



In Vitro Susceptibility of *Burkholderia cepacia* Complex Isolated from Cystic Fibrosis Patients to Ceftazidime-Avibactam and Ceftolozane-Tazobactam

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ABSTRACT We tested the *in vitro* susceptibility of ceftazidime-avibactam and ceftolozane-tazobactam and 13 other antibiotics against 91 *Burkholderia cepacia* complex (BCC) strains isolated from cystic fibrosis patients since 2012. The highest susceptibility (82%) was found for trimethoprim-sulfamethoxazole. Eighty-one and 63% of all BCC strains were susceptible to ceftazidime-avibactam and ceftolozane-tazobactam, respectively. For temocillin, ceftazidime, piperacillin-tazobactam, and meropenem, at least 50% of the strains were susceptible. *B. stabilis* seems to be more resistant than other BCC species.

KEYWORDS *Burkholderia cepacia* complex, cystic fibrosis, ceftazidime-avibactam, ceftolozane-tazobactam, *in vitro* susceptibility

The *Burkholderia cepacia* complex (BCC) is a group of Gram-negative bacteria that comprise at least 20 closely related opportunistic pathogens (1). Chronic infection with BCC is associated with severe morbidity and mortality in cystic fibrosis (CF) patients (2–4). Treatment of BCC infections requires extensive antibiotic therapy but is hampered by intrinsic resistance to common antibiotics (5–9) and *in vivo* biofilm formation (10). Currently susceptibility testing is impeded by the shortage of evidence of a relationship between the *in vitro* susceptibility of antimicrobials and clinical outcome. However, a recent Cochrane Systematic Review concluded that knowledge of *in vitro* susceptibility can guide clinicians in treating BCC infections (11). Therefore, there is still a need to explore the value of newer antimicrobials for their action against BCC.

Ceftolozane-tazobactam is a cephalosporin with a beta-lactamase inhibitor, and ceftazidime-avibactam is a combination of a cephalosporin and a non-beta-lactam inhibitor of beta-lactamases. Both combinations have the ability to inhibit class A, C, and some class D beta-lactamases (12, 13). These new antimicrobial combinations are approved for treating complicated intra-abdominal and urinary tract infections with multidrug-resistant *Enterobacteriales* and *Pseudomonas aeruginosa* (14–18).

In this study, we tested the *in vitro* susceptibility of ceftazidime-avibactam and ceftolozane-tazobactam and 13 other antibiotics to 91 unduplicated BCC isolates from CF patients attending different Belgian hospitals from 2012 to 2016. For identification to species level, *recA* gene sequence analysis was performed using the method of Spilker et al. (19), with minor modifications (20). Among the 91 BCC isolates, *B. multivorans* was the most frequently isolated species (55%), followed by *B. vietnamiensis* (18%), *B. cenocepacia* (9%), and *B. stabilis* (9%). *B. contaminans* (4%), *B. lata* (3%), and *B. cepacia* (2%) occurred less frequently.

MICs were determined by microdilution in microtiter plates and read on a Sensititre

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TABLE 1 MIC distribution and *in vitro* susceptibility of all BCC strains (*n* = 91) for the 15 tested antibiotics^a

Antibiotic	MIC (mg/liter)											EUCAST breakpoints (mg/liter) ^f	Susceptibility (%)	CLSI breakpoints for BCC (mg/liter)	Susceptibility (%)
	0.06 ^d	0.125 ^d	0.25 ^d	0.5 ^d	1 ^d	2	4	8	16 ^e	32 ^e	64 ^e				
Trimethoprim-sulfamethoxazole ^a				50	12	4	9	8	6	2		≤4/76/≥4/76	82	≤2/38/≥4/76	73
Ceftazidime-avibactam ^b				1	9	31	25	9	13	4		≤8/≥8	81		
Ceftazidime		0	0	4	33		20	9	4	20		≤8/≥8	63	≤8/16/≥32	73
Ceftolozane-tazobactam ^c			2	27	18	10	5	7	22			≤4/≥4	63		
Temocillin					0	1	5	26	29	15	15	≤16/≥32	67		
Piperacillin-tazobactam ^c			2	9	26		16	6	6	2	24	≤4/≥16	58		
Piperacillin						28	15	10	6	4	28	≤4/≥16	47		
Meropenem			1	2	14	29	15	22	4	4		≤2/≥8	51	≤4/8/≥16	67
Aztreonam		0	0	1	20	20		10	9	31		≤4/≥8	45		
Cefepime		0	1	2	20	11		16	13	28		≤4/≥8	37		
Tobramycin					0	1	2	2	86			≤4/≥8	3		
Amikacin						0	0	3	1	9	78	≤8/16/≥32	3		
Tigecycline			1	5	23	14	14	16	9	9		≤0.25/≥0.5	1		
Ciprofloxacin	0	0	1	12	24	16	16	6	5	11		≤0.25/≥0.5	1		
Colistin			0	0	0	0	0	1	4	86		≤2/≥4	0		

^aTested breakpoint concentrations were 0.5/9.5, 1/19, 2/38, 4/76, 8/152, 16/304, and 32/608 mg/liter.^bAvibactam was at a constant concentration of 4 mg/liter.^cTazobactam was at a constant concentration of 4 mg/liter.^dBelow or equal to the respective MIC.^eAbove or equal to the respective MIC.^fTemocillin breakpoints from Fuchs et al. (22).^gThe MIC above the framed number corresponds to the MIC₅₀.

Vizion System (Thermo Scientific). For determination of the *in vitro* susceptibility (Table 1), EUCAST pharmacokinetic/pharmacodynamics (PK/PD) breakpoints were used, as no EUCAST species-specific breakpoints were available. Breakpoints for aminoglycosides, colistin, and trimethoprim-sulfamethoxazole were based on those from EUCAST for nonfermenters (21). For temocillin, breakpoints described by Fuchs et al. were used (22). These *in vitro* susceptibilities were compared with those derived from CLSI breakpoints for BCC where available (Table 1).

As expected, little or no *in vitro* activity was noted for amikacin, tobramycin, and colistin (23). Ciprofloxacin and tigecycline also were scarcely active. Using the EUCAST breakpoint for nonfermenters (≤4 and 76 mg/liter, or ≤4/76 mg/liter), the highest *in vitro* susceptibility (82%) of BCC isolates was found for trimethoprim-sulfamethoxazole, which is in line with other studies (24, 25). However, the CLSI breakpoint for BCC is more stringent (≤2/38 mg/liter), resulting in an *in vitro* activity of 73%.

In general, MICs varied widely for beta-lactam antibiotics. This variation can be explained by the potential presence of several resistance mechanisms. It has been shown that BCC species contain class A beta-lactamases (like PenA and PenB) with broad-spectrum carbapenemase characteristics, class C beta-lactamases (like AmpC), and class D beta-lactamases. Non-beta-lactamase-mediated resistance mechanisms, like efflux pumps and reduced outer membrane permeability, also play a role in the decreased susceptibility of BCC species (9). Among these beta-lactam antibiotics, the newer antibiotic ceftazidime-avibactam showed the highest *in vitro* susceptibility (81%). Moreover, adding avibactam to ceftazidime increased its susceptibility by approximately 20%. In the literature, a highly variable ability of avibactam to potentiate ceftazidime activity is observed, suggesting this resistance is not due to beta-lactamase production alone (26, 27). Adding tazobactam to piperacillin only slightly improved (by about 10%) the susceptibility of BCC isolates (58% versus 47%), which was also demonstrated in other studies (28, 29). This limited increase in susceptibility may be because tazobactam does not affect AmpC beta-lactamases, whereas avibactam does. In Europe, temocillin is often used as an orphan drug for treating BCC infection (30). The high *in vitro* activity (67%) of temocillin against BCC, mainly due to its activity against ESBLs, was confirmed in our study (31–33). However, it remains important to consider that almost 50% of the susceptible strains have a MIC at the pharmacokinetic/pharmacodynamic (PK/PD) breakpoint. For cefepime and aztreonam, we found a susceptibility of about 40%,

which is between the susceptibilities from other studies (29, 34). The *in vitro* susceptibility of meropenem was only 51% and 67%, using EUCAST PK/PD and CLSI BCC breakpoints, respectively, suggesting the presence of carbapenemase production.

Remarkable differences in *in vitro* susceptibility were noticed between BCC species (see Table S1 in the supplemental material). In contrast to other BCC species, all *B. stabilis* isolates ($n = 8$) were resistant to piperacillin-tazobactam, ceftolozane-tazobactam, aztreonam, and meropenem, which suggests the presence of broad-spectrum beta-lactamases. This finding is not described elsewhere, probably because other studies tested none or only a low proportion of *B. stabilis* strains (24, 25, 29, 34, 35). However, all 8 *B. stabilis* isolates represented the same sequence type, as determined by multilocus sequence typing (19 and data not shown). We found, similar to Lupo et al. (34), a higher susceptibility to piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, and meropenem for *B. multivorans* than for *B. cenocepacia*. Likewise, *B. cenocepacia* had the highest *in vitro* susceptibility for ceftazidime-avibactam (88%), ceftolozane-tazobactam (75%), and temocillin (88%), suggesting a higher proportion of beta-lactamase-producing strains in *B. cenocepacia* isolates. *B. cenocepacia* isolates are known to contain PenA and PenB, both with broad-spectrum carbapenemase characteristics, and AmpC beta-lactamases, whereas *B. multivorans* contains PenA beta-lactamases (5, 36).

Three out of the 91 isolates were multidrug resistant. Twenty-nine (32%) isolates were only susceptible to at least 1 of the 4 antibiotics with highest *in vitro* susceptibility: trimethoprim-SXT, ceftazidime-avibactam, temocillin, and ceftolozane-tazobactam. Among the 11 strains resistant to trimethoprim-SXT, 4 strains were susceptible to temocillin, and importantly, 3 strains were only susceptible to ceftolozane-tazobactam and ceftazidime-avibactam and 3 strains were only susceptible to ceftazidime-avibactam.

For the treatment of BCC infections with strains resistant to the first-choice treatment, trimethoprim-sulfamethoxazole, there could be a role for the new antimicrobials ceftazidime-avibactam and ceftolozane-tazobactam, sparing the use of meropenem. Our results may help clinicians with the antibiotic treatment of their patients, taking into account previous clinical responses and their own experience. However, more susceptibility studies are required to reach valid specific breakpoints for BCC species, and clinical studies are needed to assess clinical outcomes.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at <https://doi.org/10.1128/AAC.00590-18>.

SUPPLEMENTAL FILE 1, PDF file, 0.2 MB.

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