Activity of Ceftolozane-Tazobactam and Comparators When Tested against Bacterial Isolates Collected from Hematology or Oncology Patients in Europe during 2011–2017 as Part of a Global Surveillance Program

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INTRODUCTION

- Ceftolozane-tazobactam is a combination of an antipseudomonal cephalosporin and a β-lactamase inhibitor
  - Ceftolozane-tazobactam has activity against most isolates with common β-lactam resistance mechanisms employed by *Pseudomonas aeruginosa,* including AmpC production, up-regulated efflux pumps, and porin reductions
  - Ceftolozane-tazobactam also has activity against most extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (new taxonomy: *Enterobacterales*)
- Ceftolozane-tazobactam has been approved in >50 countries for treatment of adults with complicated urinary tract infections, including acute pyelonephritis, and complicated intra-abdominal infections in combination with metronidazole
  - Clinical trials in hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia are in progress (clinicaltrials.gov Identifier: NCT02070757)
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors susceptibility of ceftolozane-tazobactam among gram-negative isolates worldwide
- This study analyzed pathogen susceptibility in cancer patients on the hematology and oncology (H/O) service in 43 European hospitals

MATERIALS AND METHODS

- In 2011-2017, 1,698 gram-negative bacilli, including 1,298 *Enterobacteriaceae* (new taxonomy *Enterobacterales*) and 272 *P. aeruginosa*, were isolated from patients on the H/O service in 21 countries and tested for ceftolozane-tazobactam susceptibility by CLSI broth microdilution methods at JMI Laboratories
- Comparators tested were amikacin, cefepime, ceftazidime, colistin, levofloxacin, meropenem, and piperacillin-tazobactam
  - Ceftolozane and piperacillin were both tested with a fixed concentration of 4 mg/L of tazobactam
- Phenotypes analyzed for *P. aeruginosa* included ceftazidime-nonsusceptible (NS), meropenem-NS, and piperacillin-tazobactam-NS
- Breakpoints (2018) from CLSI or EUCAST were used

RESULTS

- The 3 most common infections were bloodstream infection (n=1,032), pneumonia (n=272), and skin and skin structure infection (n=201), shown in Figure 1
- The 3 most common pathogens were *Escherichia coli* (n=642), *Klebsiella pneumoniae* (n=279), and *P. aeruginosa* (n=272)
- Table 1 and Figure 2A show the % susceptible for ceftolozane-tazobactam and comparators for all enteric isolates and Figure 2B shows *P. aeruginosa* and resistant phenotypes
- Ceftolozane-tazobactam inhibited 95.2% of *P. aeruginosa* and 89.7% of all *Enterobacteriaceae*
  - Meropenem and amikacin were most active against *Enterobacteriaceae*
  - Ceftolozane-tazobactam and colistin were the most active agents against *P. aeruginosa*
  - Levofloxacin was the least active agent overall
- For *P. aeruginosa* that were nonsusceptible to ceftazidime, meropenem, or piperacillin-tazobactam, the ceftolozane-tazobactam susceptibility ranged from 77.6%–82.1%

Figure 1 Distribution of 3 most common pathogens by infection type in European cancer patients

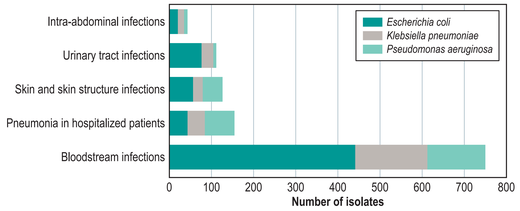


Table 1 Activity of ceftolozane-tazobactam and comparator antimicrobial agents when tested against 1,298 *Enterobacteriaceae* isolates and 272 *P. aeruginosa* isolates from European cancer patients

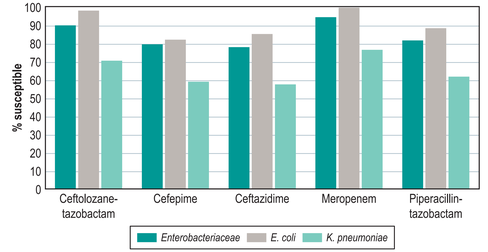
				CLSI[a]			EUCAST[a]		
Antimicrobial agent	MIC_{50}	MIC_{90}	Range	%S	%I	%R	%S	%I	%R
Enterobacteriaceae (n=1,298)									
Ceftolozane-tazobactam	0.25	4	0.06 to >32	89.7	1.5	8.9	86.4		13.6
Amikacin	2	8	≤0.25 to >32	96.0	2.8	1.2	93.8	2.2	4.0
Cefepime	≤0.5	>16	≤0.5 to >16	79.3	3.5	17.2[d]	77.5	3.9	18.7
Ceftazidime	0.25	>32	0.03 to >32	77.8	2.9	19.3	74.0	3.8	22.2
Colistin	≤0.5	>4	≤0.5 to >4				87.2		12.8
Levofloxacin	≤0.12	>4	≤0.12 to >4	70.6	2.5	26.9	65.6	3.5	30.9
Meropenem	≤0.06	≤0.06	≤0.06 to >8	94.2	0.6	5.2	94.8	1.2	3.9
Piperacillin-tazobactam	2	>64	≤0.5 to >64	81.5	5.6	12.9	76.7	4.9	18.5
E. coli (n=642)									
Ceftolozane-tazobactam	0.25	0.5	0.06 to >32	97.8	0.8	1.4	97.4		2.6
Amikacin	2	4	≤0.25 to >32	98.9	0.6	0.5	97.2	1.7	1.1
Cefepime	≤0.5	>16	≤0.5 to >16	81.9	4.2	13.9[d]	79.8	4.7	15.6
Ceftazidime	0.25	16	0.06 to >32	85.0	3.4	11.5	80.5	4.5	15.0
Colistin	≤0.5	≤0.5	≤0.5 to 8				98.6		1.4
Levofloxacin	≤0.12	>4	≤0.12 to >4	61.4	3.4	35.2	59.3	1.6	39.1
Meropenem	≤0.06	≤0.06	≤0.06 to 4	99.5	0.3	0.2	99.8	0.2	0.0
Piperacillin-tazobactam	2	32	≤0.5 to >64	88.2	5.0	6.9	83.8	4.4	11.8
K. pneumoniae (n=279)									
Ceftolozane-tazobactam	0.5	>32	0.12 to >32	70.3	1.8	28.0	64.9		35.1
Amikacin	1	32	≤0.25 to >32	84.9	11.5	3.6	81.0	3.9	15.1
Cefepime	≤0.5	>16	≤0.5 to >16	58.8	2.9	38.4[d]	58.4	1.1	40.5
Ceftazidime	0.5	>32	0.06 to >32	57.3	2.5	40.1	55.6	1.8	42.7
Colistin	≤0.5	1	≤0.5 to >4				91.3		8.7
Levofloxacin	0.5	>4	≤0.12 to >4	65.2	0.7	34.1	56.6	6.5	36.9
Meropenem	≤0.06	>8	≤0.06 to >8	76.3	1.4	22.2	77.8	4.3	17.9
Piperacillin-tazobactam	8	>64	≤0.5 to >64	61.6	6.5	31.9	57.7	3.9	38.4
P. aeruginosa (n=272)									
Ceftolozane-tazobactam	0.5	2	0.12 to >32	95.2	1.1	3.7	95.2		4.8
Amikacin	2	8	≤0.25 to >32	92.6	2.6	4.8	90.1	2.6	7.4
Cefepime	2	16	≤0.5 to >16	83.1	10.3	6.6	83.1		16.9
Ceftazidime	2	32	0.25 to >32	78.7	7.0	14.3	78.7		21.3
Colistin	1	2	≤0.5 to 4	99.3		0.7	99.3		0.7
Levofloxacin	0.5	>4	≤0.12 to >4	77.1	3.7	19.2	70.1		29.9
Meropenem	0.5	>8	≤0.06 to >8	77.2	7.0	15.8	77.2	12.1	10.7
Piperacillin-tazobactam	4	>64	≤0.5 to >64	75.4	11.8	12.9	75.4		24.6

[a] Criteria as published by CLSI [2018] and EUCAST [2018].
[b] Dilution range did not extend high enough to determine between I and R so only Susceptible Percentage is displayed
[c] Using Other than Uncomplicated UTI breakpoints
[d] Intermediate interpreted as susceptible-dose dependent

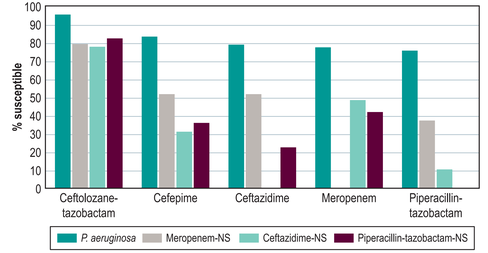
Organisms include: *Citrobacter braakii* (1), *C. farmeri* (1), *C. freundii* (19), *C. freundii* species complex (4), *C. koseri* (8), *Enterobacter aerogenes* (21), *E. cancerogenus* (1), *E. cloacae* (105), *E. cloacae* species complex (15), *E. kobei* (3), *Escherichia coli* (642), *Hafnia alvei* (6), *Klebsiella oxytoca* (71), *K. pneumoniae* (279), *K. variicola* (1), *Leclercia adecarboxylata* (1), *Lelliottia amnigena* (1), *Morganella morganii* (18), *Pantoea agglomerans* (1), *Proteus mirabilis* (42), *P. vulgaris* (8), *P. vulgaris* group (1), *Providencia rettgeri* (1), *Serratia liquefaciens* (4), *S. marcescens* (38), unspeciated *Citrobacter* (1), unspeciated *Enterobacter* (3), unspeciated *Kluyvera* (1)

Figure 2 Susceptibilities of ceftolozane-tazobactam and other β-lactams against most common organisms and organism groups

A. *Enterobacteriaceae* and the most common species, *E. coli* and *K. pneumoniae*



B. *P. aeruginosa* and nonsusceptible phenotypes



CONCLUSIONS

- Ceftolozane-tazobactam demonstrated activity against 89.7% of *Enterobacteriaceae* from H/O patients
  - Meropenem and amikacin were the most active agents
- Ceftolozane-tazobactam demonstrated activity against most *P. aeruginosa* (95.2% susceptible) and was the most active β-lactam, with similar activity to colistin (99.3%)
- Ceftolozane-tazobactam also had activity against *P. aeruginosa* isolates nonsusceptible to meropenem, ceftazidime, and piperacillin-tazobactam
- These data suggest that ceftolozane-tazobactam may be a useful treatment for cancer patients, including those who are immunocompromised, particularly when *P. aeruginosa* infection is suspected

Acknowledgements

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