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The Activity of Ceftolozane/Tazobactam Against Gram-Negative Pathogens Isolated From Patients Hospitalized in Intensive Care Units in US Hospitals (2013-2014)

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Introduction

- Antimicrobial resistance in Gram-negative pathogens is high in the intensive care unit (ICU) setting because of selective pressure, enhanced transmission dynamics, and the ability of these pathogens to efficiently up-regulate and/or acquire genes that code for antimicrobial resistance
- Antimicrobial resistance in the ICU is an important determinant of clinical outcome and hospital length of stay. Antimicrobial drug resistance caused by the presence of multidrug-resistant (MDR) and extended-spectrum β-lactamase (ESBL)–producing strains of bacteria is a common feature of ICU infections and is increasing; hence, investigation into and availability of new antimicrobial treatments are urgently needed
- Ceftolozane/tazobactam is a novel antibacterial with activity against *Pseudomonas aeruginosa*, including MDR strains, and other common Gram-negative pathogens, including most ESBL-producing Enterobacteriaceae; is in clinical development in patients with ventilator-associated nosocomial bacterial pneumonia; and was recently approved for complicated urinary tract infection (cUTI), including pyelonephritis, and for complicated intra-abdominal infection (cIAI) (in combination with metronidazole) in the United States
- We evaluated the activity of ceftolozane/tazobactam and comparator agents tested against Gram-negative organisms collected from patients in ICUs in US hospitals from 2013 to 2014

Materials and Methods

Organism collection

- The organism collection included only aerobic Gram-negative bacilli collected from patients hospitalized in an ICU
- In 2013 and 2014, a total of 1052 unique patient organisms were consecutively collected from US medical centers (26 hospitals) by the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS)
- Species identification was performed at the participant medical center and confirmed at the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using standard phenotypic and biochemical methods or the MALDI-TOF (Bruker, Billerica, Massachusetts, USA), when necessary; only 1 strain per patient infection episode was included in this surveillance study

Susceptibility testing

- Isolates were tested for susceptibility to multiple antimicrobial agents at a reference laboratory (JMI Laboratories) by standardized broth microdilution methods, as described by the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document
- Minimum inhibitory concentration (MIC) results were interpreted according to CLSI criteria in M100-S25 (2015) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint tables (version 5.0, January 2015); *Escherichia coli* and *Klebsiella* spp. isolates with MIC ≥2 µg/mL for ceftazidime and/or ceftriaxone and/or aztreonam were categorized as ESBL phenotypes

Results

- The most frequently isolated Gram-negative pathogens from patients in ICUs were *P. aeruginosa* (n = 285; 27.1%) and Enterobacteriaceae (n = 697; 66.3%; **Table 1** and **Figure 1**)
  - The most prevalent Enterobacteriaceae species were *E. coli* (n = 212; 20.2% of all 1052 isolates), *Klebsiella pneumoniae* (n = 160; 15.2%), and *Enterobacter* spp. (129; 12.3%; **Figure 1**)
  - In *E. coli* and *K. pneumoniae*, the ESBL-positive rates were 17.9% and 28.1%, respectively (**Table 1**)

Table 1. Prevalence and cumulative ceftolozane/tazobactam MIC distributions and prevalence of 1052† Gram-negative ICU pathogens (2013-2014)

Organism†	No. of isolates	No. of isolates (cumulative %) inhibited at ceftolozane/tazobactam MIC (µg/mL)										MIC_{50}, µg/mL	MIC_{90}, µg/mL
		≤0.12	0.25	0.5	1	2	4	8	16	32	>32		
Pseudomonas aeruginosa	285	2 (0.7)	14 (5.6)	151 (58.6)	69 (82.8)	31 (93.7)	6 (95.8)‡	8 (98.6)	0 (98.6)	1 (98.9)	3 (100.0)	0.5	2
Enterobacteriaceae (all)§	697	119 (17.1)	261 (54.5)	154 (76.6)	50 (83.8)	32 (88.4)	21 (91.4)	10 (92.8)	16 (95.1)	7 (96.1)	27 (100.0)	0.25	4
Escherichia coli	212	65 (30.7)	105 (80.2)	23 (91.0)	9 (95.3)	5 (97.6)	1 (98.1)	2 (99.1)	1 (99.5)	0 (99.5)	1 (100.0)	0.25	0.5
Non-ESBL phenotype	174	64 (36.8)	97 (92.5)	12 (99.4)	0 (99.4)	1 (100.0)	–	–	–	–	–	0.25	0.25
ESBL phenotype	38	1 (2.6)	8 (23.7)	11 (52.6)	9 (76.3)	4 (86.8)	1 (89.5)	2 (94.7)	1 (97.4)	0 (97.4)	1 (100.0)	0.5	8
Klebsiella pneumoniae	160	21 (13.1)	65 (53.8)	25 (69.4)	9 (75.0)	3 (76.9)	0 (76.9)	4 (79.4)	4 (81.9)	7 (86.2)	22 (100.0)	0.25	>32
Non-ESBL phenotype	115	21 (18.3)	64 (73.9)	22 (93.0)	7 (99.1)	1 (100.0)	–	–	–	–	–	0.25	0.5
ESBL phenotype	45	–	1 (2.2)	3 (8.9)	2 (13.3)	2 (17.8)	0 (17.8)	4 (26.7)	4 (35.6)	7 (51.1)	22 (100.0)	32	>32
MEM-S-ESBL phenotype	13	–	1 (7.7)	3 (30.8)	1 (46.2)	1 (53.9)	0 (53.9)	2 (69.2)	2 (84.6)	0 (84.6)	2 (100.0)	2	>32
Enterobacter spp.	129	10 (7.8)	52 (48.1)	23 (65.9)	7 (71.3)	10 (79.1)	13 (89.1)	4 (92.2)	9 (99.2)	0 (99.2)	1 (100.0)	0.5	8
Acinetobacter spp.‖	43	4 (9.3)	0 (9.3)	1 (11.6)	6 (25.6)	3 (32.6)	3 (39.5)	3 (46.5)	4 (55.8)	1 (58.1)	18 (100.0)	16	>32
Stenotrophomonas maltophilia	26	–	–	1 (3.9)	3 (15.4)	3 (26.9)	4 (42.3)	1 (46.2)	3 (57.7)	5 (76.9)	6 (100.0)	16	>32

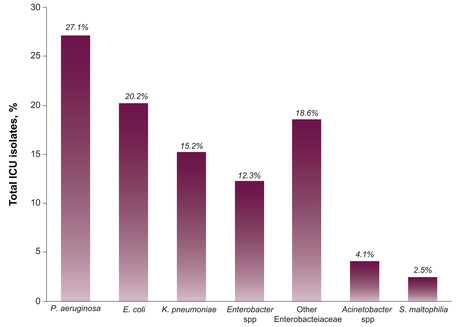
CAZ = ceftazidime; MEM = meropenem; S = susceptible.
†One isolate of *Pseudomonas fluorescens/putida* not included in the table.
‡Underlined values are the values at the US Food and Drug Administration susceptibility breakpoint.
§Includes: *Citrobacter braakii* (2 strains), *Citrobacter freundii* (12 strains), *C. freundii* spp. complex (3 strains), *Citrobacter koseri* (6 strains), *Enterobacter aerogenes* (37 strains), *Enterobacter asburiae* (3 strains), *E. coli* (212 strains), *Enterobacter cancerogenus* (1 strain), *Enterobacter cloacae* (73 strains), *E. cloacae* spp. complex (15 strains), *Klebsiella varricola* (2 strains), *Klebsiella oxytoca* (49 strains), *Klebsiella pneumoniae* (160 strains), *K. pneumoniae* subsp. *ozaenae* (2 strains), *Morganella morganii* (10 strains), *Proteus mirabilis* (31 strains), *Proteus vulgaris* (3 strains), *Providencia rettgeri* (1 strain), *Providencia stuartii* (6 strains), *Serratia marcescens* (68 strains), *Serratia odorifera* (1 strain).
‖Includes: *Acinetobacter baumannii-Acinetobacter calcoaceticus* spp. complex (39 strains), *Acinetobacter nosocomialis* (1 strain), *Acinetobacter lwoffii* (1 strain), *Acinetobacter ursingii* (2 strains).

Table 2. Activity of ceftolozane/tazobactam and comparator agents against aerobic Gram-negative bacilli isolated from ICUs in the United States (2013-2014)

Organism (no. tested)	$MIC_{50/90}$, µg/mL (% susceptible by CLSI criteria)				
	Ceftolozane/tazobactam	Piperacillin/tazobactam	Ceftazidime	Cefepime	Meropenem
Pseudomonas aeruginosa (285)	0.5/2 (95.8)	8/>64 (79.6)	2/32 (83.2)	2/16 (84.5)	0.5/8 (79.6)
Enterobacteriaceae (697)	0.25/4 (88.4)	2/>64 (82.9)	0.25/32 (81.6)	≤0.5/8 (87.2)	≤0.06/≤0.06 (94.3)
Escherichia coli (212)	0.25/0.5 (97.6)	2/16 (91.5)	0.25/16 (86.3)	≤0.5/16 (85.4)	≤0.06/≤0.06 (99.1)
Klebsiella pneumoniae (160)	0.25/>32 (76.9)	4/>64 (75.0)	0.25/>32 (73.8)	≤0.5/16 (75.0)	≤0.06/>8 (80.0)
Enterobacter spp. (129)	0.5/8 (79.1)	4/64 (73.2)	0.5/>32 (66.7)	≤0.5/2 (92.2)	≤0.06/≤0.06 (98.4)
Acinetobacter spp. (43)	16/>32 (–†)	>64/>64 (34.9)	>32/>32 (44.2)	>16/>16 (39.5)	>8/>8 3(9.5)
Stenotrophomonas maltophilia (26)	16/>32 (–)	64/>64 (–)	8/>32 (50.0)	>16/>16 (–)	>32/>32 (–)

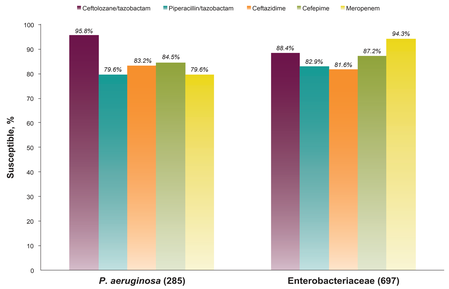
† "–" = no breakpoint available.

Figure 1. Prevalence of Gram-negative pathogens isolated from ICU patients in the United States (2013-2014).



- Overall, ceftolozane/tazobactam was very active against the most prevalent pathogens with MIC_{50} (µg/mL)/MIC_{90} (µg/mL)/percentage susceptible values of 0.5/2/95.8, 0.25/4/88.4, 0.25/0.5/97.6, 0.25/>32/76.9, and 0.5/8/79.1 for *P. aeruginosa*, all Enterobacteriaceae, *E. coli*, *K. pneumoniae*, and *Enterobacter* spp., respectively (**Tables 1** and **2**)
  - After meropenem (94.3% susceptible), ceftolozane/tazobactam was the second most active (88.4% susceptible) β-lactam agent tested against all 697 Enterobacteriaceae isolates combined (**Table 2**, **Figure 2**)

Figure 2. Activity of ceftolozane/tazobactam and comparator agents against *Pseudomonas aeruginosa* and Enterobacteriaceae isolated from ICU patients in the United States (2013-2014).



- Ceftolozane/tazobactam inhibited 86.8% of ESBL-phenotype *E. coli* at the US Food and Drug Administration susceptibility breakpoint of 2 µg/mL (**Table 1**)
- In contrast, only 17.8% of ESBL-phenotype *K. pneumoniae* were susceptible to ceftolozane/tazobactam, increasing to 53.9% in the meropenem-susceptible subpopulation (**Table 1**)
- Meropenem susceptibility (CLSI criteria) was 94.3%, 99.1%, and 80.0% for Enterobacteriaceae, *E. coli*, and *K. pneumoniae*, respectively
- The activity of meropenem (80.0%) against *K. pneumoniae* reflected the lower activity of other agents tested (susceptibility ranged from 73.8% for ceftazidime to 76.9% for ceftolozane/tazobactam) (**Table 2**)
- Ceftolozane/tazobactam was very active ($MIC_{50/90}$, 0.5/2 µg/mL, 95.8% susceptible) against 285 *P. aeruginosa* isolates (**Table 2**)
- In contrast, susceptibility rates for piperacillin/tazobactam, ceftazidime, cefepime, and meropenem were lower at 79.6%, 83.2%, 84.5%, and 79.6%, respectively (**Table 2**, **Figure 2**)
- Similar to other β-lactams, ceftolozane/tazobactam demonstrated limited activity against *Acinetobacter* spp. (prevalence of 4.1%) and *Stenotrophomonas maltophilia* isolates (prevalence of 2.5%; **Tables 1** and **2**, **Figure 1**)

Conclusions

- Ceftolozane/tazobactam demonstrated potent activity against contemporary (2013-2014) aerobic Gram-negative pathogens from patients in ICUs in the United States
- After meropenem, ceftolozane/tazobactam was the most active β-lactam agent tested against Enterobacteriaceae, including many ESBL-phenotype strains
- Against *P. aeruginosa*, ceftolozane/tazobactam demonstrated in vitro activity superior to that of piperacillin/tazobactam, ceftazidime, cefepime, and meropenem
- These data support a role for ceftolozane/tazobactam in the treatment of ICU patients in the United States

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