Ceftolozane-Tazobactam Activity against Difficult-to-Treat Resistance in *Pseudomonas aeruginosa* from Bloodstream Infections in US Hospitals

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Introduction

- *Pseudomonas aeruginosa* is a common and often drug-resistant pathogen in bloodstream infections in the United States
- Kadri et al. recently described the category of difficult-to-treat resistance (DTR) as intermediate or resistant to all tested first-line agents (fluoroquinolones, carbapenems, and extended-spectrum cephalosporins) to define resistant isolates more precisely than current definitions, such as extensively drug-resistant (XDR)
  - Gram-negative (GN) bloodstream infections caused by DTR isolates were associated with decreased survival
  - When an isolate was known to be DTR, patients were more likely to receive reserve toxic treatment options, such as amikacin and colistin
- Ceftolozane-tazobactam is an antibacterial combination of an antipseudomonal cephalosporin and a β-lactamase inhibitor
- Ceftolozane-tazobactam has been approved in >60 countries to treat complicated urinary tract infections, acute pyelonephritis, and complicated intra-abdominal infections
- Ceftolozane-tazobactam was recently approved for the treatment of hospital-acquired pneumonia and ventilator-associated pneumonia
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors GN isolates resistant to ceftolozane-tazobactam worldwide
- In this study, the activity of ceftolozane-tazobactam and comparators against *P. aeruginosa* bloodstream isolates that are DTR, carbapenem-resistant, multidrug-resistant (MDR), or XDR was analyzed

Materials and Methods

- A total of 922 *P. aeruginosa* isolates from bloodstream infections were collected during 2011 to 2018 from 35 PACTS hospitals in the United States
  - Sites collected consecutive blood culture isolates
  - Only 1 isolate per patient per infection episode was included
- Isolates were tested for ceftolozane-tazobactam susceptibility by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07, 2018)
  - Other antibiotics tested included cefepime, ceftazidime, ciprofloxacin, levofloxacin, doripenem, imipenem, meropenem, piperacillin-tazobactam, amikacin, and colistin
- Antibiotic-resistant phenotypes analyzed using CLSI (M100, 2019) breakpoints included: resistant to all carbapenems (CR), MDR (nonsusceptible to ≥1 agent in ≥3 drug classes), XDR (susceptible to ≤1 agent in ≤2 drug classes), or DTR (intermediate or resistant to all carbapenems, fluoroquinolones, piperacillin-tazobactam, and extended-spectrum cephalosporins tested)

Results

- *P. aeruginosa* was the third most frequent cause of gram-negative bloodstream infections (Figure 1)
  - The prevalence of *P. aeruginosa* was similar throughout the study period (data not shown)
- The percent of DTR isolates from bloodstream infections was 4.6% as compared to 15.2% MDR and 9.3% XDR (Figure 2)
  - The percent of all resistant phenotypes varied by year over the study period, with no obvious trend to increasing resistant phenotypes (Figure 2)
  - DTR varied from 6.6% in 2011 to 2.0% in 2018
- The % susceptible for ceftolozane-tazobactam and other first- and second-line agents is shown in Table 1 for each phenotype
  - Ceftolozane-tazobactam had a higher % susceptible than meropenem or piperacillin-tazobactam against all resistant phenotypes
  - Ceftolozane-tazobactam had susceptibility >80% for MDR and CR and >70% for XDR
  - Colistin was the only agent that had >99% susceptible for all phenotypes
- The ceftolozane-tazobactam MIC distributions for all isolates and each resistant phenotype are shown in Table 2

Conclusions

- Ceftolozane-tazobactam demonstrated 97.1% susceptibility overall for *P. aeruginosa* bloodstream infection isolates, similar to amikacin (97.8%) and colistin (99.5%)
- Ceftolozane-tazobactam had better coverage than first-line drugs (meropenem and piperacillin-tazobactam) against CR (80.5%), MDR (81.4%), XDR (72.1%), and DTR (50%) isolates
- The rate of DTR isolates was 4.6% of the total and has decreased slightly in the last 2 years
- Only amikacin and colistin had >80% susceptible for DTR isolates

Figure 1 Prevalence of the 5 most common gram-negative pathogens isolated from bloodstream infections in US medical centers (2011–2018)

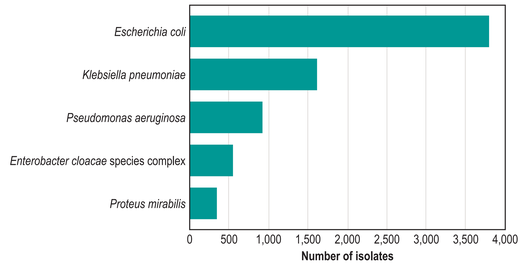
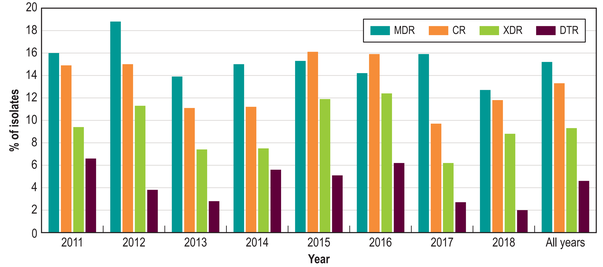


Figure 2 Percent of MDR, CR, XDR, and DTR isolates by year, over the 8 years of the study, and for all years



MDR, multidrug-resistant; XDR, extensively drug-resistant; CR, carbapenem-resistant; DTR, difficult-to-treat resistant

Table 1 Susceptibilities of *P. aeruginosa* from bloodstream infections to ceftolozane-tazobactam and comparators

P. aeruginosa		% susceptible[a]							
Phenotype	*n*	C-T	FEP	CAZ	MEM	PIP-TAZ	LEV	AMK	COL
All isolates	922	97.1	87.2	86.1	81.9	82.2	70.9	97.8	99.5
MDR	140	81.4	32.1	31.4	17.9	16.4	10.7	86.4	100.0
CR	123	80.5	45.5	46.3	0.0	33.3	20.3	89.4	100.0
XDR	86	72.1	12.8	20.9	4.7	4.7	0.0	80.2	100.0
DTR	42	50.0	0.0	0.0	0.0	0.0	0.0	81.0	100.0

[a] CLSI (2019)
Abbreviations: C-T, ceftazidime-tazobactam; FEP, cefepime; CAZ, ceftazidime; MEM, meropenem; PIP-TAZ, piperacillin-tazobactam; LEV, levofloxacin; AMK, amikacin; COL, colistin; MDR, multidrug-resistant; CR, carbapenem-resistant; XDR, extensively drug-resistant; DTR, difficult-to-treat resistant

Table 2 MIC distribution of *P. aeruginosa* isolates and resistant phenotypes collected from bloodstream infections in US medical centers

Phenotype (*n*)	Ceftolozane-tazobactam MIC (mg/L)											MIC_{50}	MIC_{90}
	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
All (922)	0	3	84	537	188	49	34	13	2	0	12	0.5	2
	0.0%	0.3%	9.4%	67.7%	88.1%	93.4%	97.1%	98.5%	98.7%	98.7%	100.0%		
MDR (140)		0	1	10	49	34	20	12	2	0	12	2	8
		0.0%	0.7%	7.9%	42.9%	67.1%	81.4%	90.0%	91.4%	91.4%	100.0%		
XDR (86)			0	2	28	21	11	11	1	0	12	2	>32
			0.0%	2.3%	34.9%	59.3%	72.1%	84.9%	86.0%	86.0%	100.0%		
DTR (42)				0	6	10	5	10	1	0	10	4	>32
				0.0%	13.6%	38.1%	50.0%	73.8%	76.2%	76.2%	100.0%		
CR (123)		0	1	16	52	18	12	11	2	0	11	1	16
		0.0%	0.8%	13.8%	56.1%	70.7%	80.5%	89.4%	91.1%	91.1%	100.0%		

MDR, multidrug-resistant; XDR, extensively drug-resistant; DTR, difficult-to-treat resistant; CR, carbapenem-resistant
CLSI breakpoints are indicated by color: green is susceptible, yellow is intermediate, and red is resistant.

Acknowledgements

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