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CLINICAL THERAPEUTICS

In Vitro Activities of β-Lactam–β-Lactamase Inhibitor Antimicrobial Agents against Cystic Fibrosis Respiratory Pathogens

Lindsay J. Caverly,[a] Theodore Spilker,[a] Linda M. Kalikin,[a] Terri Stillwell,[a] Carol Young,[b] David B. Huang,[c,d] John J. LiPuma[a]

[a]Department of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan, USA
[b]Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA
[c]Motif BioSciences, Princeton, New Jersey, USA
[d]Rutgers New Jersey Medical School, Trenton, New Jersey, USA

ABSTRACT We tested the *in vitro* activities of ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, piperacillin-tazobactam, and 11 other antimicrobial agents against 420 *Burkholderia*, *Achromobacter*, *Stenotrophomonas*, and *Pandoraea* strains, 89% of which were cultured from respiratory specimens from persons with cystic fibrosis. Among the β-lactam–β-lactamase inhibitor agents, meropenem-vaborbactam had the greatest activity against *Burkholderia* and *Achromobacter*, including multidrug-resistant and extensively-drug-resistant strains. None of the newer β-lactam–β-lactamase combination drugs showed increased activity compared to that of the older agents against *Stenotrophomonas maltophilia* or *Pandoraea* spp.

KEYWORDS cystic fibrosis, respiratory tract infection, ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam

Persons with cystic fibrosis (CF) are susceptible to respiratory tract infection with a suite of opportunistic bacterial pathogens that are relatively infrequent causes of infection in healthy hosts. Species within the *Burkholderia cepacia* complex, *Burkholderia gladioli*, *Stenotrophomonas maltophilia*, and certain *Achromobacter* species can cause chronic infection of CF airways that may be associated with poorer outcomes (1). *Pandoraea* species are less frequently encountered but are also capable of chronic airway infection in CF (2). A common feature of these species is broad-range resistance to antimicrobial agents, which contributes to the difficulty in effectively managing infection in this patient population. While a robust pipeline exists to develop novel anti-infective therapies for CF airway infection, there is an immediate need to explore the utility of newer commercially available antimicrobials for their activity against this group of CF respiratory pathogens.

The development of new β-lactam–β-lactamase inhibitor agents has been spurred by the increasing prevalence of Gram-negative bacteria carrying transmissible β-lactamases (3). Although antimicrobial resistance in CF respiratory pathogens is attributable to multiple mechanisms, the role of β-lactamases has garnered recent attention, particularly with respect to species in the *Burkholderia cepacia* complex (4, 5). We tested the activity of ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, piperacillin-tazobactam, and 11 comparator antimicrobial agents against 420 isolates from the strain collection of the *Burkholderia cepacia* Research Laboratory and Repository (BcRLR) at the University of Michigan. This set included 200 *Burkholderia* isolates, 100 *Achromobacter* isolates, 100 *S. maltophilia* isolates, and 20 *Pandoraea* isolates. Isolates were recovered between 2013 and 2018 from 420 persons receiving care in 171 medical centers in 119 cities in 43 U.S. states, plus Toronto, ON, Canada.

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Address correspondence to John J. LiPuma, jlipuma@umich.edu.

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TABLE 1 Activities of β-lactam–β-lactamase inhibitor antimicrobial agents and comparators against bacterial strains

Species or group (no. of isolates)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[a]
		Range	MIC_{50}	MIC_{90}	
Achromobacter (100)	Ceftazidime	1 to >32	8	32	71
	Ceftazidime-avibactam	1 to >32	8	32	78
	Ceftolozane-tazobactam	≤0.5 to >32	>32	>32	1
	Meropenem	≤0.5 to >32	1	>32	72
	Meropenem-vaborbactam	≤0.5 to 32	≤0.5	8	86
	Piperacillin-tazobactam	≤2 to >128	≤2	128	87
Burkholderia cepacia complex (150)	Ceftazidime	≤0.5 to >32	4	8	91
	Ceftazidime-avibactam	≤0.5 to >32	4	4	97
	Ceftolozane-tazobactam	≤0.5 to >32	1	8	89
	Meropenem	≤0.5 to >32	2	4	90
	Meropenem-vaborbactam	≤0.5 to >32	1	2	97
	Piperacillin-tazobactam	≤2 to >128	4	64	85
Burkholderia gladioli (50)	Ceftazidime	4 to >32	16	32	20
	Ceftazidime-avibactam	2 to >32	16	16	24
	Ceftolozane-tazobactam	2 to >32	16	32	12
	Meropenem	≤0.5 to 4	1	2	100
	Meropenem-vaborbactam	≤0.5 to 4	1	2	100
	Piperacillin-tazobactam	≤2 to 4	≤2	≤2	100
Stenotrophomonas maltophilia (100)	Ceftazidime	≤0.5 to >32	32	>32	34
	Ceftazidime-avibactam	≤0.5 to >32	16	>32	40
	Ceftolozane-tazobactam	≤0.5 to >32	32	>32	27
	Meropenem	≤0.5 to >32	>32	>32	11
	Meropenem-vaborbactam	≤0.5 to >32	>32	>32	12
	Piperacillin-tazobactam	≤2 to >128	128	>128	18
Pandoraea (20)	Ceftazidime	>32	>32	>32	0
	Ceftazidime-avibactam	>32	>32	>32	0
	Ceftolozane-tazobactam	>32	>32	>32	0
	Meropenem	32 to >32	>32	>32	0
	Meropenem-vaborbactam	32 to >32	>32	>32	0
	Piperacillin-tazobactam	8 to >128	64	>128	5

[a]Susceptibility based on CLSI breakpoints established for *Pseudomonas aeruginosa* as follows: ceftazidime, ≤8 μg/ml; ceftazidime-avibactam, ≤8 μg/ml; ceftolozane-tazobactam, ≤4 μg/ml; meropenem, ≤4 μg/ml; meropenem-vaborbactam, ≤4 μg/ml; piperacillin-tazobactam, ≤16 μg/ml.

Most isolates (89%) were cultured from respiratory specimens from persons with CF, and most (88%) were isolated between 2014 and 2017.

All strains had been putatively identified by referring laboratories and sent to the BcRLR for species level confirmation using genetic-based methods previously described (6–9). All *Burkholderia* strains were distinct by genotypic analyses (10), and strains of all other species were recovered from different patients across a wide geographic range. The distribution of species within each genus roughly reflected that found in CF patients as follows: *Burkholderia cenocepacia* (50 isolates), *Burkholderia multivorans* (50 isolates), *Burkholderia gladioli* (50 isolates), *Burkholderia vietnamiensis* (20 isolates), *Burkholderia cepacia* (20 isolates), *Burkholderia contaminans* (10 isolates), *Achromobacter xylosoxidans* (50 isolates), *Achromobacter ruhlandii* (25 isolates), *Achromobacter dolens* (25 isolates), *Pandoraea apista* (10 isolates), and *Pandoraea sputorum* (10 isolates). MIC values were measured using the reference Clinical and Laboratory Standards broth microdilution method (11), with β-lactamase inhibitors added at fixed concentrations. Custom-dried antibiotic plates were read on a Sensititre ARIS instrument (Thermo Fisher Scientific, Waltham, MA, USA).

The results of susceptibility testing comparing ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, and piperacillin-tazobactam, as well as ceftazidime and meropenem, are shown in Table 1. These agents showed a wide range of activity against *Achromobacter* spp., *Burkholderia* spp., and *S. maltophilia*. Whereas the activity of meropenem-vaborbactam was consistent across all *Burkholderia* spp. tested, ceftazidime-avibactam and ceftolozane-tazobactam were 4- to 16-fold less active against *B.*

gladioli than against *B. cepacia* complex spp. Although piperacillin-tazobactam had relatively poor activity against *Burkholderia* spp. as a group (MIC_{90} of 32 μg/ml), it showed good activity against *B. gladioli* and *B. vietnamiensis* (MIC_{90} values of $\leq$2 μg/ml) (see Table S1 in the supplemental material).

Meropenem-vaborbactam and piperacillin-tazobactam demonstrated the greatest activity among the β-lactam–β-lactamase inhibitor agents against *Achromobacter* spp.; a comparable majority of strains would be considered susceptible based on CLSI breakpoints established for *Pseudomonas aeruginosa* (Table 1; see also Table S2 in the supplemental material). Whereas ceftazidime and ceftazidime-avibactam showed intermediate activity (MIC_{50} of 8 μg/ml; MIC_{90} of 32 μg/ml) against *Achromobacter* spp., ceftolozane-tazobactam showed poor activity (MIC_{50} of $>$32 μg/ml). None of the β-lactam–β-lactamase inhibitor agents showed good activity against *S. maltophilia* or *Pandoraea* spp. (MIC_{90} values of $\geq$32 μg/ml).

Detailed results of susceptibility testing at the species level, along with 11 comparator drugs, are shown in Table S3 in the supplemental material. Ceftazidime-avibactam and ceftazidime had equivalent activities overall against *Burkholderia* spp. and against *Achromobacter* spp. An exception was the greater activity of ceftazidime-avibactam versus ceftazidime against *B. multivorans* (MIC_{90} values of 4 and 16 μg/ml, respectively). Similarly, the activity of meropenem-vaborbactam was comparable to that of meropenem against *Burkholderia* spp., while meropenem-vaborbactam showed greater potency than meropenem against *Achromobacter* spp. (MIC_{90} values of 8 and $>$32 μg/ml, respectively).

Among the comparator drugs, trimethoprim-sulfamethoxazole, minocycline, and tigecycline had the greatest activities overall against the species tested, while aztreonam and colistin had generally poor activity. The fluoroquinolone and carbapenem agents showed greater activity against *B. gladioli* than against the other *Burkholderia* spp. tested. The fluoroquinolone agents also exhibited good activity (MIC_{50} values of 4 μg/ml) against *Pandoraea* strains; however, while imipenem showed good activity (MIC_{50} of 2 μg/ml), meropenem and meropenem-vaborbactam did not (both with MIC_{50} values of $>$32 μg/ml).

As is typical for the genera included in this study, the majority (67%) of isolates tested were multidrug resistant (MDR) and 6% were extensively drug resistant (XDR) based on criteria used to define MDR and XDR in *P. aeruginosa* (12). All four of the β-lactam–β-lactamase inhibitor drugs showed good activity (MICs of $\leq$4 μg/ml) against the majority of MDR/XDR *Burkholderia* spp., while only meropenem-vaborbactam and piperacillin-tazobactam showed good activity against the majority of MDR/XDR *Achromobacter* spp. (see Fig. S1 in the supplemental material). Meropenem-vaborbactam and ceftazidime-avibactam were the most active against the nine XDR strains of *Burkholderia* tested, with 67% and 22%, respectively, of strains being inhibited by $\leq$4 μg/ml of these agents. The activity of all four β-lactam–β-lactamase drugs was poor against most MDR/XDR *S. maltophilia* strains.

Airway infection in CF typically involves complex polymicrobial bacterial communities that often include more than one opportunistic pathogen (13). As such, *in vitro* susceptibility testing of a single species isolated from the community performs poorly in predicting clinical outcomes of antimicrobial therapy (14). Despite this limitation, the relative activity of antimicrobial agents against species recovered in culture is an important consideration in guiding antibiotic choice. Clearly, choosing an agent with greater *in vitro* activity than one with little or no activity against a species known to be associated with poor outcomes in CF (i.e., the species included in this study) remains a goal of therapy.

The *in vitro* data presented here indicate that β-lactam–β-lactamase inhibitor agents, including the newer agents ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam, offer therapeutic options for managing airway infections due to opportunistic respiratory pathogens in persons with CF.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

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