)

Species or group (n^a)	Antibiotic(s)	MICs (μg/ml)		
		Range	MIC_{50}	MIC_{90}
	Chloramphenicol	≤8 to >32	16	32
	Ciprofloxacin	≤2 to 4	≤2	≤2
	Doripenem	4 to 8	4	8
	Levofloxacin	≤1 to 8	2	4
	Meropenem	2 to 8	4	4
	Minocycline	≤1 to 16	2	4
	Piperacillin-tazobactam	≤4 to 128	8	32
	Tigecycline	≤2 to 16	≤2	4
	Tobramycin	16 to >16	>16	>16
	Trimethoprim-sulfamethoxazole	≤1	≤1	≤1
Other Bcc spp.[b] (39)	Ceftolozane-tazobactam	≤0.25 to >64	2	16
	Amikacin	≤16 to >64	64	>64
	Aztreonam	≤4 to >32	16	>32
	Ceftazidime	≤0.5 to >64	4	16
	Chloramphenicol	≤8 to >32	16	32
	Ciprofloxacin	≤2 to >8	≤2	4
	Doripenem	≤1 to >8	4	8
	Levofloxacin	≤1 to >8	≤1	4
	Meropenem	≤1 to >16	4	8
	Minocycline	≤1 to >16	2	8
	Piperacillin-tazobactam	≤4 to 128	8	128
	Tigecycline	≤2 to 16	≤2	8
	Tobramycin	≤2 to >16	>16	>16
	Trimethoprim-sulfamethoxazole	≤1 to 4	≤1	≤1
Burkholderia gladioli (46)	Ceftolozane-tazobactam	2 to 32	8	16
	Amikacin	≤16 to 64	≤16	≤16
	Aztreonam	16 to >32	32	>32
	Ceftazidime	1 to 64	16	16
	Chloramphenicol	≤8 to >32	32	32
	Ciprofloxacin	≤2 to >8	≤2	≤2
	Doripenem	≤1 to 4	≤1	2
	Levofloxacin	≤1 to >8	≤1	2
	Meropenem	≤1 to 8	≤1	2
	Minocycline	≤1 to 16	2	4
	Piperacillin-tazobactam	≤4 to 64	≤4	≤4
	Tigecycline	≤2 to 16	≤2	≤2
	Tobramycin	≤2 to >16	≤2	≤2
	Trimethoprim-sulfamethoxazole	≤1 to 2	≤1	≤1

[a]Number tested in each category.
[b]Includes (number of isolates) *Burkholderia contaminans* (11), *Burkholderia dolosa* (10), *Burkholderia ambifaria* (9), and *Burkholderia stabilis* (9).

pacia, *B. multivorans*, and *B. gladioli* accounted for 62% of the strains (1). Ceftolozane-tazobactam MIC values were determined, in triplicate, using the reference Clinical and Laboratory Standards Institute broth microdilution method (9), and custom-dried antibiotic plates were read on a Sensititre ARIS instrument (Thermo Scientific).

The results of susceptibility testing are summarized in Table 1. Ceftolozane-tazobactam demonstrated good overall activity (MIC_{50}, 2 μg/ml; MIC_{90}, 32 μg/ml) against the 221 *Burkholderia* strains tested. Although the range of inhibitory activities was broad (MIC range, ≤0.25 to >64 μg/ml), 77% of the strains were inhibited by concentrations of ≤8 μg/ml, which was comparable to the activity demonstrated by ceftazidime, arguably the most relevant drug among the comparator agents tested; 76% of the strains were susceptible (MICs, ≤8 μg/ml) to ceftazidime. Further, ceftolozane-tazobactam was at least 2-fold more active than ceftazidime against 82% of ceftazidime-susceptible strains and at least 4-fold more active against 33% of these strains (Fig. 1). In contrast, ceftazidime was at least 2-fold more active than ceftolozane-tazobactam against only 5% of ceftazidime-susceptible strains and at least 4-fold more active against only 3% of these strains. When MIC_{50} values were used, ceftolozane-tazobactam showed potency equivalent to that of meropenem and minocycline (MIC_{50}

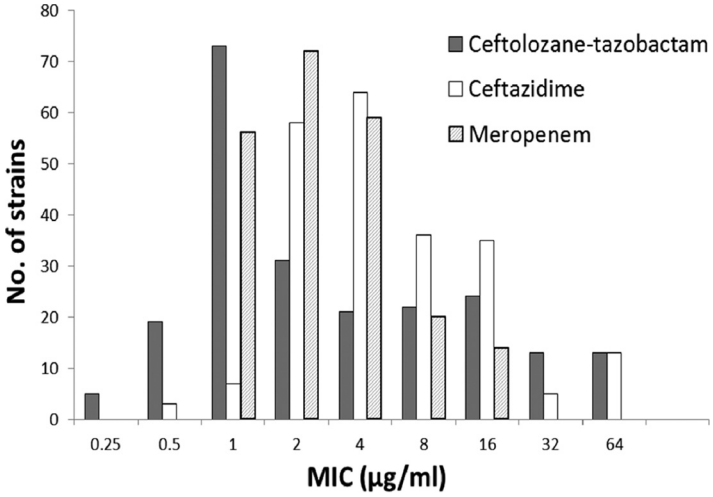

FIG 1 Distribution of MICs of ceftolozane-tazobactam, ceftazidime, and meropenem for 221 *Burkholderia* strains.

for all three agents, 2 μg/ml). Ceftolozane-tazobactam showed good activities (MICs, $\leq$8 μg/ml) against 19 (76%) of the 25 multidrug-resistant (MDR) (10) strains in the test set and against 5 (25%) of the 20 extensively drug-resistant (10) strains. Other agents retaining activities against the MDR strains included ceftazidime (MIC_{50}, 4 μg/ml; 50% susceptible), meropenem (MIC_{50}, 4 μg/ml; 64% susceptible), piperacillin-tazobactam (MIC_{50}, 16 μg/ml), and trimethoprim-sulfamethoxazole (MIC_{50}, $\leq$1 μg/ml; 80% susceptible).

The activities of ceftolozane-tazobactam varied between species within the Bcc. Most notable were the at least 8-fold-poorer activities against *B. cenocepacia* (MIC_{90}, 32 μg/ml) and *B. multivorans* (MIC_{90}, >64 μg/ml) relative to those against all other Bcc species tested (MIC_{90}, 4 μg/ml). Other noteworthy differences of the comparator drugs against strains in the test panel included (i) the greater activities of ceftazidime and piperacillin-tazobactam against *Burkholderia vietnamiensis* strains (MIC_{90}s, 4 μg/ml and 16 μg/ml, respectively) relative to those against all other Bcc species (MIC_{90}s, 16 μg/ml and >128 μg/ml, respectively) and (ii) the greater activities (based on MIC_{90} values) of piperacillin-tazobactam, tigecycline, and the quinolone and carbapenem antibiotics against *B. gladioli* compared to those against the Bcc species. The activities of the aminoglycoside antibiotics against *B. gladioli*, which are in stark contrast to the very poor activities of this class of antibiotics against Bcc species, are well-known distinguishing features of *B. gladioli* (11).

Although interpretive criteria for ceftolozane-tazobactam susceptibility testing of *Burkholderia* spp. are not yet established, the MICs of this combination antimicrobial were in a range comparable to those of other agents used to treat *Burkholderia* infections. It demonstrated marginally superior activity over that of ceftazidime against ceftazidime-susceptible strains and retained activity against most (60%) multidrug-resistant and extensively drug-resistant strains in the test set. Although the Food and Drug Administration does not include infection with *Burkholderia* in its list of indications for ceftolozane-tazobactam, these results suggest that this combination agent offers a potentially effective additional therapy for the management of *Burkholderia* infection in CF patients.

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