Antimicrobial Activity of Ceftazidime-Avibactam and Comparator Agents against *Pseudomonas aeruginosa* and *Enterobacterales* Causing Pneumonia in Cystic Fibrosis Patients

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INTRODUCTION

- More than 50% of cystic fibrosis (CF) individuals aged 18 years and older in the USA are infected with *Pseudomonas aeruginosa*, of which approximately one-third is multidrug-resistant (MDR).
- Very few agents remain active against MDR *P. aeruginosa* and rapidly introducing appropriate antimicrobial therapy is crucial to reduce morbidity and mortality of patients with infections caused by these organisms.
- Ceftazidime-avibactam is approved by the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA) to treat hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia (HABP/VABP), complicated intra-abdominal infections (cIAIs) in combination with metronidazole, and complicated urinary tract infections (UTIs), including pyelonephritis.
- We evaluated the antimicrobial susceptibility patterns of *P. aeruginosa* and *Enterobacterales* isolated from CF patients with pneumonia.

MATERIALS AND METHODS

- Bacterial isolates determined to be significant by local criteria as the reported probable cause of respiratory infection were consecutively collected from CF patients (1/patient).
- Isolates were collected from 43 medical centers worldwide (19 nations) in 2018–2019.
- The organism collection included 273 *P. aeruginosa* and 62 *Enterobacterales* isolates.
- Susceptibility testing was performed by reference broth microdilution methods at a central laboratory (JMI Laboratories, North Liberty, Iowa).
- Antimicrobial agents tested include ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), piperacillin-tazobactam (PIP-TAZ), meropenem (MEM), ceftazidime (CAZ), ceftriaxone (CRO; *Enterobacterales* only), levofloxacin (LEV), tobramycin (TOB), and gentamicin (GEN).
- MDR was defined as nonsusceptibility (CLSI breakpoints) to at least 1 drug in 3 classes.

RESULTS

- Ceftazidime-avibactam ($MIC_{50/90}$, 2/8 mg/L; 96.0% susceptible [S]) was the most active agent against *P. aeruginosa*, followed by ceftolozane-tazobactam ($MIC_{50/90}$, 1/4 mg/L; 90.5%S), ceftazidime ($MIC_{50/90}$, 2/>32 mg/L; 80.6%S), piperacillin-tazobactam ($MIC_{50/90}$, 4/128 mg/L; 80.2%S), and tobramycin ($MIC_{50/90}$, 2/>16 mg/L; 76.6%S; Figure 1).
- Ceftazidime-avibactam retained activity against *P. aeruginosa* isolates nonsusceptible to meropenem (86.5%S to ceftazidime-avibactam), piperacillin-tazobactam (85.2%S to ceftazidime-avibactam), or ceftazidime (79.2%S to ceftazidime-avibactam; Table 1 and Figure 2).
- Moreover, 65.4% of ceftolozane-tazobactam-nonsusceptible isolates remained susceptible to ceftazidime-avibactam (Table 1).
- Among *P. aeruginosa*, 36.3% were multidrug-resistant (MDR, resistant to ≥3 classes), and 88.9% and 73.7% of MDR *P. aeruginosa* were susceptible to ceftazidime-avibactam and ceftolozane-tazobactam, respectively (Figure 2).
- Among *P. aeruginosa* isolates nonsusceptible to piperacillin-tazobactam, meropenem, and ceftazidime (13.9% of total), susceptibility to ceftazidime-avibactam and ceftolozane-tazobactam was 78.9% and 47.4%, respectively (Figure 2).
- The most active agents against *Enterobacterales* were ceftazidime-avibactam ($MIC_{50/90}$, 0.12/0.5 mg/L; 100.0%S) and meropenem ($MIC_{50/90}$, 0.03/0.12 mg/L; 96.8%S; Figure 3).
- Ceftolozane-tazobactam ($MIC_{50/90}$, 0.25/4 mg/L) was active against 88.7% of ENT.
- Among *Enterobacterales* isolates, 17.7% were MDR.

Table 1. Cross-resistance among β-lactams and β-lactamase inhibitor combinations when tested against *P. aeruginosa* isolates from CF patients (2018–2019)

Antimicrobial	% Susceptible by resistant subset (no. of isolates)				
	MEM-NS (74)	PIP-TAZ-NS (54)	CAZ-NS (53)	C-T-NS (26)	CAZ-AVI-NS (11)
MEM	0.0	20.4	17.0	3.8	9.1
PIP-TAZ	41.9	0.0	15.1	3.8	27.2
CAZ	40.5	16.7	0.0	3.8	0.0
C-T	66.2	63.0	52.8	0.0	18.2
CAZ-AVI	86.5	85.2	79.2	65.4	0.0

Abbreviations: CAZ, ceftazidime; MEM, meropenem; PIP-TAZ, piperacillin-tazobactam; C-T, ceftolozane-tazobactam; AVI, avibactam; NS, not susceptible.

CONCLUSIONS

- Ceftazidime-avibactam exhibited potent and broad-spectrum activity against *P. aeruginosa* (96.0%S) and *Enterobacterales* (100.0%S) isolated from CF patients worldwide and retained good activity against isolates resistant to other antimicrobials, including MDR organisms.
- Ceftazidime-avibactam and ceftolozane-tazobactam exhibited similar *P. aeruginosa* coverage, but ceftazidime-avibactam was more active than ceftolozane-tazobactam against *P. aeruginosa* resistant subsets.
- Ceftazidime-avibactam represents a valuable option to treat CF patients with respiratory tract infections.

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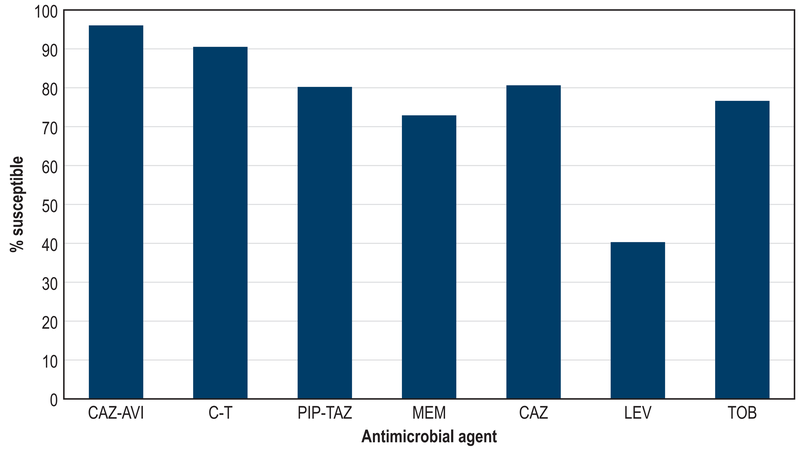
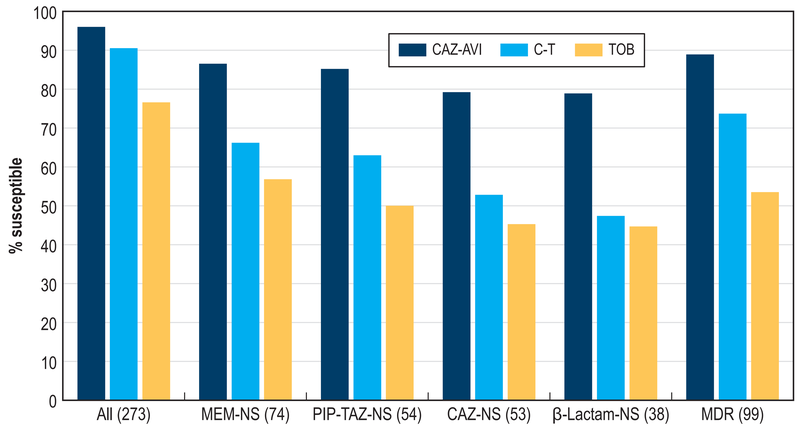
Figure 1. Antimicrobial susceptibility of *P. aeruginosa* (n=273) collected from cystic fibrosis patients worldwide (2018–2019)



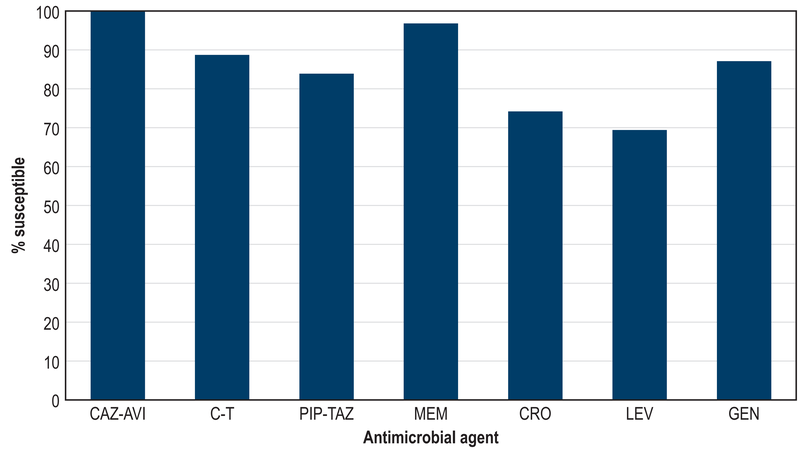
Abbreviations: CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem; CAZ, ceftazidime; LEV, levofloxacin; TOB, tobramycin.

Figure 2. Antimicrobial activity of ceftazidime-avibactam (CAZ-AVI), ceftolozane-tazobactam (C-T), and tobramycin (TOB) tested against *P. aeruginosa* resistant subsets from cystic fibrosis patients (2018–2019)



Abbreviations: MEM, meropenem; NS, nonsusceptible; PIP-TAZ, piperacillin-tazobactam; CAZ, ceftazidime; β-lactam-NS, isolates not susceptible to meropenem, piperacillin-tazobactam, and ceftazidime; and MDR, multidrug-resistant.

Figure 3. Antimicrobial susceptibility of *Enterobacterales* (n=62) collected from cystic fibrosis patients worldwide (2018–2019)



Abbreviations: CAZ-AVI, ceftazidime-avibactam; C-T, ceftolozane-tazobactam; PIP-TAZ, piperacillin-tazobactam; MEM, meropenem; CRO, ceftriaxone; LEV, levofloxacin; GEN, gentamicin.

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