Sunday-392

Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2015–2017) Gram-Negative Isolates from Intensive Care Unit Patients with Pneumonia in US Medical Centers

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INTRODUCTION

- Ceftolozane-tazobactam is a combination of an antipseudomonal cephalosporin and a β-lactamase inhibitor
 - Ceftolozane-tazobactam has activity against isolates with the most 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 (ESBL)-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
- In the current study, gram-negative isolates were collected from pneumonia in hospitalized patients in the intensive care unit (ICU) in the US from 2015–2017

MATERIALS AND METHODS

- A total of 1,951 gram-negative isolates, including 1,113 *Enterobacteriaceae* and 571 *P. aeruginosa*, were collected from pneumonia in hospitalized patients during 2015-2017 from 29 US hospital ICUs and tested for C-T susceptibility by CLSI broth microdilution at JMI Laboratories
 - Only 1 isolate per patient per infection episode was included
- Other antibiotics tested were amikacin, cefepime, ceftazidime, colistin, levofloxacin, meropenem, and piperacillin-tazobactam
 - Ceftolozane-tazobactam and piperacillin-tazobactam were tested with a fixed 4 mg/L concentration of tazobactam
 - CLSI (2018) and EUCAST (2018) breakpoints were applied; EUCAST breakpoints were used for colistin against *Enterobacteriaceae*
- Resistant phenotypes included *Enterobacteriaceae* resistant to doripenem, imipenem, or meropenem (carbapenem-resistant *Enterobacteriaceae*, CRE) and ESBL-screen-postive phenoytpe isolates, not resistant to carbapenems (ESBL, non-CRE)
 - ESBL and CRE phenotypes were based on CLSI M100 criteria.
- For *P. aeruginosa*, the phenotypes analyzed were ceftazidime-NS, meropenem-NS, cefepime-NS, piperacillin-tazobactam-NS, and NS to all 4 β-lactams (BL-NS)

RESULTS

- The top 3 species isolated from ICU patients hospitalized with pneumonia were *P. aeruginosa* (n=571), *Klebsiella pneumoniae* (n=296), and *Escherichia coli* (n=216)
- The susceptibilities of ceftolozane-tazobactam and comparators for the top enteric pathogens are shown in Tables 1 and 2
- Ceftolozane-tazobactam MIC distributions are shown in Table 3

Figure 1 Susceptibility of ceftolozane-tazobactam and β-lactam comparators against all *P. aeruginosa* isolates and resistance phenotypes

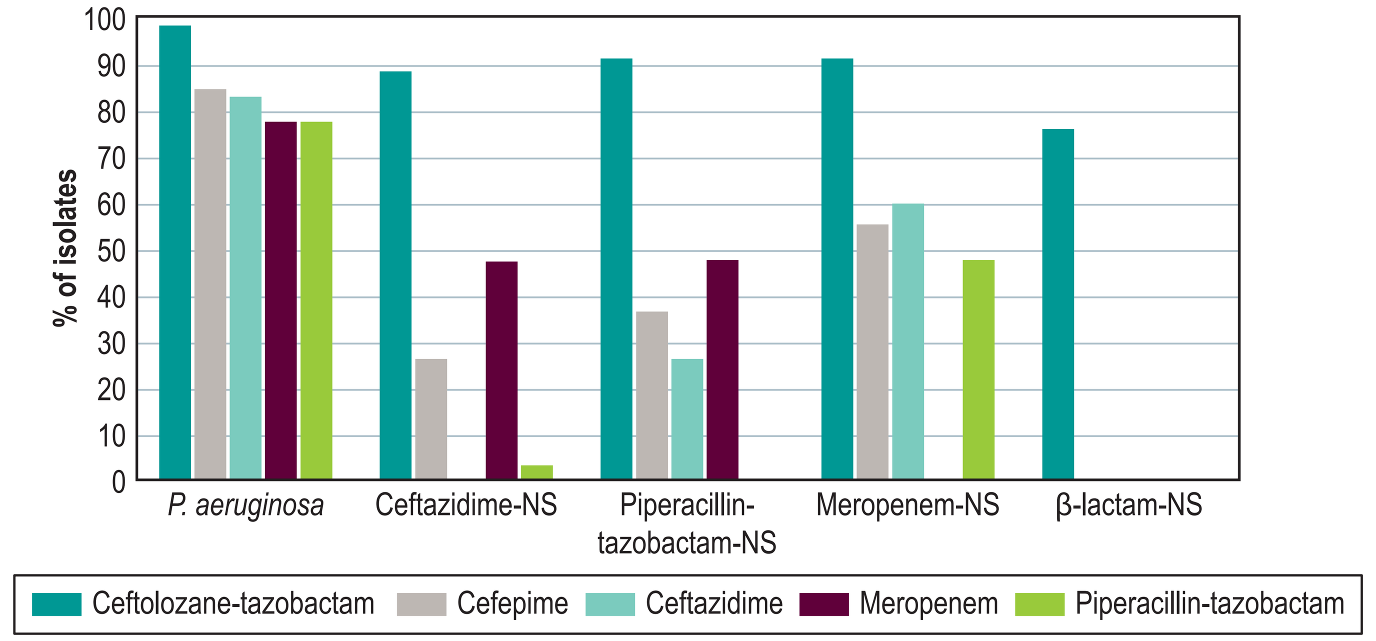

100
90
80
70
60
50
40
30
20
10
0
% of isolates
P. aeruginosa
Ceftazidime-NS
Piperacillin-tazobactam-NS
Meropenem-NS
β-lactam-NS
Ceftolozane-tazobactam
Cefepime
Ceftazidime
Meropenem
Piperacillin-tazobactam

Table 1 Susceptibilities of ceftolozane-tazobactam and comparators for *E. coli* and *K. pneumoniae* isolated from US ICU patients hospitalized with pneumonia

		% susceptible[a]							
	n	Ceftolozane-tazobactam	Cefepime	Ceftazidime	Meropenem	Piperacillin-tazobactam	Levofloxacin	Amikacin	Colistin
E. coli	216	95.8	78.2	79.2	99.1	90.7	61.9	99.1	100.0
Ceftazidime-NS	45	80.0	11.1	0.0	95.6	80.0	17.8	97.8	100.0
Piperacillin-tazobactam-NS	20	65.0	55.0	55.0	90.0	0.0	35.0	95.0	100.0
K. pneumoniae	296	93.6	89.2	85.8	95.3	87.8	92.5	99.3	98.3
Ceftazidime-NS	42	54.8	23.8	0.0	66.7	42.9	50.0	95.2	95.2
Piperacillin-tazobactam-NS	36	47.2	44.4	33.3	63.9	0.0	61.1	94.4	94.4

[a] CLSI (2018), EUCAST (2018) for *E. coli* and *K. pneumoniae* versus colistin

- For *Enterobacteriaceae,* amikacin (99.5% susceptible) and meropenem (97.0% susceptible) were the most active agents followed by ceftolozane-tazobactam (91.9% susceptible) (Table 2)
 - Ceftolozane-tazobactam was not active against 2 CRE *E. coli* and 14 CRE *K. pneumoniae* isolates (Table 3)
- For *P. aeruginosa*, ceftolozane-tazobactam (97.9%) and colistin (99.6%) were the most active agents, followed by amikacin (96.5%), as shown in Table 2 and Figure 2
 - Other β-lactams had <85% susceptibility
 - Levofloxacin had 76.0% susceptibility

Table 2 Ceftolozane-tazobactam and comparator susceptibilities when tested against isolates from US ICU patients hospitalized with pneumonia

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
Enterobacteriaceae (n=1,113)									
Ceftolozane-tazobactam	0.25	2	0.03 to >32	91.9	2.2	5.8	89.7		10.3
Amikacin	2	4	≤0.25 to 32	99.5	0.5	0	98.7	0.8	0.5
Cefepime	≤0.12	8	≤0.12 to >16	88.8	2.4	8.8 [b]	86.9	3.1	10.1
Ceftazidime	0.25	32	0.03 to >32	83.5	1.3	15.2	80.8	2.7	16.5
Colistin	0.12	>8	≤0.06 to >8				79.4		20.6
Levofloxacin	0.06	>4	≤0.03 to >4	87.2	1.3	11.5	83	2.7	14.3
Meropenem	0.03	0.06	≤0.015 to >32	97	0.7	2.2	97.8	1.3	1
Piperacillin-tazobactam	2	64	≤0.5 to >64	87.4	5.1	7.5	82.4	5	12.6
E. coli (n=216)									
Ceftolozane-tazobactam	0.25	0.5	0.06 to >32	95.8	1.4	2.8	95.4		4.6
Amikacin	2	4	0.5 to 32	99.1	0.9	0	96.8	2.3	0.9
Cefepime	≤0.12	>16	≤0.12 to >16	78.2	2.3	19.4 [b]	77.8	1.9	20.4
Ceftazidime	0.25	32	0.06 to >32	79.2	1.9	19	75.5	3.7	20.8
Colistin	0.12	0.25	≤0.06 to 1				100		0
Levofloxacin	0.25	>4	≤0.03 to >4	61.9	0.9	37.2	60.5	1.4	38.1
Meropenem	≤0.015	0.03	≤0.015 to 8	99.1	0	0.9	99.1	0.9	0
Piperacillin-tazobactam	2	16	≤0.5 to >64	90.7	0.9	8.3	87	3.7	9.3
K. pneumoniae (n=296)									
Ceftolozane-tazobactam	0.25	1	0.06 to >32	93.6	1	5.4	92.2		7.8
Amikacin	1	2	≤0.25 to 32	99.3	0.7	0	98.6	0.7	0.7
Cefepime	≤0.12	8	≤0.12 to >16	89.2	1	9.8 [b]	87.2	2	10.8
Ceftazidime	0.25	32	0.03 to >32	85.8	1	13.2	82.8	3	14.2
Colistin	0.12	0.25	≤0.06 to >8				98.3		1.7
Levofloxacin	0.06	1	≤0.03 to >4	92.5	1	6.4	86.1	4.4	9.5
Meropenem	0.03	0.03	≤0.015 to >32	95.3	1.4	3.4	96.6	1.4	2
Piperacillin-tazobactam	4	32	0.12 to >64	87.8	4.7	7.4	79.1	8.8	12.2
P. aeruginosa (n=571)									
Ceftolozane-tazobactam	0.5	2	0.12 to >32	97.9	0.4	1.8	97.9		2.1
Amikacin	4	8	≤0.25 to >32	96.5	1.6	1.9	91.6	4.9	3.5
Cefepime	4	16	≤0.5 to >16	84.2	11.2	4.6	84.2		15.8
Ceftazidime	2	32	≤0.25 to >32	82.5	5.6	11.9	82.5		17.5
Colistin	1	1	≤0.5 to 4	99.6		0.4	99.6		0.4
Levofloxacin	0.5	>4	≤0.12 to >4	76.0	7.2	16.8	65.8		34.2
Meropenem	0.5	8	≤0.015 to >32	77.1	7.9	15.1	77.1	13.3	9.6
Piperacillin-tazobactam	4	>64	≤0.5 to >64	77.1	12.4	10.5	77.1		22.9

[a] Criteria as published by CLSI (2018) and EUCAST (2018)
[b] Intermediate interpreted as susceptible-dose dependent

Organisms include: *Citrobacter amalonaticus/farmeri* (1), *C. freundii* species complex (13), *C. koseri* (23), *Enterobacter aerogenes* (98), *E. asburiae* (2), *E. cloacae* (77), *E. cloacae* species complex (82), *E. kobei* (1), *E. taylorae* (1), *Escherichia coli* (216), *Hafnia alvei* (3), *Klebsiella oxytoca* (96), *K. pneumoniae* (296), *K. variicola* (2), *Morganella morganii* (6), *Pantoea agglomerans* (2), *P. dispersa* (1), *Proteus mirabilis* (31), *P. vulgaris* (1), *P. vulgaris* group (2), *Providencia rettgeri* (5), *P. stuartii* (8), *Rahnella aquatilis* (1), *Raoultella ornithinolytica* (4), *R. planticola* (3), *Serratia liquefaciens* (4), *S. marcescens* (132), unspeciated *Pantoea* (1), unspeciated *Raoultella* (1)

Table 3 Antimicrobial activity of ceftolozane-tazobactam tested against the main organisms and organism groups of isolates

Organism/organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)												MIC_{50}	MIC_{90}
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>		
Enterobacteriaceae (1,113)	1 0.1	15 1.4	314 29.6	373 63.2	217 82.7	78 89.7	25 91.9	25 94.2	21 96	16 97.5	5 97.9	23 100	0.25	2
Escherichia coli (216)	0 0	7 3.2	100 49.5	71 82.4	21 92.1	7 95.4	1 95.8	3 97.2	1 97.7	2 98.6	1 99.1	2 100	0.25	0.5
CRE (2)							0 0	1 50	0 50	1 100			4	
ESBL non-CRE (53)		0 0	5 9.4	19 45.3	15 73.6	6 84.9	1 86.8	2 90.6	1 92.5	1 94.3	1 96.2	2 100	0.5	4
Levofloxacin-nonsusceptible (82)	0 0	2 2.4	12 17.1	39 64.6	15 82.9	6 90.2	1 91.5	2 93.9	1 95.1	2 97.6	1 98.8	1 100	0.25	1
Klebsiella pneumoniae (296)	0 0	2 0.7	91 31.4	114 69.9	37 82.4	29 92.2	4 93.6	3 94.6	2 95.3	7 97.6	1 98	6 100	0.25	1
CRE (13)							0 0	1 7.7	1 15.4	4 46.2	1 53.8	6 100	32	>32
ESBL, non-CRE (37)		0 0	1 2.7	7 21.6	7 40.5	14 78.4	3 86.5	2 91.9	1 94.6	2 100			1	4
Levofloxacin-nonsusceptible (22)			0 0	2 9.1	5 31.8	2 40.9	2 50	1 54.5	1 59.1	3 72.7	1 77.3	5 100	2	>32
Pseudomonas aeruginosa (571)		0 0	6 1.1	60 11.6	336 70.4	108 89.3	30 94.6	19 97.9	2 98.2	1 98.4	2 98.8	7 100	0.5	2
β lactam-nonsusceptible (45)					0 0	11 24.4	12 51.1	11 75.6	2 80	1 82.2	1 84.4	7 100	2	>32
Meropenem-nonsusceptible (131)			0 0	1 0.8	45 35.1	45 69.5	16 81.7	12 90.8	2 92.4	1 93.1	2 94.7	7 100	1	4
Ceftazidime-nonsusceptible (100)				0 0	10 10	32 42	27 69	19 88	2 90	1 91	2 93	7 100	2	8

CLSI (2018) susceptible breakpoint indicated by shaded column.

CONCLUSIONS

- Ceftolozane-tazobactam demonstrated activity against gram-negative isolates from US patients hospitalized with pneumonia in the ICU
- Ceftolozane-tazobactam, amikacin, and colistin had >93% susceptibility for each of the 3 most common pathogens in pneumonia patients in the ICU: *E. coli, K. pneumoniae,* and *P. aeruginosa*
 - Ceftolozane-tazobactam was the only β-lactam that had >90% susceptibility for *E. coli, K. pneumoniae,* and *P. aeruginosa*
- For *P. aeruginosa,* ceftolozane-tazobactam was the most active β-lactam tested and second in activity to colistin
- Although clinical data are needed to confirm these findings, these data suggest that ceftolozane-tazobactam may be a useful treatment option against gram-negative pathogens obtained from ICU patients hospitalized with pneumonia

Acknowledgements

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ USA

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Presented at ASM-Microbe 2018, June 7–11, 2018; Atlanta, Georgia

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