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Antimicrobial activity of ceftolozane–tazobactam tested against gram-negative contemporary (2015–2017) isolates from hospitalized patients with pneumonia in US medical centers

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ABSTRACT

Pseudomonas aeruginosa ($n = 1531$) and Enterobacteriaceae ($n = 2373$) clinical isolates from hospitalized patients with pneumonia were collected from 31 US medical centers during 2015–2017. Isolates were susceptibility tested against ceftolozane–tazobactam and comparators by broth microdilution. Results from intensive care unit (ICU) patients and patients with ventilator-associated bacterial pneumonia (VABP) were analyzed separately. Ceftolozane–tazobactam was very active against *P. aeruginosa* ($MIC_{50/90}$, 0.5/2 mg/L; 97.5% susceptible), including multidrug-resistant (87.9% susceptible) and extensively drug-resistant (82.9% susceptible). Ceftolozane–tazobactam inhibited 90.3% of Enterobacteriaceae isolates ($MIC_{50/90}$, 0.25/2 mg/L), including non–carbapenem-resistant Enterobacteriaceae isolates with an extended-spectrum β-lactamase phenotype (85.7% susceptible). Ceftolozane–tazobactam activity was stable against *P. aeruginosa* regardless of the US census division or ICU and VABP subsets (>90%); small differences were noted among Enterobacteriaceae isolates from the Middle Atlantic (range 78.3–88.9%) and West South Central (range 86.4–89.2%) divisions. These in vitro results indicate that ceftolozane–tazobactam may represent a valuable option for hospital-acquired bacterial pneumonia and VABP caused by Enterobacteriaceae and *P. aeruginosa* in the United States.

1. Introduction

Pneumonia is one of the leading causes of mortality in the United States, accounting for more than 50,000 deaths in 2015 (CDC, 2017). Optimal treatment of pneumonia involves selecting an empiric antibiotic regimen that provides early appropriate antibiotic coverage and avoiding unnecessary treatment that may lead to adverse drug effects, *Clostridium difficile* infection, and antibiotic resistance (Jones et al., 2015). Selecting the most appropriate empiric therapy regimen requires knowledge of local epidemiology and antimicrobial susceptibility patterns. In 2016, the Infectious Disease Society of America and the American Thoracic Society recommended empiric coverage of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and other Gram-negative bacilli in patients with hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) (Kalil et al., 2016). Considering that *P. aeruginosa* isolates are intrinsically less susceptible (S) to several antimicrobial agents, the current clinically available antipseudomonal antibiotics include ceftazidime, cefepime, piperacillin–tazobactam, aztreonam, carbapenems (except ertapenem), fluoroquinolones, aminoglycosides, and polymyxins. However, *P. aeruginosa* isolates displaying resistance to these agents are not uncommon in the hospital setting, and the prevalence of extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, which are usually resistant to these agents, is increasing worldwide (Biehl et al., 2016).

Since aminoglycosides and polymyxins should be avoided if alternative agents with adequate Gram-negative activity are available (Kalil et al., 2016), carbapenems, new agents, and inhibitor combinations have been suggested in the literature for treating HABP caused by resistant pathogens (Perez and Bonomo, 2012; Rodriguez-Bano, et al., 2012). Among these options, ceftolozane–tazobactam has been demonstrated to overcome the most prevalent resistance mechanisms, such as chromosomal Ambler class C cephalosporinase, several ESBLs, loss of the outer membrane porin, and upregulation of efflux pumps. Ceftolozane–tazobactam also demonstrated activity against carbapenem-resistant strains that do not produce carbapenemases (Bassetti et al., 2018; Pfaller et al., 2017). However, this agent is not active against serine carbapenemases, such as *Klebsiella pneumoniae* carbapenemase (KPC), or metallo-β-lactamases (Sucher et al., 2015).

Ceftolozane–tazobactam is a combination of a new cephalosporin with a well-known β-lactamase inhibitor. It is approved for clinical use in over 50 countries worldwide, including the United States and Europe, for the treatment of complicated intra-abdominal infections

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(in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis, in adults (EMA, 2015; ZERBAXA, 2016). Ceftolozane–tazobactam has demonstrated acceptable treatment success rates for serious infections caused by *P. aeruginosa*, including carbapenem-resistant isolates (Dinh et al., 2017; Munita et al., 2017) and ESBL-producing Enterobacteriaceae (Popejoy et al., 2017). A phase 3 clinical trial to assess the safety and efficacy of ceftolozane–tazobactam (3 g every 8 h intravenous, 60-min infusion) compared with meropenem (1 g every 8 h intravenous, 60-min infusion) for the treatment of HABP, including VABP, has met the primary endpoint of noninferiority, although results have not yet been published (ClinicalTrials.gov registration no. NCT02070757).

In this study, we evaluated the activity of ceftolozane–tazobactam against 1531 *P. aeruginosa* and 2373 Enterobacteriaceae isolates from pneumonia in hospitalized patients (PHP) in US medical centers during 2015–2017. Results were stratified by US census division. Isolates from patients hospitalized in an intensive care unit (ICU) and those with VABP were analyzed separately. The collection included multidrug-resistant (MDR) and extensively drug-resistant (XDR) *P. aeruginosa* and ESBL-phenotype Enterobacteriaceae isolates.

2. Materials and methods

2.1. Frequency of occurrence of bacterial organisms from PHP

Consecutive unique bacterial isolates were cultured from hospitalized patients with pneumonia in a prevalence sampling design as part of the Program to Assess Ceftolozane–Tazobactam Susceptibility (PACTS) surveillance program (Castanheira et al., 2018). Medical records were not available to make epidemiological inferences about the origin of infection. Thus, hospitalized patients with pneumonia include patients hospitalized for any reason and presenting with pneumonia at any point during their hospital stay. Each participating center was requested to collect 100 consecutive bacterial isolates from lower respiratory tract sites determined to be significant by local criteria as the reported probable cause of pneumonia. Isolates were recovered by transtracheal aspiration, bronchoalveolar lavage, protected brush samples, qualified sputum samples, etc. The frequency of occurrence of organisms in ICU patients (regardless of VABP status) and the frequency of those from ICU patients with VABP were analyzed separately. Although all organisms were collected, only *P. aeruginosa* and Enterobacteriaceae isolates were tested for susceptibility against ceftolozane–tazobactam and comparator agents.

2.2. Enterobacteriaceae and P. aeruginosa tested against ceftolozane–tazobactam and comparator agents

A total of 1531 *P. aeruginosa* and 2373 Enterobacteriaceae isolates were recovered from 31 US medical centers distributed among 22 states from all 9 census divisions from 2015 through 2017. Isolates were processed locally and were forwarded to a central laboratory (JMI Laboratories, Inc., North Liberty, IA) for reference identification and susceptibility testing. Only 1 isolate referred per patient infection episode was included in the study. Isolates referred by the participating medical center as ICU-only or ICU and VABP were analyzed separately from those not designated as ICU or VABP. Bacterial identification was confirmed by matrix-assisted laser desorption ionization–time of flight mass spectrometry using Biotyper (Bruker Daltonics, Billerica, MA) according to the manufacturer's instructions.

2.3. Resistant subsets

P. aeruginosa isolates were categorized as MDR or XDR according to criteria initially published by Magiorakos et al. (2012) and adapted by Farrell et al. (2013), which define MDR as nonsusceptible to 1 agent in ≥3 antimicrobial classes, XDR as nonsusceptible to 1 agent in all but ≤2 antimicrobial classes, and pan-drug resistant as nonsusceptible to all agents in all antimicrobial classes tested, using CLSI criteria to define nonsusceptibility. The antimicrobial classes and drug representatives used in the analysis for *P. aeruginosa* were antipseudomonal cephalosporins (ceftazidime and cefepime), carbapenems (meropenem), broad-spectrum penicillins combined with a β-lactamase inhibitor (piperacillin–tazobactam), fluoroquinolones (levofloxacin), aminoglycosides (amikacin), and the polymyxins (colistin). *Escherichia coli*, *K. pneumoniae, Klebsiella oxytoca*, and *P. mirabilis* isolates were grouped as "ESBL screening-positive phenotype" based on the CLSI screening criteria for ESBL production, i.e., MIC of >1 mg/L for ceftazidime, ceftriaxone, and/or aztreonam, for the purpose of susceptibility testing results analysis. Carbapenem-resistant Enterobacteriaceae (CRE) isolates were defined as displaying MIC values ≥4 mg/L for imipenem (*P. mirabilis* and indole-positive Proteeae were not included due to the intrinsically elevated MIC values), meropenem, and/or doripenem. Since carbapenemase-producing isolates may also appear to have an ESBL phenotype, non–carbapenem-resistant ESBL-phenotype (ESBL, non-CRE) isolates were analyzed.

2.4. Susceptibility tests

Broth microdilution test methods conducted according to CLSI methods were performed to determine the antimicrobial susceptibility of ceftolozane–tazobactam (inhibitor at fixed concentration of 4 mg/L) and comparator agents (CLSI, 2018a). Categorical interpretations for all antimicrobials were those found in CLSI document M100 (CLSI, 2018b) and EUCAST guidelines (colistin for Enterobacteriaceae only) (EUCAST, 2018). Quality control was performed using *E. coli* ATCC 25922 and ATCC 35218, *K. pneumoniae* ATCC 700603, and *P. aeruginosa* ATCC 27853, and results were within the CLSI published ranges (CLSI, 2018b).

3. Results

3.1. Frequency of occurrence of bacterial organisms from PHP

The frequency was calculated based on the total number of isolates collected from PHP in 2017. Although all organisms were collected, only *P. aeruginosa* and Enterobacteriaceae isolates were tested for susceptibility to ceftolozane–tazobactam and comparator agents. *S. aureus* (27.5%) was the most frequent pathogen, followed by *P. aeruginosa* (24.7%); *K. pneumoniae* (7.8%), and *E. coli* (6.5%). Isolates recovered from ICU patients (40.7%) presented similar frequency distributions: *S. aureus* (26.9%), *P. aeruginosa* (20.9%), *K. pneumoniae* (8.6%), and *E. coli* (7.6%). However, although *S. aureus* (23.1%) and *P. aeruginosa* (22.9%) were the most frequent pathogens among VABP isolates (11.6%), *Stenotrophomonas maltophilia* (6.8%) was the third most frequent pathogen followed closely by *K. pneumoniae* (6.7%) and *E. coli* (6.1%). Overall, *P. aeruginosa* and Enterobacteriaceae isolates combined represented 54.5% of pathogens recovered from PHP, 57.3% recovered from ICU patients, and 60.0% recovered from patients with VABP.

3.2. Ceftolozane–tazobactam activity against P. aeruginosa

Ceftolozane–tazobactam inhibited 97.5% of *P. aeruginosa* isolates ($n = 1531$) at the current CLSI, US FDA, and EUCAST susceptible breakpoint criterion of ≤4/4 mg/L and displayed greater in vitro activity than all other antipseudomonal β-lactams tested (Tables 1 and 2). This compound remained active against isolates nonsusceptible to other β-lactams, inhibiting 89.1% of isolates nonsusceptible to piperacillin–tazobactam ($MIC_{50/90}$, 1/8 mg/L), 85.7% of isolates nonsusceptible to ceftazidime ($MIC_{50/90}$, 2/8 mg/L), 86.1% of isolates nonsusceptible to cefepime ($MIC_{50/90}$, 2/8 mg/L), and 90.8% of isolates nonsusceptible to meropenem ($MIC_{50/90}$, 1/4 mg/L; Tables 1 and 2). In addition,

Table 1
Antimicrobial activity of ceftolozane–tazobactam tested against *P. aeruginosa* and Enterobacteriaceae from pneumonia in hospitalized patients in US medical centers (2015–2017).

Organism/organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)													MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]		
***P. aeruginosa* (1531)**	0	1	5	18	214	780	327	96	**52**	13	7	2	16	0.5	2
	0.0	0.1	0.4	1.6	15.5	66.5	87.9	94.1	**97.5**	98.4	98.8	99.0	100.0		
Piperacillin–tazobactam nonsusceptible (>16 mg/L) (341)				0	1	53	121	78	**51**	12	7	2	16	1	8
				0.0	0.3	15.8	51.3	74.2	**89.1**	92.7	94.7	95.3	100.0		
Ceftazidime nonsusceptible (>8 mg/L) (266)					0	16	85	75	**52**	13	7	2	16	2	8
					0.0	6.0	38.0	66.2	**85.7**	90.6	93.2	94.0	100.0		
Cefepime nonsusceptible (>2 mg/L) (251)					0	8	90	72	**46**	12	7	1	15	2	8
					0.0	3.2	39.0	67.7	**86.1**	90.8	93.6	94.0	100.0		
Meropenem nonsusceptible (>2 mg/L) (368)				0	7	107	130	55	**35**	11	7	2	14	1	4
				0.0	1.9	31.0	66.3	81.2	**90.8**	93.8	95.7	96.2	100.0		
MDR (307)				0	2	33	121	74	**40**	12	7	2	16	1	8
				0.0	0.7	11.4	50.8	74.9	**87.9**	91.9	94.1	94.8	100.0		
XDR (193)					0	6	76	46	**32**	9	7	2	15	2	16
					0.0	3.1	42.5	66.3	**82.9**	87.6	91.2	92.2	100.0		
Enterobacteriaceae (2373)	0	1	33	656	739	492	156	**67**	60	50	29	16	74	0.25	2
	0.0	< 0.1	1.4	29.1	60.2	81.0	87.5	**90.3**	92.9	95.0	96.2	96.9	100.0		
Non-ESBL (1059)		0	21	470	397	133	35	**3**						0.25	0.5
		0.0	2.0	46.4	83.9	96.4	99.7	**100.0**							
ESBL, non-CRE (280)		0	2	17	64	81	52	**24**	17	8	7	1	7	0.5	4
		0.0	0.7	6.8	29.6	58.6	77.1	**85.7**	91.8	94.6	97.1	97.5	100.0		
***Escherichia coli* (435)**		0	10	202	132	56	18	**2**	6	3	2	1	3	0.25	0.5
		0.0	2.3	48.7	79.1	92.0	96.1	**96.6**	97.9	98.6	99.1	99.3	100.0		
Non-ESBL (298)		0	9	189	87	10	3							0.12	0.25
		0.0	3.0	66.4	95.6	99.0	100.0								
ESBL, non-CRE (134)		0	1	13	45	46	15	**2**	5	3	1	1	2	0.5	2
		0.0	0.7	10.4	44.0	78.4	89.6	**91.0**	94.8	97.0	97.8	98.5	100.0		
***Klebsiella* spp. (864)**		0	13	282	284	117	65	**24**	13	9	11	7	39	0.25	2
		0.0	1.5	34.1	67.0	80.6	88.1	**90.9**	92.4	93.4	94.7	95.5	100.0		
K. pneumoniae (664)		0	6	184	229	97	62	**18**	10	7	11	5	35	0.25	4
		0.0	0.9	28.6	63.1	77.7	87.0	**89.8**	91.3	92.3	94.0	94.7	100.0		
Non-ESBL (503)		0	5	180	214	73	29	**2**						0.25	0.5
		0.0	1.0	36.8	79.3	93.8	99.6	100.0							
ESBL, non-CRE (116)		0	1	4	15	24	33	**16**	9	4	6	0	4	1	8
		0.0	0.9	4.3	17.2	37.9	66.4	**80.2**	87.9	91.4	96.6	96.6	100.0		
K. oxytoca (196)		0	7	95	55	20	3	**6**	3	2	0	2	3	0.12	0.5
		0.0	3.6	52.0	80.1	90.3	91.8	**94.9**	96.4	97.4	97.4	98.5	100.0		
Non-ESBL (170)		0	7	95	51	16	1							0.12	0.25
		0.0	4.1	60.0	90.0	99.4	100.0								
***Enterobacter* spp. (510)**	0	1	4	105	186	58	23	**30**	34	33	11	5	20	0.25	8
	0.0	0.2	1.0	21.6	58.0	69.4	73.9	**79.8**	86.5	92.9	95.1	96.1	100.0		
E. cloacae species complex (334)	0	1	3	66	117	36	12	**16**	21	27	10	5	20	0.25	16
	0.0	0.3	1.2	21.0	56.0	66.8	70.4	**75.1**	81.4	89.5	92.5	94.0	100.0		
E. aerogenes (175)		0	1	39	69	21	11	**14**	13	6	1			0.25	4
		0.0	0.6	22.9	62.3	74.3	80.6	**88.6**	96.0	99.4	100.0				
***Citrobacter* spp. (96)**		0	2	39	30	7	5	**1**	2	3	3	1	3	0.25	8
		0.0	2.1	42.7	74.0	81.2	86.5	**87.5**	89.6	92.7	95.8	96.9	100.0		
C. koseri (51)		0	2	27	16	5	1							0.12	0.5
		0.0	3.9	56.9	88.2	98.0	100.0								
C. freundii species complex (44)			0	11	14	2	4	**1**	2	3	3	1	3	0.25	16
			0.0	25.0	56.8	61.4	70.5	**72.7**	77.3	84.1	90.9	93.2	100.0		
***P. mirabilis* (96)**			0	3	45	41	5	**1**	0	0	0	0	1	0.25	0.5
			0.0	3.1	50.0	92.7	97.9	**99.0**	99.0	99.0	99.0	99.0	100.0		
Non-ESBL (85)			0	3	45	34	2	**1**						0.25	0.5
			0.0	3.5	56.5	96.5	98.8	100.0							
Indole-positive *Proteus* spp. (65)		0	3	7	26	22	1	**1**	3	1	0	1		0.25	1
		0.0	4.6	15.4	55.4	89.2	90.8	**92.3**	96.9	98.5	98.5	100.0			
***Serratia* spp. (275)**			0	3	31	187	36	**8**	1	1	0	0	8	0.5	1
			0.0	1.1	12.4	80.4	93.5	**96.4**	96.7	97.1	97.1	97.1	100.0		
S. marcescens (267)			0	2	29	182	36	**8**	1	1	0	0	8	0.5	1
			0.0	0.7	11.6	79.8	93.3	**96.3**	96.6	97.0	97.0	97.0	100.0		

[a] Greater than the highest dilution tested.

ceftolozane–tazobactam was the most active β-lactam compound tested against the entire *P. aeruginosa* collection (Table 2).

MDR (n = 307) and XDR (n = 193) *P. aeruginosa* isolates represented 20.1% and 12.6% of the *P. aeruginosa* isolates tested, and ceftolozane–tazobactam was active against 87.9% and 82.9% of these isolates, respectively. In contrast, cefepime, ceftazidime, piperacillin–tazobactam, and meropenem displayed reduced susceptibility rates against MDR (20.2–34.2%S) and XDR (9.3–25.4%S) *P. aeruginosa* isolates. Colistin ($MIC_{50/90}$, ≤0.5/1 mg/L; >99%S) and amikacin ($MIC_{50/90}$, 4–8/16–>32 mg/L; 73.1–93.7%S) were also very active against the entire *P. aeruginosa* collection, including MDR and XDR isolates. Only 1 pan-drug-resistant *P. aeruginosa* isolate was observed in this collection: an isolate recovered in 2016 from an ICU patient in the New England US census division that was susceptible only to ceftolozane–tazobactam (MIC, 2 mg/L) among the antimicrobial agents tested.

P. aeruginosa isolates recovered from the ICU and VABP patients had slightly higher susceptibility rates to ceftolozane–tazobactam (97.9% and 99.5%S, respectively) compared to the entire *P. aeruginosa* collection

Table 2
Antimicrobial activity of ceftolozane–tazobactam and comparator agents tested against 1531 *P. aeruginosa* and 2373 Enterobacteriaceae isolates from pneumonia in hospitalized patients.

Organism/organism group (no. of isolates)	MIC_{50}	MIC_{90}	Range	CLSI[a]		EUCAST[a]	
Antimicrobial agent	(mg/L)			%S	%R	%S	%R
P. aeruginosa							
All isolates (1531)							
Ceftolozane–tazobactam	0.5	2	0.03 to >32	97.5	1.6	97.5	2.5
Amikacin	4	16	≤0.25 to >32	93.7	3.7	87.0	6.3
Aztreonam	8	>16	≤0.12 to >16	69.0	19.3	10.5	19.3
Cefepime	4	16	≤0.5 to >16	83.6	5.4	83.6	16.4
Ceftazidime	2	32	≤0.25 to >32	82.6	12.4	82.6	17.4
Colistin	≤0.5	1	≤0.5 to 4	99.9	0.1	99.9	0.1
Levofloxacin	1	>4	≤0.12 to >4	71.7	18.7	60.8	39.2
Meropenem	0.5	16	≤0.015 to >32	76.0	17.4	76.0	10.6
Piperacillin–tazobactam	4	>64	≤0.5 to >64	77.7	11.0	77.7	22.3
Piperacillin–tazobactam nonsusceptible (341)							
Ceftolozane–tazobactam	1	8	0.25 to >32	89.1	7.3	89.1	10.9
Amikacin	4	32	≤0.25 to >32	85.9	9.4	74.2	14.1
Aztreonam	>16	>16	2 to >16	11.7	68.6	0.0	68.6
Cefepime	16	>16	2 to >16	40.9	21.2	40.9	59.1
Ceftazidime	32	>32	1 to >32	27.0	54.3	27.0	73.0
Colistin	≤0.5	1	≤0.5 to 4	99.4	0.6	99.4	0.6
Levofloxacin	4	>4	≤0.12 to >4	42.2	41.3	28.4	71.6
Meropenem	8	32	≤0.015 to >32	40.2	52.2	40.2	36.1
Piperacillin–tazobactam	64	>64	32 to >64	0.0	49.3	0.0	100.0
Ceftazidime nonsusceptible (266)							
Ceftolozane–tazobactam	2	8	0.5 to >32	85.7	9.4	85.7	14.3
Amikacin	8	>32	≤0.25 to >32	81.2	12.4	70.3	18.8
Aztreonam	>16	>16	1 to >16	8.3	71.4	0.4	71.4
Cefepime	16	>16	2 to >16	30.8	27.8	30.8	69.2
Ceftazidime	32	>32	16 to >32	0.0	71.4	0.0	100.0
Colistin	≤0.5	1	≤0.5 to 4	99.6	0.4	99.6	0.4
Levofloxacin	4	>4	≤0.12 to >4	42.1	44.7	30.5	69.5
Meropenem	8	32	0.06 to >32	39.1	52.3	39.1	33.8
Piperacillin–tazobactam	>64	>64	≤0.5 to >64	6.4	60.9	6.4	93.6
Cefepime nonsusceptible (251)							
Ceftolozane–tazobactam	2	8	0.5 to >32	86.1	9.2	86.1	13.9
Amikacin	8	>32	≤0.25 to >32	79.3	13.1	62.5	20.7
Aztreonam	>16	>16	0.5 to >16	11.2	73.3	3.2	73.3
Cefepime	16	>16	16 to >16	0.0	32.7	0.0	100.0
Ceftazidime	32	>32	0.25 to >32	26.7	59.8	26.7	73.3
Colistin	≤0.5	1	≤0.5 to 4	99.6	0.4	99.6	0.4
Levofloxacin	>4	>4	≤0.12 to >4	33.1	52.6	19.5	80.5
Meropenem	8	32	0.06 to >32	35.1	56.6	35.1	41.0
Piperacillin–tazobactam	>64	>64	1 to >64	19.9	53.4	19.9	80.1
Meropenem nonsusceptible (368)							
Ceftolozane–tazobactam	1	4	0.25 to >32	90.8	6.2	90.8	9.2
Amikacin	8	32	≤0.25 to >32	85.3	9.8	74.2	14.7
Aztreonam	>16	>16	0.5 to >16	27.2	51.4	1.4	51.4
Cefepime	8	>16	1 to >16	55.7	17.7	55.7	44.3
Ceftazidime	8	>32	1 to >32	56.0	31.2	56.0	44.0
Colistin	≤0.5	1	≤0.5 to 4	99.7	0.3	99.7	0.3
Levofloxacin	>4	>4	≤0.12 to >4	31.0	52.2	17.9	82.1
Meropenem	8	32	4 to >32	0.0	72.6	0.0	44.0
Piperacillin–tazobactam	32	>64	≤0.5 to >64	44.6	27.7	44.6	55.4
MDR (307)							
Ceftolozane–tazobactam	1	8	0.25 to >32	87.9	8.1	87.9	12.1
Amikacin	8	>32	≤0.25 to >32	78.8	13.0	61.9	21.2
Aztreonam	>16	>16	0.5 to >16	16.0	64.5	2.6	64.5
Cefepime	16	>16	4 to >16	34.2	24.4	34.2	65.8
Ceftazidime	16	>32	0.25 to >32	34.2	48.9	34.2	65.8
Colistin	≤0.5	1	≤0.5 to 4	99.3	0.7	99.3	0.7
Levofloxacin	>4	>4	≤0.12 to >4	19.2	62.5	9.1	90.9
Meropenem	8	32	0.12 to >32	20.2	66.4	20.2	44.6
Piperacillin–tazobactam	64	>64	1 to >64	20.8	43.3	20.8	79.2
XDR (193)							
Ceftolozane–tazobactam	2	16	0.5 to >32	82.9	12.4	82.9	17.1
Amikacin	8	>32	0.5 to >32	73.1	17.6	52.8	26.9
Aztreonam	>16	>16	0.5 to >16	8.8	72.5	1.6	72.5
Cefepime	16	>16	4 to >16	22.8	33.2	22.8	77.2
Ceftazidime	32	>32	1 to >32	25.4	55.4	25.4	74.6
Colistin	≤0.5	1	≤0.5 to 4	99.0	1.0	99.0	1.0
Levofloxacin	>4	>4	≤0.12 to >4	6.7	72.5	2.6	97.4
Meropenem	16	32	0.12 to >32	11.4	75.6	11.4	52.3
Piperacillin–tazobactam	64	>64	2 to >64	9.3	49.2	9.3	90.7
Enterobacteriaceae[b]							
All isolates (2373)							
Ceftolozane–tazobactam	0.25	2	0.03 to >32	90.3	7.1	87.5	12.5

Table 2 *(continued)*

Organism/organism group (no. of isolates)	MIC_{50}	MIC_{90}	Range	CLSI[a]		EUCAST[a]	
Antimicrobial agent	(mg/L)			%S	%R	%S	%R
Amikacin	2	4	≤0.25 to >32	98.7	0.3	97.3	1.3
Ampicillin–sulbactam	16	>32	≤0.5 to >32	39.5	44.5	39.5	60.5
Aztreonam	≤0.12	>16	≤0.12 to >16	80.3	18.1	77.4	19.7
Cefepime	≤0.12	16	≤0.12 to >16	85.5	11.0	83.4	12.8
Ceftazidime	0.25	>32	0.03 to >32	80.5	18.2	76.8	19.5
Ceftriaxone	0.12	>8	≤0.06 to >8	75.9	22.4	75.9	22.4
Colistin	0.12	>8	≤0.06 to >8	78.7 [d]		78.7	21.3
Gentamicin	0.5	8	≤0.12 to >8	89.5	8.6	88.5	10.5
Levofloxacin	0.06	>4	≤0.03 to >4	83.0	15.1	78.4	18.7
Meropenem	0.03	0.06	≤0.015 to >32	96.0	3.2	96.8	1.8
Piperacillin–tazobactam	2	64	≤0.5 to >64	86.0	8.2	80.6	14.0
ESBL, non-CRE (280)[c]							
Ceftolozane–tazobactam	0.5	4	0.06 to >32	85.7	8.2	77.1	22.9
Amikacin	2	8	≤0.25 to >32	97.1	0.4	91.1	2.9
Ampicillin–sulbactam	32	>32	4 to >32	9.3	77.5	9.3	90.7
Aztreonam	>16	>16	≤0.12 to >16	22.1	70.4	9.6	77.9
Cefepime	>16	>16	≤0.12 to >16	26.1	57.5 [b]	20.7	65.4
Ceftazidime	32	>32	0.06 to >32	28.9	66.1	8.6	71.1
Ceftriaxone	>8	>8	0.12 to >8	11.8	85.4	11.8	85.4
Colistin	0.12	0.25	≤0.06 to >8	95.4 [d]		95.4	4.6
Gentamicin	1	>8	≤0.12 to >8	59.6	37.9	57.1	40.4
Levofloxacin	>4	>4	≤0.03 to >4	40.0	55.7	31.8	61.8
Meropenem	0.03	0.06	≤0.015 to 2	98.2	0.0	100.0	0.0
Piperacillin–tazobactam	8	>64	≤0.5 to >64	69.5	21.9	51.6	30.5
E. coli							
All isolates (435)							
Ceftolozane–tazobactam	0.25	0.5	0.06 to >32	96.6	2.1	96.1	3.9
Amikacin	2	8	0.5 to 32	99.1	0.0	95.9	0.9
Ampicillin–sulbactam	16	>32	≤0.5 to >32	39.3	43.9	39.3	60.7
Aztreonam	≤0.12	>16	≤0.12 to >16	73.1	23.0	68.7	26.9
Cefepime	≤0.12	>16	≤0.12 to >16	74.3	21.6	73.1	23.4
Ceftazidime	0.25	>32	0.06 to >32	76.6	21.6	70.1	23.4
Ceftriaxone	≤0.06	>8	≤0.06 to >8	69.4	29.9	69.4	29.9
Colistin	0.12	0.25	≤0.06 to 4	99.5 [d]		99.5	0.5
Gentamicin	1	>8	0.25 to >8	79.1	20.2	78.2	20.9
Levofloxacin	0.5	>4	≤0.03 to >4	55.5	42.9	54.4	44.5
Meropenem	≤0.015	0.03	≤0.015 to 16	99.3	0.7	99.3	0.2
Piperacillin–tazobactam	2	16	≤0.5 to >64	90.6	6.5	83.6	9.4
ESBL, non-CRE (134)							
Ceftolozane–tazobactam	0.5	2	0.06 to >32	91.0	5.2	89.6	10.4
Amikacin	4	16	0.5 to 32	97.8	0.0	89.6	2.2
Ampicillin–sulbactam	32	>32	4 to >32	12.7	73.9	12.7	87.3
Aztreonam	>16	>16	0.5 to >16	14.9	72.4	0.7	85.1
Cefepime	>16	>16	≤0.12 to >16	18.7	67.9 [b]	14.9	73.9
Ceftazidime	32	>32	0.5 to >32	26.1	67.9	5.2	73.9
Ceftriaxone	>8	>8	0.5 to >8	3.0	94.8	3.0	94.8
Colistin	0.12	0.25	≤0.06 to 4	99.3 [d]		99.3	0.7
Gentamicin	1	>8	0.25 to >8	59.0	40.3	57.5	41.0
Levofloxacin	>4	>4	≤0.03 to >4	16.4	82.8	15.7	83.6
Meropenem	0.03	0.03	≤0.015 to 0.5	100.0	0.0	100.0	0.0
Piperacillin–tazobactam	8	64	≤0.5 to >64	85.0	9.8	66.9	15.0
Klebsiella pneumoniae							
All isolates (664)							
Ceftolozane–tazobactam	0.25	4	0.06 to >32	89.8	8.7	87.0	13.0
Amikacin	1	4	≤0.25 to >32	96.8	0.8	94.7	3.2
Ampicillin–sulbactam	8	>32	1 to >32	63.6	25.5	63.6	36.4
Aztreonam	≤0.12	>16	≤0.12 to >16	79.8	19.6	78.6	20.2
Cefepime	≤0.12	>16	≤0.12 to >16	81.3	16.0	80.0	17.6
Ceftazidime	0.25	>32	0.03 to >32	79.2	20.0	76.2	20.8
Ceftriaxone	≤0.06	>8	≤0.06 to >8	79.1	20.6	79.1	20.6
Colistin	0.12	0.25	≤0.06 to >8	98.0 [d]		98.0	2.0
Gentamicin	0.25	8	≤0.12 to >8	89.2	8.9	88.1	10.8
Levofloxacin	0.06	>4	≤0.03 to >4	86.4	11.9	79.8	14.9
Meropenem	0.03	0.06	≤0.015 to >32	92.8	6.0	94.0	4.1
Piperacillin–tazobactam	4	>64	0.12 to >64	84.8	11.6	77.1	15.2
ESBL, non-CRE (116)							
Ceftolozane–tazobactam	1	8	0.06 to >32	80.2	12.1	66.4	33.6
Amikacin	1	8	0.5 to >32	95.7	0.9	92.2	4.3
Ampicillin–sulbactam	>32	>32	4 to >32	4.3	81.9	4.3	95.7
Aztreonam	>16	>16	≤0.12 to >16	23.3	73.3	16.4	76.7
Cefepime	16	>16	≤0.12 to >16	31.9	56.9	25.0	62.9
Ceftazidime	32	>32	1 to >32	19.8	76.7	2.6	80.2
Ceftriaxone	>8	>8	0.12 to >8	19.0	79.3	19.0	79.3
Colistin	0.12	0.25	≤0.06 to >8	97.4 [d]		97.4	2.6

(continued on next page)

Table 2 *(continued)*

Organism/organism group (no. of isolates)	MIC_{50}	MIC_{90}	Range	CLSI[a]		EUCAST[a]	
Antimicrobial agent	(mg/L)			%S	%R	%S	%R
Gentamicin	2	>8	≤0.12 to >8	54.3	41.4	50.9	45.7
Levofloxacin	1	>4	≤0.03 to >4	60.3	31.9	43.1	42.2
Meropenem	0.03	0.12	≤0.015 to 2	95.7	0.0	100.0	0.0
Piperacillin–tazobactam	16	>64	0.5 to >64	58.6	27.6	37.1	41.4
Enterobacter spp. (510)[e]							
Ceftolozane–tazobactam	0.25	8	0.03 to >32	79.8	13.5	73.9	26.1
Amikacin	1	2	0.5 to 32	99.8	0.0	99.2	0.2
Ampicillin–sulbactam	32	>32	2 to >32	14.1	64.1	14.1	85.9
Aztreonam	≤0.12	>16	≤0.12 to >16	71.0	26.9	68.2	29.0
Cefepime	≤0.12	4	≤0.12 to >16	89.0	7.1	84.9	9.0
Ceftazidime	0.5	>32	0.03 to >32	69.6	28.8	67.3	30.4
Ceftriaxone	0.25	>8	≤0.06 to >8	66.5	32.0	66.5	32.0
Colistin	0.12	>8	≤0.06 to >8	86.2 [d]		86.2	13.8
Gentamicin	0.25	0.5	≤0.12 to >8	93.3	4.1	93.1	6.7
Levofloxacin	≤0.03	1	≤0.03 to >4	93.1	5.3	89.0	9.6
Meropenem	0.03	0.12	≤0.015 to >32	95.7	2.7	97.3	0.6
Piperacillin–tazobactam	4	64	≤0.5 to >64	76.2	9.2	70.5	23.8
Citrobacter spp. (96)							
Ceftolozane–tazobactam	0.25	8	0.06 to >32	87.5	10.4	86.5	13.5
Amikacin	1	2	≤0.25 to 4	100.0	0.0	100.0	0.0
Ampicillin–sulbactam	8	>32	1 to >32	69.8	24.0	69.8	30.2
Aztreonam	≤0.12	>16	≤0.12 to >16	81.2	18.8	81.2	18.8
Cefepime	≤0.12	1	≤0.12 to >16	94.8	4.2	90.6	4.2
Ceftazidime	0.25	>32	0.06 to >32	81.2	16.7	79.2	18.8
Ceftriaxone	0.12	>8	≤0.06 to >8	81.2	17.7	81.2	17.7
Colistin	0.12	0.25	≤0.06 to 1			100.0	0.0
Gentamicin	0.5	1	≤0.12 to >8	91.7	7.3	90.6	8.3
Levofloxacin	≤0.03	1	≤0.03 to >4	94.8	3.1	89.6	5.2
Meropenem	≤0.015	0.06	≤0.015 to 16	96.9	2.1	97.9	1.0
Piperacillin–tazobactam	2	64	0.5 to >64	84.4	8.3	80.2	15.6
P. mirabilis (96)							
Ceftolozane–tazobactam	0.25	0.5	0.12 to >32	99.0	1.0	97.9	2.1
Amikacin	4	4	1 to 32	97.9	0.0	97.9	2.1
Ampicillin–sulbactam	2	16	≤0.5 to >64	84.4	6.2	84.4	15.6
Aztreonam	≤0.12	≤0.12	≤0.12 to >16	97.9	2.1	94.8	2.1
Cefepime	≤0.12	2	≤0.12 to >16	91.7	3.1	89.6	4.2
Ceftazidime	0.06	0.25	0.03 to >32	94.8	4.2	91.7	5.2
Ceftriaxone	≤0.06	0.25	≤0.06 to >8	92.7	5.2	92.7	5.2
Colistin	>8	>8	8 to >8			0.0	100.0
Gentamicin	1	4	0.25 to >8	91.7	6.2	88.5	8.3
Levofloxacin	0.06	>4	≤0.03 to >4	64.6	30.2	61.5	37.5
Meropenem	0.06	0.12	0.03 to 16	99.0	1.0	99.0	1.0
Piperacillin–tazobactam	≤0.5	1	≤0.5 to 4	100.0	0.0	100.0	0.0
S. marcescens (267)							
Ceftolozane–tazobactam	0.5	1	0.12 to >32	96.3	3.4	93.3	6.7
Amikacin	2	4	0.5 to >32	98.5	0.4	98.5	1.5
Ampicillin–sulbactam	>32	>32	4 to >32	1.9	92.9	1.9	98.1
Aztreonam	≤0.12	4	≤0.12 to >16	92.9	6.4	88.0	7.1
Cefepime	≤0.12	0.5	≤0.12 to >16	94.8	2.2	92.9	4.1
Ceftazidime	0.25	1	0.06 to >32	94.4	5.6	92.5	5.6
Ceftriaxone	0.5	8	≤0.06 to >8	79.4	13.5	79.4	13.5
Colistin	>8	>8	0.12 to >8			9.8	90.2
Gentamicin	0.5	1	0.12 to >8	95.9	3.4	95.1	4.1
Levofloxacin	0.12	1	≤0.03 to >4	94.8	3.0	88.0	8.2
Meropenem	0.06	0.06	0.03 to >32	95.5	4.1	95.9	2.6
Piperacillin–tazobactam	2	16	≤0.5 to >128	91.0	3.4	86.5	9.0

[a] Criteria as published by CLSI, 2018a, 2018b and EUCAST, 2018.
[b] Organisms include *Citrobacter amalonaticus/farmeri* (1), *C. freundii* (14), *C. freundii* species complex (30), *C. koseri* (51), *Cronobacter sakazakii* (1), *Enterobacter aerogenes* (175), *E. asburiae* (5), *E. cloacae* (165), *E. cloacae* species complex (163), *E. kobei* (1), *E. taylorae* (1), *Escherichia coli* (435), *Ewingella americana* (1), *Hafnia alvei* (6), *Klebsiella oxytoca* (196), *K. pneumoniae* (664), *K. variicola* (4), *Kluyvera ascorbata* (1), *Kosakonia cowanii* (1), *Morganella morganii* (24), *Pantoea agglomerans* (3), *P. dispersa* (1), *Pluralibacter gergoviae* (1), *P. mirabilis* (96), *P. vulgaris* (2), *P. vulgaris* group (4), *Providencia rettgeri* (12), *P. stuartii* (23), *Rahnella aquatilis* (2), *Raoultella ornithinolytica* (7), *R. planticola* (1), *S. liquefaciens* (8), *S. marcescens* (267), unspeciated *Cedecea* (1), unspeciated *Pantoea* (3), and unspeciated *Raoultella* (3).
[c] Organisms include *E. coli* (134), *K. oxytoca* (21), *K. pneumoniae* (116), and *P. mirabilis* (9).
[d] Percentage of wild type based on epidemiologic cutoff value. (CLSI, 2018b).
[e] Organisms include: *Enterobacter aerogenes* (175), *E. asburiae* (5), *E. cloacae* (165), *E. cloacae* species complex (163), *E. kobei* (1), *E. taylorae* (1).

(MIC_{50}/MIC_{90}, 0.5/2 mg/L; 97.5%S; Table 3). Ceftolozane–tazobactam was the most active β-lactam compound against isolates recovered from ICU patients (MIC_{50}/MIC_{90}, 0.5/2 mg/L; 97.9%S) and patients with VABP (MIC_{50}/MIC_{90}, 0.5/2 mg/L; 99.5%S), in contrast to piperacillin–tazobactam (MIC_{50}/MIC_{90}, 4/>64 mg/L; 76.4–77.3%S) and meropenem (MIC_{50}/MIC_{90}, 0.5/16 mg/L; 73.9–76.8%S) that demonstrated limited activity against these *P. aeruginosa* subsets (Table 3). Interestingly, ceftolozane–tazobactam remained active against highly resistant subgroups, demonstrating 97.6% and 95.0% susceptibility against MDR and XDR *P. aeruginosa* isolates recovered from VABP, respectively

Table 3
Antimicrobial activity of ceftolozane–tazobactam and comparator agents tested against *P. aeruginosa* and Enterobacteriaceae isolates from US medical centers (2015–2017).

Antimicrobial agent	PHP (all isolates)		ICU		VABP	
	%S[a]	%R[a]	%S[a]	%R[a]	%S[a]	%R[a]
P. aeruginosa	(*n* = 1531)		(*n* = 564)		(*n* = 203)	
Ceftolozane–tazobactam	**97.5**	**1.6**	**97.9**	**1.6**	**99.5**	**0.0**
Amikacin	93.7	3.7	96.1	2.0	96.1	1.5
Aztreonam	69.0	19.3	70.2	19.1	69.5	19.7
Cefepime	83.6	5.4	84.5	4.6	85.1	5.4
Ceftazidime	82.6	12.4	82.8	11.5	84.7	9.9
Colistin	99.9	0.1	99.6	0.4	100.0	0.0
Levofloxacin	71.7	18.7	75.5	16.8	75.9	15.8
Meropenem	76.0	17.4	76.8	15.4	73.9	17.2
Piperacillin–tazobactam	77.7	11.0	77.3	9.9	76.4	7.4
Enterobacteriaceae	(*n* = 2373)		(*n* = 1129)		(*n* = 349)	
Ceftolozane–tazobactam	**90.3**	**7.1**	**91.9**	**5.9**	**92.0**	**5.4**
Amikacin	98.7	0.3	99.5	0.0	99.4	0.0
Ampicillin–sulbactam	39.5	44.5	39.9	43.2	38.7	43.8
Aztreonam	80.3	18.1	83.2	15.8	85.4	13.5
Cefepime	85.5	11.0 [b]	88.4	9.1 [b]	91.7	6.9 [b]
Ceftazidime	80.5	18.2	83.7	15.1	85.4	12.6
Ceftriaxone	75.9	22.4	79.6	18.9	81.9	16.0
Colistin	78.7 [c]		79.1 [c]		76.5 [c]	
Gentamicin	89.5	8.6	91.9	6.8	94.8	4.6
Levofloxacin	83.0	15.1	86.7	12.0	87.9	11.5
Meropenem	96.0	3.2	96.9	2.3	97.7	2.0
Piperacillin–tazobactam	86.0	8.2	87.6	7.3	87.7	8.0
K. pneumoniae	(*n* = 864)		(*n* = 403)		(*n* = 79)	
Ceftolozane–tazobactam	90.9	7.6	94.0	5.0	96.2	3.8
Amikacin	97.6	0.6	99.3	0.0	100.0	0.0
Ampicillin–sulbactam	58.9	24.0	69.1	18.9	78.5	13.9
Aztreonam	82.2	17.4	88.0	11.6	91.1	8.9
Cefepime	83.4	13.0 [b]	89.7	9.3 [b]	91.1	7.6 [b]
Ceftazidime	82.9	16.4	87.4	12.0	91.1	7.6
Ceftriaxone	81.2	18.4	87.4	12.6	91.1	8.9
Colistin	98.5 [c]		98.7 [c]		100.0 [c]	
Gentamicin	90.5	7.6	93.0	6.0	97.5	2.5
Levofloxacin	89.2	9.4	93.4	5.6	97.5	2.5
Meropenem	93.9	5.2	95.7	3.0	96.2	2.5
Piperacillin–tazobactam	85.6	11.5	87.7	7.6	93.7	5.1
E. coli	(*n* = 435)		(*n* = 214)		(*n* = 72)	
Ceftolozane–tazobactam	96.6	2.1	96.3	2.8	95.8	1.4
Amikacin	99.1	0.0	99.1	0.0	98.6	0.0
Ampicillin–sulbactam	39.3	43.9	36.9	44.4	30.6	51.4
Aztreonam	73.1	23.0	74.3	22.9	80.6	18.1
Cefepime	74.3	21.6 [b]	75.7	21.5 [b]	80.6	18.1 [b]
Ceftazidime	76.6	21.6	78.0	20.1	81.9	15.3
Ceftriaxone	69.4	29.9	72.4	27.6	77.8	22.2
Colistin	99.5 [c]		100.0 [c]		100.0 [c]	
Gentamicin	79.1	20.2	81.3	18.2	86.1	0.0
Levofloxacin	55.5	42.9	58.7	39.9	61.1	0.0
Meropenem	99.3	0.7	99.1	0.9	98.6	0.0
Piperacillin–tazobactam	90.6	6.5	90.7	7.9	86.1	1.4

Organisms include *Citrobacter amalonaticus/farmeri* (1), *C. freundii* (14), *C. freundii* species complex (30), *C. koseri* (51), *Cronobacter sakazakii* (1), *Enterobacter aerogenes* (175), *E. asburiae* (5), *E. cloacae* (165), *E. cloacae* species complex (163), *E. kobei* (1), *E. taylorae* (1), *Escherichia coli* (435), *Ewingella americana* (1), *Hafnia alvei* (6), *Klebsiella oxytoca* (196), *K. pneumoniae* (664), *K. variicola* (4), *Kluyvera ascorbata* (1), *Kosakonia cowanii* (1), *Morganella morganii* (24), *Pantoea agglomerans* (3), *P. dispersa* (1), *Pluralibacter gergoviae* (1), *P. mirabilis* (96), *P. vulgaris* (2), *P. vulgaris* group (4), *Providencia rettgeri* (12), *P. stuartii* (23), *Rahnella aquatilis* (2), *Raoultella ornithinolytica* (7), *R. planticola* (1), *S. liquefaciens* (8), *S. marcescens* (267), unspeciated *Cedecea* (1), unspeciated *Pantoea* (3), and unspeciated *Raoultella* (3).

[a] Criteria as published by CLSI (2018a, 2018b).

[b] Intermediate interpreted as susceptible-dose dependent.

[c] FDA breakpoints published 2017-DEC-13.

(Fig. 1). Ceftazidime, the second most active β-lactam agent, displayed limited activity against MDR (50.0%) and XDR (45.0%) *P. aeruginosa* isolates recovered from patients with VABP (Fig. 1).

The activity of ceftolozane–tazobactam against *P. aeruginosa* isolates was comparable across all US census divisions, ranging from 91.2% in the Pacific division to 100% in the East South Central and West North Central divisions (Fig. 2). The activity of this combination was also similar among ICU (90.5–100.0%S) and VABP (96.3–100.0%S) isolates in all census divisions. Of note, the activity of ceftolozane–tazobactam was not affected by the frequency of MDR and XDR *P. aeruginosa* in some census divisions, i.e., East South Central division demonstrated 100%S of ceftolozane–tazobactam despite the high frequency of MDR and XDR isolates (45% of all *P. aeruginosa* isolates from this division). In contrast, 38% of all *P. aeruginosa* isolates from the New England division were classified as MDR or XDR isolates, but a decrease in ceftolozane–tazobactam activity was observed in this division (82.4% for MDR and 76.0% for XDR isolates; Fig. 2).

3.3. Ceftolozane–tazobactam activity against Enterobacteriaceae

Ceftolozane–tazobactam inhibited >90% of all Enterobacteriaceae isolates (*n* = 2373) at the current CLSI and US FDA susceptible breakpoint criterion (≤2/4 mg/L) and 87.5% at the current EUCAST susceptible breakpoint criterion (≤1/4 mg/L) (Tables 1 and 2). Meropenem ($MIC_{50/90}$, 0.03/0.06 mg/L; 96.0% susceptible) and ceftolozane–tazobactam ($MIC_{50/90}$, 0.25/2 mg/L; 90.3% susceptible) were the most active β-lactam agents. Amikacin ($MIC_{50/90}$, 2/4 mg/L; 98.7% susceptible) was also very active against all Enterobacteriaceae. When the ESBL-phenotype non–carbapenem-resistant Enterobacteriaceae (ESBL, non-CRE) subgroup was evaluated, colistin and the 4 agents described above remained the most active antimicrobial agents.

Among Enterobacteriaceae species, ceftolozane–tazobactam inhibited 89.8% of 664 *K. pneumoniae* isolates, 96.6% of 435 *E. coli* isolates, 96.3% of 267 *Serratia marcescens* isolates, and 79.8% of 510 *Enterobacter* spp. isolates at the CLSI susceptible breakpoint (Table 1). This combination also exhibited good activity against *Proteus mirabilis* (99.0%S) and *Citrobacter* spp. (87.5%S). Compared to other cephalosporins, such as cefepime, ceftazidime, and ceftriaxone, ceftolozane–tazobactam had considerably higher susceptibility rates against ESBL, non-CRE *K. pneumoniae* isolates (31.9%, 19.8%, 19.0%, and 80.2%, respectively). As expected, CRE isolates exhibited low susceptibility to ceftolozane–tazobactam and all β-lactams evaluated (*n* = 89; 4.5%, data not shown).

Interestingly, ceftolozane–tazobactam activity was similar for Enterobacteriaceae isolates recovered from ICU patients and patients with VABP ($MIC_{50/90}$, 0.25/1–2; 91.9% and 92.0% susceptible, respectively) (Table 3). Of note, *K. pneumoniae* isolates from ICU patients and patients with VABP had slightly higher susceptibility rates than all *K. pneumoniae* combined for all antimicrobials tested. In addition, in the VABP subset, ceftolozane–tazobactam was as active as meropenem against *K. pneumoniae* isolates (96.2%; Table 3). Meropenem (96.3% susceptible), ceftolozane–tazobactam (81.5%), and piperacillin–tazobactam (74.1%) were the most active β-lactams against ESBL, non-CRE isolates recovered from patients with VABP (Fig. 1).

Ceftolozane–tazobactam exhibited high susceptibility rates against Enterobacteriaceae isolates from most US census divisions, including against ICU and VABP subsets (>90%S; Fig. 2). The lowest ceftolozane–tazobactam susceptibility rate (78.3%S) for all Enterobacteriaceae isolates combined was observed in the Middle Atlantic division; however, this region also exhibited the highest frequency of ESBL, non-CRE isolates (25% of all Enterobacteriaceae). In contrast, 7.9% of Enterobacteriaceae isolates from the East South Central division were categorized as ESBL, non-CRE, and all isolates were susceptible to ceftolozane–tazobactam (Fig. 2).

4. Discussion

Pneumonia in hospitalized patients is a challenging infection that requires timely introduction of optimal empiric antimicrobial therapy to achieve good clinical outcomes, especially among patients in need of intensive care or mechanical ventilation. The frequency distribution of

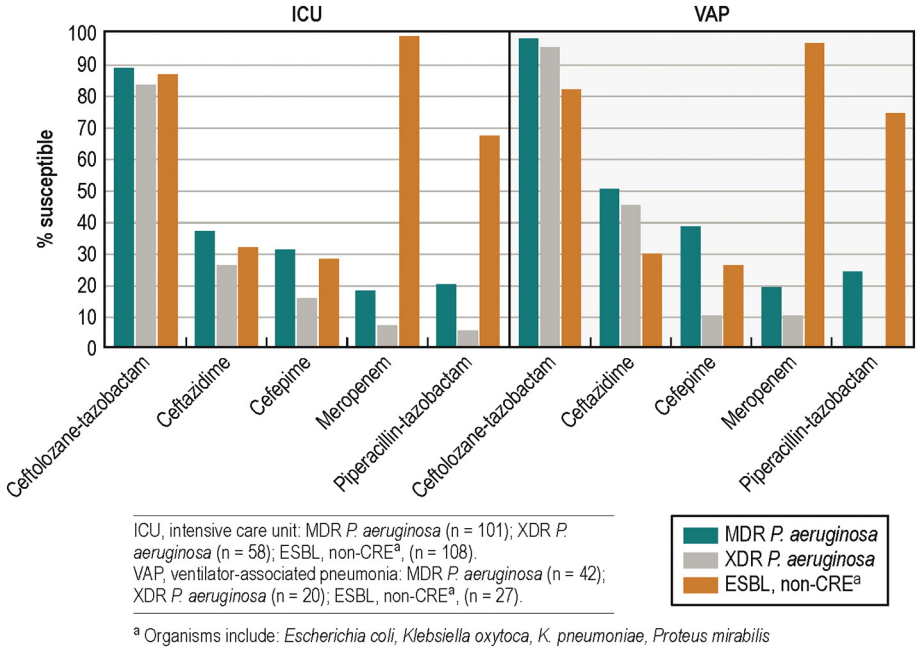

Fig. 1. β-lactam agent susceptibility (%) against MDR and XDR *P. aeruginosa* and ESBL, non-CRE isolates from ICU and VABP subsets in US medical centers (2015–2017).

organisms in the 2015–2017 surveillance program presented in this study is very similar to that previously reported for health care–associated pneumonia and VABP (Kalil et al., 2016; Sievert, et al., 2013). It is important to note that Enterobacteriaceae and *P. aeruginosa*, in addition to *S. aureus*, represented the main causative pathogens for PHP, including ICU and VABP subsets, in this multicenter US surveillance study. As there has been a dramatic increase worldwide in the number of MDR Gram-negative bacteria, ESBL-producing Enterobacteriaceae and MDR *P. aeruginosa* are among the most challenging pathogens to treat in clinical practice (CDC, 2013; Giacobbe et al., 2018). In this collection, MDR *P. aeruginosa* isolates corresponded to 20.1% of all *P. aeruginosa* isolates referred as the cause of PHP. An alarming ESBL, non-CRE rate (280; 20.1%) was also observed among Enterobacteriaceae. Furthermore, CRE isolates represented 3.8% of all Enterobacteriaceae. Similar rates of MDR/XDR *P. aeruginosa* (18.1–33.4%) and ESBL-producing Enterobacteriaceae (6.1–11.4%) were reported during previous surveillance studies in US hospitals (Castanheira et al., 2013, 2018).

The results of this study confirm the high in vitro potency and broad spectrum of ceftolozane–tazobactam against Enterobacteriaceae and *P. aeruginosa* isolates circulating in US hospitals as presented in earlier studies (Castanheira et al., 2018; Farrell et al., 2013). Furthermore, the relevance of the data presented here relies on the evaluation of the ICU and VABP subsets of PHP, where ceftolozane–tazobactam also exhibited in vitro activity against highly resistant *P. aeruginosa* and ESBL-phenotype Enterobacteriaceae isolates. In addition, since the most active comparator agents in this study were amikacin (>97%) and meropenem (>93%) for Enterobacteriaceae and colistin (>99%) and amikacin (>93%) for *P. aeruginosa*, this new compound achieved >90% susceptibility rates for both groups and may have an important role in the treatment of these pathogens. Although under low-quality evidence and stated as a weak recommendation, Infectious Diseases Society of America guidelines for the management of adults with HABP and VABP recommend avoiding aminoglycosides and polymyxins if alternative agents are available (Kalil et al., 2016). In addition, the emergence of CRE infections has caused a concern in the use of carbapenem-based therapy and led to the search for alternative treatments for infections caused by ESBL, non-CRE infections (Giacobbe et al., 2018; Tamma and Rodriguez-Bano, 2017). As previously reported, ceftolozane–tazobactam has limited activity against carbapenemase-producing isolates, and resistance among clinical isolates has also been reported in high-risk clone of *P. aeruginosa* (ST175) due to mutations leading to the structural modifications of ampC (Castanheira et al., 2013, 2018; Giacobbe et al., 2018).

Among the 9 US census divisions, ceftolozane–tazobactam showed a uniformly high in vitro activity (range, 80–100%) against *P. aeruginosa*, including isolates from ICU patients and those from VABP, except for specific subsets from some census divisions, such as XDR and MDR isolates from the Pacific division, ICU-XDR isolates from the Middle Atlantic division, and XDR and MDR-ICU isolates from the New England division. Similar distributions of ceftolozane–tazobactam activity in US census divisions against MDR and XDR *P. aeruginosa* isolates were previously reported among respiratory tract samples collected from 2013 to 2015 (Castanheira et al., 2018). In that investigation, Castanheira and colleagues also performed the molecular characterization of ESBL-producing Enterobacteriaceae and observed that ceftolozane–tazobactam retained activity against isolates carrying CTX-M and TEM enzymes but not against those carrying SHV and KPC, which mostly occur among northeastern coastal regions (Castanheira et al., 2018). In our study, we observed a decrease of ceftolozane–tazobactam susceptibility rates among ESBL, non-CRE isolates recovered from ICU and VABP subsets in the West North Central, South Atlantic, and Mountain divisions. However, ceftolozane–tazobactam demonstrated good activity (>80% to 100%) in most US census divisions, including against ESBL, non-CRE isolates and even against those recovered from ICU patients or patients with VABP.

In summary, ceftolozane–tazobactam demonstrated potent in vitro activity and a broad antimicrobial spectrum against a large collection ($n = 3904$) of contemporary Gram-negative bacilli isolated from hospitalized patients with pneumonia in 31 US hospitals during a 3-year period (2015–2017). Our results indicate that ceftolozane–tazobactam may represent a valuable treatment option for PHP, including patients in the ICU and on mechanical ventilation (VABP), caused by Enterobacteriaceae and *P. aeruginosa*, along with those caused by organisms resistant to most antimicrobial agents currently available. The results of the recently completed clinical trial of ceftolozane–tazobactam against organisms causing hospital-associated pneumonia is expected to further

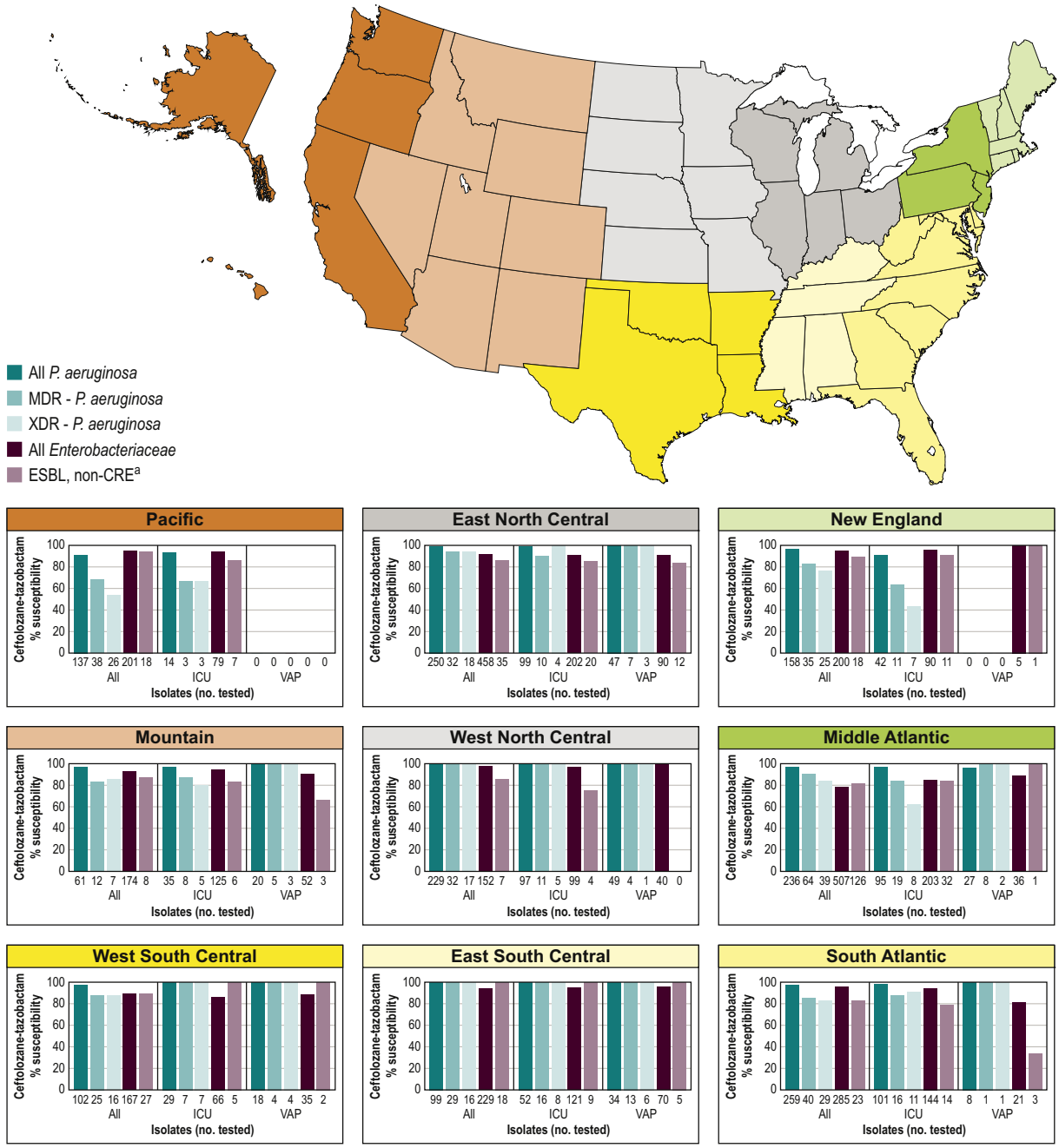

Fig. 2. Ceftolozane–tazobactam activity against *P. aeruginosa* and Enterobacteriaceae by US census division. No *P. aeruginosa* or Enterobacteriaceae isolates were recovered from VABP patients in the Pacific division, and no *P. aeruginosa* isolates were recovered from patients in the New England division.

elucidate the role of this compound in treating these challenging infections.

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Conflict of interest

The authors declare no conflicts of interest.

References

Bassetti M, Vena A, Castaldo N, Righi E, Peghin M. New antibiotics for ventilator-associated pneumonia. Curr Opin Infect Dis 2018;31:177–86.

Biehl LM, Schmidt-Hieber M, Liss B, Cornely OA, Vehreschild MJ. Colonization and infection with extended spectrum beta-lactamase producing Enterobacteriaceae in high-risk patients - review of the literature from a clinical perspective. Crit Rev Microbiol 2016;42:1–16.

Castanheira M, Farrell SE, Deshpande LM, Mendes RE, Jones RN. Prevalence of beta-lactamase-encoding genes among Enterobacteriaceae bacteremia isolates collected in 26 U.S. hospitals: report from the SENTRY antimicrobial surveillance program (2010). Antimicrob Agents Chemother 2013;57:3012–20.

Castanheira M, Duncan LR, Mendes RE, Sader HS, Shortridge D. Activity of ceftolozane-tazobactam against *Pseudomonas aeruginosa* and Enterobacteriaceae isolates collected from respiratory tract specimens of hospitalized patients in the United States during 2013 to 2015. Antimicrob Agents Chemother 2018;62, e02125.

Centers for Disease Control & Prevention (CDC). Antibiotic resistance threats in the United States. Available at http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf, 2013.

Centers for Disease Control & Prevention (CDC). Pneumonia. Available at https://www.cdc.gov/nchs/fastats/pneumonia.htm, 2017.

Clinical and Laboratory Standards Institute (CLSI). M07Ed11E. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eleventh edition. Wayne, PA: Clinical and Laboratory Standards Institute; 2018a.

Clinical and Laboratory Standards Institute (CLSI). M100Ed28E. Performance standards for antimicrobial susceptibility testing: 28th informational supplement. Wayne, PA: Clinical and Laboratory Standards Institute; 2018b.

Dinh A, Wyplosz B, Kerneis S, Lebeaux D, Bouchand F, Duran C, et al. Use of ceftolozane/tazobactam as salvage therapy for infections due to extensively drug-resistant *Pseudomonas aeruginosa*. Int J Antimicrob Agents 2017;49:782–3.

EMA. Zerbaxa ®. Annex I. Summary of product characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003772/WC500194595.pdf, 2015.

EUCAST. Breakpoint tables for interpretation of MIC's and zone diameters. Version 8.0. January 2018. Available at http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf, 2018.

Farrell DJ, Flamm RK, Sader HS, Jones RN. Antimicrobial activity of ceftolozane-tazobactam tested against Enterobacteriaceae and *Pseudomonas aeruginosa* with various resistance patterns isolated in U.S. hospitals (2011-2012). Antimicrob Agents Chemother 2013;57:6305–10.

Giacobbe DR, Bassetti M, De Rosa FG, Del Bono V, Grossi PA, Menichetti F, et al. Ceftolozane/tazobactam: place in therapy. Expert Rev Anti Infect Ther 2018;16:307–20.

Jones BE, Jones MM, Huttner B, Stoddard G, Brown KA, Stevens VW, et al. Trends in antibiotic use and nosocomial pathogens in hospitalized veterans with pneumonia at 128 medical centers, 2006–2010. Clin Infect Dis 2015;61:1403–10.

Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:e61-111.

Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81.

Munita JM, Aitken SL, Miller WR, Perez F, Rosa R, Shimose LA, et al. Multicenter evaluation of ceftolozane/tazobactam for serious infections caused by carbapenem-resistant *Pseudomonas aeruginosa*. Clin Infect Dis 2017;65:158–61.

Perez F, Bonomo RA. Can we really use beta-lactam/beta-lactam inhibitor combinations for the treatment of infections caused by extended-spectrum beta-lactamase–producing bacteria? Clin Infect Dis 2012;54:175–7.

Pfaller MA, Bassetti M, Duncan LR, Castanheira M. Ceftolozane/tazobactam activity against drug-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* causing urinary tract and intraabdominal infections in Europe: report from an antimicrobial surveillance programme (2012-15). J Antimicrob Chemother 2017;72:1386–95.

Popejoy MW, Paterson DL, Cloutier D, Huntington JA, Miller B, Bliss CA, et al. Efficacy of ceftolozane/tazobactam against urinary tract and intra-abdominal infections caused by ESBL-producing Escherichia coli and *Klebsiella pneumoniae*: a pooled analysis of phase 3 clinical trials. J Antimicrob Chemother 2017;72:268–72.

Rodriguez-Bano J, Navarro MD, Retamar P, Picon E, Pascual A, Extended-Spectrum Beta-Lactamases-Red Espanola de Investigacion en Patologia Infecciosa/Grupo de Estudio de Infeccion Hospitalaria, G. beta-Lactam/beta-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum beta-lactamase–producing *Escherichia coli*: a post hoc analysis of prospective cohorts. Clin Infect Dis 2012;54:167–74.

Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol 2013;34:1–14.

Sucher AJ, Chahine EB, Cogan P, Fete M. Ceftolozane/tazobactam: a new cephalosporin and beta-lactamase inhibitor combination. Ann Pharmacother 2015;49:1046–56.

Tamma PD, Rodriguez-Bano J. The use of noncarbapenem beta-lactams for the treatment of extended-spectrum beta-lactamase infections. Clin Infect Dis 2017;64:972–80.

ZERBAXA. ZERBAXA® (ceftolozane/tazobactam). Whitehouse Station, NJ: Merck & Co. Inc; 2016.