

Ceftolozane/Tazobactam Activity Against Drug-Resistant *Pseudomonas aeruginosa* and Enterobacterales Causing Healthcare-Associated Infections in Eight Asian Countries: Report from an Antimicrobial Surveillance Program (2016–2018)

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Purpose: To evaluate the in vitro activity of ceftolozane/tazobactam and comparator agents tested against *Pseudomonas aeruginosa* and Enterobacterales isolates from hospitalised patients in Asia. Ceftolozane/tazobactam is an antipseudomonal cephalosporin combined with a well-established β -lactamase inhibitor.

Methods: A total of 2038 Gram-negative organisms (376 *P. aeruginosa* and 1662 Enterobacterales) were collected consecutively using a prevalence-based approach from 11 medical centres. Organisms were susceptibility tested by broth microdilution according to CLSI guidelines. CLSI and EUCAST breakpoint criteria were used.

Results: Ceftolozane/tazobactam was the most potent (MIC_{50/90}, 0.5/4 mg/L) β -lactam agent tested against *P. aeruginosa* isolates, inhibiting 91.0% of the isolates at an MIC of ≤ 4 mg/L. *P. aeruginosa* exhibited high rates of susceptibility to amikacin (92.0/92.0% [CLSI/EUCAST]) and colistin by EUCAST criteria only (99.2% intermediate [CLSI]/99.2% susceptible [EUCAST]). Ceftolozane/tazobactam (MIC_{50/90}, 0.25/16 mg/L; 86.8/86.8% susceptible [CLSI/EUCAST]) and meropenem (MIC_{50/90}, 0.03/0.12 mg/L; 93.0/93.3% susceptible [CLSI/EUCAST]) were the most active compounds tested against Enterobacterales. Isolates displayed susceptibility rates to other β -lactam agents, ranging from 81.5/77.7% for piperacillin/tazobactam, 66.0/64.5% for cefepime, and 65.3/60.9% for ceftazidime using CLSI/EUCAST breakpoints. Among the Enterobacterales isolates, 6.8% were carbapenem-resistant Enterobacterales (CRE) and 29.6% exhibited an extended-spectrum β -lactamase (ESBL) non-CRE phenotype. Ceftolozane/tazobactam showed good activity against ESBL non-CRE phenotype strains of Enterobacterales (MIC_{50/90}, 0.5/8 mg/L; 84.8/84.8% susceptible), but not against isolates with a CRE phenotype (MIC_{50/90}, >32/>32 mg/L).

Conclusion: Ceftolozane/tazobactam was the most active β -lactam agent tested against *P. aeruginosa* and demonstrated higher in vitro activity than the available cephalosporins when tested against Enterobacterales from Asian countries.

Keywords: Asia, ceftolozane/tazobactam, drug resistance, Enterobacterales, *P. aeruginosa*, surveillance

Introduction

Antimicrobial resistance (AMR) is a grave threat to the global healthcare system.^{1–5} Whereas Gram-positive cocci remain a concern due to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci, recent years have seen the emergence of multidrug-resistant (MDR; resistant to 3 or more classes of antimicrobial agents) strains of Gram-negative bacilli (GNB).^{1–5} MDR GNBs are especially prominent in Asian countries compared to the United States (US) and western Europe.^{1,4,6–16} Regional variation in antimicrobial susceptibility is considerable in Asia^{1,7,8,10,11} due in part to the lack of diagnostic laboratory facilities outside of major cities, varying standards of antimicrobial usage, self-medication, poor

adherence to complete antimicrobial regimens, low quality and often counterfeit antimicrobials, and differing standards of public hygiene between countries.^{6,12}

Enterobacterales and *Pseudomonas aeruginosa* constitute the greatest source of AMR in hospitalised individuals.^{1–5} These GNBs account for 70% of hospital-associated infections (HAIs) acquired in the intensive care unit (ICU) and respond to the pressure of antimicrobial exposure with the development of resistance to various classes of agents, often resulting in an MDR phenotype.^{1–5} The MDR nature of these pathogens is associated with delays in appropriate therapy and corresponding increases in morbidity and mortality.^{5,17–19} Therapeutic options for treating infections caused by MDR GNBs are extremely limited, with only a few agents, such as the carbapenems, providing sufficient coverage.^{2,3,5,17,20}

Ceftolozane/tazobactam is a β -lactam/ β -lactamase inhibitor combination that represents a potential carbapenem-sparing treatment option for extended-spectrum β -lactamase (ESBL)-producing Enterobacterales and MDR *P. aeruginosa*.^{13,20–22} Ceftolozane/tazobactam has potent activity against *P. aeruginosa*, including antibiotic-resistant strains, as well as Enterobacterales, including most ESBL-producing strains.^{13,20,23–26} Ceftolozane/tazobactam has limited activity against *Acinetobacter* spp., *Stenotrophomonas maltophilia*, and GPC or against organisms producing carbapenemases, metallo- β -lactamases, and a small number of AmpC β -lactamases found in Enterobacterales strains.^{13,20–22} Ceftolozane/tazobactam has been approved by the US and Europe for the treatment of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) with a dose of 1.5 grams of ceftolozane/tazobactam every 8 hrs, and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia with a higher dose of 3.0 grams of ceftolozane/tazobactam q 8 hrs.^{20,22}

In the present study, we examined the activity of ceftolozane/tazobactam and comparators against 2038 isolates of *P. aeruginosa* and Enterobacterales from hospitalised patients at 11 medical centres in 8 countries in Asia from 2016 to 2018 collected in the SENTRY Antimicrobial Surveillance Program. Our analysis includes the activity of ceftolozane/tazobactam against specific resistant phenotypes (ESBL non-CRE phenotype and MDR strains of Enterobacterales and *P. aeruginosa*) and the frequency of resistance patterns in each of these 8 Asian countries.

Materials and Methods

Sampling Sites and Organisms

A total of 2038 non-duplicate isolates of GNB, including 1662 Enterobacterales and 376 *P. aeruginosa*, were collected consecutively across 4 infection types from 11 medical centres located in 8 countries in Asia from 2016 to 2018. These centres were participants in the SENTRY Antimicrobial Surveillance Program. All centres followed a common protocol for isolate collection, which was previously described.²⁷ Only 1 isolate per patient per infection type was submitted (1 infection per patient). All organisms were isolated from hospitalised patients with bloodstream infection (554 isolates), pneumonia in hospitalised patients (521 isolates), skin and skin structure infection (370 isolates), intra-abdominal infection (185 isolates), and other sites (32 isolates). Species identification was performed at each participating medical centre and confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker, Billerica, Massachusetts, USA) or standard biochemicals when necessary.

Antimicrobial Susceptibility Testing

Minimal inhibitory concentrations (MICs) were determined using the frozen broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI).²⁸ Ceftolozane/tazobactam and piperacillin/tazobactam were both tested with a fixed tazobactam concentration of 4 mg/L. Quality control and the interpretation of results were performed according to CLSI M100-S31 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2021 guidelines.^{29,30} *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* were grouped as an ESBL screen-positive phenotype based on the CLSI screening criteria for presumptive ESBL production, i.e., ceftazidime, ceftriaxone, or aztreonam MICs ≥ 2 mg/L.²⁹ CRE isolates were defined as those displaying MIC values ≥ 4 mg/L for imipenem (*P. mirabilis* and indole-positive Proteae were not included due to intrinsically elevated MIC values), meropenem, and/or doripenem.²⁹ Results for doripenem and imipenem were used, along with meropenem, to

determine the presumptive CRE phenotype and are not reported individually. In version 10.0 of the EUCAST breakpoints, the Enterobacterales and *P. aeruginosa* breakpoints of several antimicrobial agents (aztreonam, ciprofloxacin, cefepime, ceftazidime, imipenem, and piperacillin/tazobactam) were changed to recategorize all isolates in the wild-type population as “susceptible, increased exposure”. The arbitrary susceptible breakpoint of ≤ 0.001 mg/L was chosen by EUCAST to ensure that no isolates were labeled susceptible to these agents. As a result, *P. aeruginosa* isolates previously susceptible to aztreonam, cefepime, ceftazidime, ciprofloxacin, imipenem, and piperacillin/tazobactam as well as previously imipenem-susceptible isolates of *Morganella morganii*, *Proteus* spp., and *Providencia* spp. are shown in parentheses in the table as susceptible, increased exposure. In addition, CLSI removed the susceptible category for colistin, reporting only intermediate or resistant categories for Enterobacterales and *P. aeruginosa*.

P. aeruginosa isolates were classified as ceftazidime-nonsusceptible (NS; MIC, >8 mg/L), levofloxacin-NS (MIC, >1 mg/L), meropenem-NS (MIC, >2 mg/L), or piperacillin/tazobactam-NS (MIC, >16 mg/L). Multidrug-resistant (MDR; nonsusceptible to at least 3 antimicrobial classes) and extensively drug resistant (XDR; susceptible to 2 or fewer antimicrobial classes) *P. aeruginosa* isolates were classified according to Magiorakos et al and used the following antimicrobial class representative agents: ceftazidime, doripenem, gentamicin, levofloxacin, meropenem, piperacillin/tazobactam, tigecycline (for species with breakpoints), and colistin (7 classes).³¹ Results for doripenem and tigecycline were used to determine the MDR phenotype and are not reported individually.

Results

Among the 2038 isolates tested, there were 1662 Enterobacterales isolates (including 716 *E. coli*, 610 *Klebsiella* spp., 152 *Enterobacter* spp., 50 *Citrobacter* spp., 48 *P. mirabilis*, 25 indole-positive Proteae, and 53 *Serratia marcescens*) and 376 *P. aeruginosa* isolates (Table 1). Countries that provided the isolates for this survey included Japan (85 isolates), Korea (496), Malaysia (279), Philippines (430), Singapore (60), Taiwan (241), Thailand (346), and Vietnam (101).

Overall Activity of Ceftolozane/Tazobactam

During the years 2016 to 2018, ceftolozane/tazobactam maintained a consistent and potent level of activity against the target pathogens from the study sites in Asia (Table 1). Ceftolozane/tazobactam MIC values ranged from 0.06 mg/L to >32 mg/L against isolates of *P. aeruginosa*, and 91.0% of the tested isolates were susceptible at the CLSI/EUCAST breakpoint of ≤ 4 mg/L. Among the resistant phenotypes, 56.8% (ceftazidime-NS), 71.4% (levofloxacin-NS), 66.0% (meropenem-NS), 67.1% (piperacillin/tazobactam-NS), 55.8% (MDR), and 43.9% (XDR) isolates were susceptible to ceftolozane/tazobactam (Table 1).

Among the Enterobacterales isolates tested, 6.8% were CRE (range 0.0% [Japan and Singapore] to 26.6% [Vietnam]) and 29.6% exhibited a presumptive ESBL non-CRE phenotype (range 7.3% [Singapore] to 40.4% [Vietnam]) (Table 2). A presumptive ESBL non-CRE phenotype was observed in 42.3% of *E. coli* (range 30.0% [Singapore] to 65.4% [Vietnam]) and 32.0% of *K. pneumoniae* (range 0.0% [Singapore] to 40.7% [Korea]) isolates. Important resistant phenotypes among the *P. aeruginosa* isolates included ceftazidime-NS (19.7%; range 10.8% [Taiwan] to 28.6% [Vietnam]), meropenem-NS (25.0%; range 10.3% [Philippines] to 35.6% [Thailand]), piperacillin/tazobactam-NS (21.0%; range 8.3% [Malaysia] to 32.1% [Korea]), MDR (20.5%; range 10.3% [Philippines] to 32.1% [Korea]) and XDR (15.2%; range 8.3% [Malaysia] to 28.6% [Vietnam]) (Table 2).

Ceftolozane/tazobactam MIC values ranged from 0.03 to >32 mg/L, and 86.8% of the tested Enterobacterales isolates were inhibited at an MIC value of ≤ 2 mg/L (88.6% at ≤ 4 mg/L) (Table 1). Whereas ceftolozane/tazobactam showed good activity against presumptive ESBL non-CRE phenotype strains of Enterobacterales (MIC_{50/90}, 0.5/8 mg/L; 84.8/84.8% susceptible [CLSI/EUCAST]), it lacked useful activity (MIC_{50/90}, $>32/>32$ mg/L) against isolates with a presumptive CRE phenotype.

Table I Antimicrobial Activity of Ceftolozane/Tazobactam Tested Against the Main Organisms and Organism Groups

Organism/Organism Group (No. of Isolates)	No. and Cumulative % of Isolates Inhibited at MIC (mg/L) of:													MIC ₅₀	MIC ₉₀
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> ^a		
<i>Pseudomonas aeruginosa</i> (376)		0	1	1	39	229	51	10	11	5	2	2	25	0.5	4
Ceftazidime-nonsusceptible (>8 mg/L) (74)		0.0	0.3	0.5	10.9	71.8	85.4	88.0	91.0	92.3	92.8	93.4	100.0	4	>32
Meropenem-nonsusceptible (>2 mg/L) (94)				0	2	24	22	6	8	5	1	2	24	1	>32
Piperacillin/tazobactam-nonsusceptible (>16 mg/L) (79)				0.0	2.1	27.7	51.1	57.4	66.0	71.3	72.3	74.5	100.0	2	>32
Levofloxacin-nonsusceptible (>1 mg/L) (112)				0	3	28	32	7	10	5	1	2	24	1	>32
MDR (77)				0	1	3	21	8	10	5	2	2	25	4	>32
XDR (57)				0.0	1.3	5.2	32.5	42.9	55.8	62.3	64.9	67.5	100.0	8	>32
Enterobacterales (1662)	0	2	20	434	552	261	100	73	31	21	19	24	125	0.25	16
Non-ESBL-phenotype (721)	0.0	0.1	1.3	27.4	60.6	76.4	82.4	86.8	88.6	89.9	91.0	92.5	100.0	0.12	0.25
Presumptive ESBL-phenotype (590)	0	2	18	341	305	50	4	1						0.5	>32
Carbapenem-resistant (CRE) (113)	0.0	0.3	2.8	50.1	92.4	99.3	99.9	100.0						>32	>32
Presumptive ESBL-phenotype non-carbapenem-resistant (CRE) (492)			0	36	127	134	69	54	23	8	12	19	108	0.5	8
MDR (431)			0.0	7.3	33.1	60.4	74.2	84.8	89.4	90.9	92.7	94.7	100.0	2	>32
XDR (58)			0.0	1.2	15.8	35.7	45.7	56.1	60.6	63.1	66.6	71.2	100.0	>32	>32
<i>Escherichia coli</i> (716)	0	1	12	286	228	105	38	16	6	1	3	4	16	0.25	1
Non-ESBL-phenotype (402)	0.0	0.1	1.8	41.8	73.6	88.3	93.6	95.8	96.6	96.8	97.2	97.8	100.0	0.12	0.25
Presumptive ESBL-phenotype (314)	0	1	12	255	123	10	1							0.5	2
Carbapenem-resistant (CRE) (11)	0.0	0.2	3.2	66.7	97.3	99.8	100.0							>32	>32
Presumptive ESBL-phenotype non-carbapenem-resistant (CRE) (303)			0	31	105	95	37	16	6	1	3	4	16	0.5	2
			0.0	10.2	44.9	76.2	88.4	93.7	95.7	96.0	97.0	97.7	100.0		

<i>Klebsiella</i> spp. (610)	0	1	6	100	209	64	39	43	18	12	8	15	95	0.25	>32
	0.0	0.2	1.1	17.5	51.8	62.3	68.7	75.7	78.7	80.7	82.0	84.4	100.0		
<i>Klebsiella pneumoniae</i> (547)	0	1	6	91	183	59	31	38	16	7	8	15	92	0.25	>32
	0.0	0.2	1.3	17.9	51.4	62.2	67.8	74.8	77.7	79.0	80.4	83.2	100.0		
Non-ESBL-phenotype (286)	0	1	6	86	162	29	1	1						0.25	0.5
	0.0	0.3	2.4	32.5	89.2	99.3	99.7	100.0							
Presumptive ESBL-phenotype (261)			0	5	21	30	30	37	16	7	8	15	92	4	>32
			0.0	1.9	10.0	21.5	33.0	47.1	53.3	55.9	59.0	64.8	100.0		
Carbapenem-resistant (CRE) (86)							0	2	0	1	3	7	73	>32	>32
							0.0	2.3	2.3	3.5	7.0	15.1	100.0		
Presumptive ESBL-phenotype non-carbapenem-resistant (CRE) (175)			0	5	21	30	30	35	16	6	5	8	19	2	>32
			0.0	2.9	14.9	32.0	49.1	69.1	78.3	81.7	84.6	89.1	100.0		
<i>Klebsiella oxytoca</i> (13)			0	2	7	1	1	0	0	0	0	0	2	0.25	>32
			0.0	15.4	69.2	76.9	84.6	84.6	84.6	84.6	84.6	84.6	100.0		
<i>Klebsiella aerogenes</i> (50)			0	7	19	4	7	5	2	5	0	0	1	0.25	8
			0.0	14.0	52.0	60.0	74.0	84.0	88.0	98.0	98.0	98.0	100.0		
<i>Enterobacter cloacae</i> species complex (152)	0	1	22	54	25	5	10	6	6	6	6	4	13	0.25	32
	0.0	0.7	15.1	50.7	67.1	70.4	77.0	80.9	84.9	88.8	91.4	100.0			
Ceftazidime-nonsusceptible (>4 mg/L) (65)			0	4	12	4	10	6	6	6	6	4	13	4	>32
			0.0	6.2	24.6	30.8	46.2	55.4	64.6	73.8	80.0	100.0			
<i>Citrobacter</i> spp. (50)			0	20	19	6	1	0	0	2	1	1		0.25	0.5
			0.0	40.0	78.0	90.0	92.0	92.0	92.0	96.0	98.0	100.0			
<i>Citrobacter koseri</i> (25)			0	14	8	3								0.12	0.5
			0.0	56.0	88.0	100.0									
<i>Citrobacter freundii</i> species complex (25)			0	6	11	3	1	0	0	2	1	1		0.25	8
			0.0	24.0	68.0	80.0	84.0	84.0	84.0	92.0	96.0	100.0			
<i>Proteus mirabilis</i> (48)			0	21	20	4	1	1	0	1	1			0.5	1
			0.0	43.8	85.4	93.8	95.8	97.9	97.9	100.0					
Non-ESBL-phenotype (33)			0	20	11	2								0.25	0.5
			0.0	60.6	93.9	100.0									
Presumptive ESBL-phenotype (15)			0	1	9	2	1	1	0	1				0.5	4
			0.0	6.7	66.7	80.0	86.7	93.3	93.3	100.0					
Indole-positive Proteae (25) ^a			0	3	13	8	0	1						0.25	0.5
			0.0	12.0	64.0	96.0	96.0	100.0							
<i>Morganella morganii</i> (16)			0	1	12	3								0.25	0.5
			0.0	6.2	81.2	100.0									
<i>Serratia</i> spp. (54)			0	8	31	12	2	0	0	0	0	0	1	0.5	1
			0.0	14.8	72.2	94.4	98.1	98.1	98.1	98.1	98.1	98.1	100.0		
<i>Serratia marcescens</i> (53)			0	8	31	12	1	0	0	0	0	0	1	0.5	1
			0.0	15.1	73.6	96.2	98.1	98.1	98.1	98.1	98.1	98.1	100.0		

Notes: ^aIndole-positive Proteae include: *Morganella morganii* (16), *Proteus vulgaris* group (3), *Providencia rettgeri* (3), and *P. stuartii* (3).

Table 2 Geographical Distribution of Phenotypically Resistant Isolates

Country	% of Isolates with Resistant Phenotypes (No. Resistant / No. Tested)						
	CRE	Presumptive ESBL Non-CRE		CAZ-NS		MER-NS	
	KPN	EC	KPN	ENTB	PSA	KPN	PSA
Japan	0.0%(0/15)	33.3%(11/33)	6.7%(1/15)	33.3%(1/3)	26.3%(5/19)	0.0%(0/15)	26.3%(5/19)
Korea	2.4%(3/123)	37.3%(81/217)	40.7%(50/123)	31.3%(5/16)	27.2%(22/81)	2.4%(3/123)	29.6%(24/81)
Malaysia	9.8%(9/92)	36.2%(25/69)	26.1%(24/92)	38.9%(7/18)	12.5%(9/72)	9.8%(9/92)	22.2%(16/72)
Philippines	20.4%(20/98)	41.6%(62/149)	38.8%(38/98)	47.5%(28/59)	13.2%(9/68)	20.4%(20/98)	10.3%(7/68)
Singapore	0.0%(0/21)	30.0%(3/10)	0.0%(0/21)	33.3%(1/3)	15.8%(3/19)	0.0%(0/21)	15.8%(3/19)
Taiwan	11.1%(7/63)	40.0%(30/75)	38.1%(24/63)	72.7%(16/22)	10.8%(4/37)	14.3%(9/63)	29.7%(11/37)
Thailand	26.8%(26/97)	51.4%(57/111)	35.1%(34/97)	22.6%(7/31)	27.4%(20/73)	26.8%(26/97)	35.6%(26/73)
Vietnam	55.3%(21/38)	65.4%(34/52)	10.5%(4/38)	0.0%(0/0)	28.6%(2/7)	57.9%(22/38)	28.6%(2/7)

Abbreviations: CRE, carbapenem-resistant Enterobacterales; ESBL, extended-spectrum β -lactamase; CAZ-NS, ceftazidime non-susceptible; MER-NS, meropenem non-susceptible; KPN, *Klebsiella pneumoniae*; EC, *Escherichia coli*; ENTB, *Enterobacter cloacae* species complex; PSA, *Pseudomonas aeruginosa*.

Activities of Ceftolozane/Tazobactam and Comparators Against *P. aeruginosa*

Ceftolozane/tazobactam was the most active (MIC_{50/90}, 0.5/4 mg/L) β -lactam agent tested against 376 *P. aeruginosa* isolates, inhibiting 91.0% of the isolates at a MIC of ≤ 4 mg/L (Tables 1 and 3). Overall susceptibility rates (Table 3) for cefepime (83.5% susceptible [CLSI] and 83.5% susceptible-increased exposure [EUCAST]), ceftazidime (80.3% susceptible [CLSI] and 80.3% susceptible-increased exposure [EUCAST]), meropenem (75.0/75.0% susceptible [CLSI/EUCAST]) and piperacillin/tazobactam (79.0% susceptible [CLSI] and 79.0% susceptible-increased exposure [EUCAST]), were all below that of ceftolozane/tazobactam at ≤ 4 mg/L (91.0/91.0% susceptible [CLSI/EUCAST]; Table 3). Both amikacin (MIC_{50/90}, 4/16 mg/L; 92.0/92.0% susceptible [CLSI/EUCAST]) and colistin (MIC_{50/90}, 1/1 mg/L; 99.2% intermediate [CLSI] and 99.2% susceptible [EUCAST]) showed good activity against *P. aeruginosa* (Table 3).

Ceftolozane/tazobactam retained activity against isolates of *P. aeruginosa* that were NS to the other antipseudomonal β -lactam agents (Table 3): ceftazidime-NS (56.8/56.8% susceptible [CLSI/EUCAST]), meropenem-NS (66.0% susceptible [CLSI/EUCAST]), and piperacillin/tazobactam-NS (67.1/67.1% susceptible [CLSI/EUCAST]). Ceftolozane/tazobactam was also active against MDR strains of *P. aeruginosa* (55.8/55.8% susceptible [CLSI/EUCAST]) and levofloxacin-NS isolates (71.4/71.4% [CLSI/EUCAST]). None of the other β -lactam agents inhibited more than 48% of these resistant phenotypes. Notably, colistin was highly active against ceftazidime-NS (MIC_{50/90}, 1/1 mg/L; 97.3% intermediate [CLSI] and 97.3% susceptible [EUCAST]), meropenem-NS (MIC_{50/90}, 1/1 mg/L; 97.9% intermediate [CLSI] and 97.9% susceptible [EUCAST]), piperacillin/tazobactam-NS (MIC_{50/90}, 1/1 mg/L; 97.5% intermediate [CLSI] and 97.5% susceptible [EUCAST]), and MDR (MIC_{50/90}, 1/1 mg/L; 96.1% intermediate [CLSI] and 96.1% susceptible [EUCAST]) strains of *P. aeruginosa* (Table 3). Compared to colistin, amikacin was less active against ceftazidime-NS (MIC_{50/90}, 8/>32 mg/L; 64.9/64.9% susceptible [CLSI/EUCAST]), meropenem-NS isolates (MIC_{50/90}, 8/>32 mg/L; 71.3/71.3% susceptible [CLSI/EUCAST]), piperacillin/tazobactam-NS isolates (MIC_{50/90}, 8/>32 mg/L; 73.4/73.4% susceptible [CLSI/EUCAST]), and MDR (MIC_{50/90}, 16/>32 mg/L; 61.0/61.0% susceptible [CLSI/EUCAST]) strains of *P. aeruginosa*.

The susceptibility of *P. aeruginosa* to antipseudomonal β -lactams varied markedly among the Asian nations that participated in the survey (Tables 2 and 4). The lowest susceptibility rates for ceftazidime, meropenem, and piperacillin/tazobactam were observed in Korea (72.8%, 70.4%, and 67.9%, respectively), Thailand (72.6%, 64.4%, and 78.1%, respectively), and Vietnam (71.4%, 71.4%, and 71.4%, respectively) and the highest were in the Philippines (86.8%, 89.7%, and 82.4%, respectively). Ceftolozane/tazobactam activity provided greater than 80% coverage against isolates from the 7 countries submitting 10 or more isolates (Table 4).

Table 3 Activity of Ceftolozane/Tazobactam and Comparator Agents Tested Against the Main Organisms and Organism Groups

Organism (No. Tested) Antimicrobial Agent	MIC (mg/L)		%S / %R	
	50%	90%	CLSI ^a	EUCAST ^a
<i>Pseudomonas aeruginosa</i> (376)				
Ceftolozane/tazobactam	0.5	4	91.0/7.7	91.0/9.0
Amikacin	4	16	92.0/5.6	92.0/8.0
Cefepime	2	>16	83.5/10.1	(83.5) ^c /16.5
Ceftazidime	2	>32	80.3/16.0	(80.3) ^c /19.7
Colistin	1	1	(99.2) ^b /0.8	99.2/0.8
Gentamicin	2	>8	85.4/10.9	
Levofloxacin	0.5	>4	70.2/23.4	(70.2) ^c /29.8
Meropenem	0.5	32	75.0/19.7	75.0/25.0
Piperacillin/tazobactam	4	>64	79.0/10.9	(79.0) ^c /21.0
Ceftazidime-nonsusceptible (>8 mg/L) <i>Pseudomonas aeruginosa</i> (74)				
Ceftolozane/tazobactam	4	>32	56.8/39.2	56.8/43.2
Amikacin	8	>32	64.9/24.3	64.9/35.1
Cefepime	16	>16	24.3/48.6	(24.3) ^c /75.7
Colistin	1	1	(97.3) ^b /2.7	97.3/2.7
Gentamicin	8	>8	41.9/44.6	
Levofloxacin	>4	>4	23.0/70.3	(23.0) ^c /77.0
Meropenem	16	>32	33.8/60.8	33.8/66.2
Piperacillin/tazobactam	>64	>64	14.9/51.4	(14.9) ^c /85.1
Meropenem-nonsusceptible (>2 mg/L) <i>Pseudomonas aeruginosa</i> (94)				
Ceftolozane/tazobactam	1	>32	66.0/28.7	66.0/34.0
Amikacin	8	>32	71.3/20.2	71.3/28.7
Cefepime	16	>16	45.7/38.3	(45.7) ^c /54.3
Ceftazidime	16	>32	47.9/42.6	(47.9) ^c /52.1
Colistin	1	1	(97.9) ^b /2.1	97.9/2.1
Gentamicin	4	>8	54.3/38.3	
Levofloxacin	>4	>4	21.3/71.3	(21.3) ^c /78.7
Piperacillin/tazobactam	32	>64	46.8/31.9	(46.8) ^c /53.2
Piperacillin/tazobactam-NS (>16 mg/L) <i>Pseudomonas aeruginosa</i> (79)				
Ceftolozane/tazobactam	2	>32	67.1/26.6	67.1/32.9
Amikacin	8	>32	73.4/22.8	73.4/26.6
Cefepime	16	>16	35.4/39.2	(35.4) ^c /64.6
Ceftazidime	32	>32	20.3/65.8	(20.3) ^c /79.7
Colistin	1	1	(97.5) ^b /2.5	97.5/2.5
Gentamicin	8	>8	49.4/39.2	
Levofloxacin	>4	>4	22.8/68.4	(22.8) ^c /77.2
Meropenem	8	>32	36.7/59.5	36.7/63.3
MDR <i>Pseudomonas aeruginosa</i> (77)				
Ceftolozane/tazobactam	4	>32	55.8/37.7	55.8/44.2
Amikacin	16	>32	61.0/27.3	61.0/39.0
Cefepime	16	>16	23.4/48.1	(23.4) ^c /76.6
Ceftazidime	32	>32	19.5/64.9	(19.5) ^c /80.5
Colistin	1	1	(96.1) ^b /3.9	96.1/3.9
Gentamicin	>8	>8	33.8/53.2	
Levofloxacin	>4	>4	7.8/83.1	(7.8) ^c /92.2
Meropenem	32	>32	22.1/71.4	22.1/77.9
Piperacillin/tazobactam	64	>64	15.6/48.1	(15.6) ^c /84.4

(Continued)

Table 3 (Continued).

Organism (No. Tested) Antimicrobial Agent	MIC (mg/L)		%S / %R	
	50%	90%	CLSI ^a	EUCAST ^a
Enterobacteriales (1662)				
Ceftolozane/tazobactam	0.25	16	86.8 / 11.4	86.8 / 13.2
Amikacin	2	8	97.7/1.6	94.9/5.1
Cefepime	≤0.12	>16	66.0/28.5	64.5/31.6
Ceftazidime	0.25	>32	65.3/31.8	60.9/34.7
Colistin	0.12	>8	(87.6) ^b /12.4	87.6/12.4
Gentamicin	0.5	>8	76.7/22.9	75.9/24.1
Levofloxacin	0.5	>4	58.7/37.0	58.7/37.0
Meropenem	0.03	0.12	93.0/6.7	93.3/6.7
Piperacillin/tazobactam	2	>64	81.5/12.0	77.7/22.3
Presumptive ESBL non-CRE <i>Enterobacteriales</i> (492)				
Ceftolozane/tazobactam	0.5	8	84.8/10.6	84.8/15.2
Amikacin	2	8	96.7/2.2	91.5/8.5
Cefepime	>16	>16	17.1/67.9	14.4/77.8
Ceftazidime	32	>32	22.2/69.3	8.5/77.8
Colistin	0.12	0.25	(94.3) ^b /5.7	94.3/5.7
Gentamicin	2	>8	52.6/46.7	51.6/48.4
Levofloxacin	>4	>4	22.0/71.7	22.0/71.7
Meropenem	0.03	0.12	99.2/0.0	100.0/0.0
Piperacillin/tazobactam	4	>64	75.1/11.6	66.1/33.9
<i>Escherichia coli</i> (716)				
Ceftolozane/tazobactam	0.25	1	95.8/3.4	95.8/4.2
Amikacin	2	8	99.0/0.3	96.8/3.2
Cefepime	≤0.12	>16	63.1/29.7	62.0/34.9
Ceftazidime	0.25	>32	67.3/27.8	60.1/32.7
Colistin	0.12	0.25	(99.3) ^b / 0.7	99.3/0.7
Gentamicin	1	>8	70.5/29.4	69.8/30.2
Levofloxacin	1	>4	49.6/47.6	49.6/47.6
Meropenem	≤0.015	0.03	98.6/1.4	98.6/1.4
Piperacillin/tazobactam	2	16	91.6/4.3	88.2/11.8
Presumptive ESBL non-CRE <i>Escherichia coli</i> (303)				
Ceftolozane/tazobactam	0.5	2	93.7/4.3	93.7/6.3
Amikacin	4	8	99.0/0.0	94.7/5.3
Cefepime	>16	>16	16.5/67.0	14.2/79.2
Ceftazidime	16	>32	26.4/62.0	9.2/73.6
Colistin	0.12	0.25	(99.3) ^b /0.7	99.3/0.7
Gentamicin	2	>8	52.1/47.9	51.5/48.5
Levofloxacin	>4	>4	21.1/74.9	21.1/74.9
Meropenem	0.03	0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	4	32	88.0/3.7	80.1/19.9
<i>Klebsiella</i> spp. (610)				
Ceftolozane/tazobactam	0.25	>32	75.7/21.3	75.7/24.3
Amikacin	1	8	96.1/3.1	91.5/8.5
Cefepime	≤0.12	>16	61.6/35.2	60.5/36.9
Ceftazidime	0.5	>32	57.5/41.1	55.4/42.5
Colistin	0.12	0.25	(94.6) ^b /5.4	94.6/5.4
Gentamicin	0.25	>8	81.1/18.4	80.8/19.2
Levofloxacin	0.12	>4	59.9/35.3	59.9/35.3
Meropenem	0.03	32	84.9/14.4	85.6/14.4
Piperacillin/tazobactam	4	>64	69.1/22.5	64.5/35.5

(Continued)

Table 3 (Continued).

Organism (No. Tested) Antimicrobial Agent	MIC (mg/L)		%S / %R	
	50%	90%	CLSI ^a	EUCAST ^a
<i>Klebsiella pneumoniae</i> (547)				
Ceftolozane/tazobactam	0.25	>32	74.8/22.3	74.8/25.2
Amikacin	1	8	95.6/3.5	90.5/9.5
Cefepime	≤0.12	>16	58.3/38.4	57.0/40.2
Ceftazidime	0.5	>32	56.1/42.6	53.9/43.9
Colistin	0.12	0.25	(94.3) ^b /5.7	94.3/5.7
Gentamicin	0.25	>8	79.7/19.7	79.3/20.7
Levofloxacin	0.5	>4	56.8/38.3	56.8/38.3
Meropenem	0.03	32	83.7/15.5	84.5/15.5
Piperacillin/tazobactam	4	>64	68.4/24.2	64.2/35.8
Presumptive ESBL non-CRE <i>Klebsiella pneumoniae</i> (175)				
Ceftolozane/tazobactam	2	>32	69.1/21.7	69.1/30.9
Amikacin	2	16	94.3/4.6	87.4/12.6
Cefepime	>16	>16	17.1/73.1	14.9/78.9
Ceftazidime	>32	>32	10.9/85.1	4.0/89.1
Colistin	0.12	0.25	(93.1) ^b /6.9	93.1/6.9
Gentamicin	0.5	>8	55.4/42.9	54.3/45.7
Levofloxacin	>4	>4	24.7/66.1	24.7/66.1
Meropenem	0.06	0.12	97.7/0.0	100.0 / 0.0
Piperacillin/tazobactam	16	>64	51.4/26.3	40.0/60.0
<i>Klebsiella oxytoca</i> (13)				
Ceftolozane/tazobactam	0.25	>32	84.6/15.4	84.6/15.4
Amikacin	1	4	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.12	128	84.6/15.4	84.6/15.4
Ceftazidime	0.25	>32	84.6/15.4	84.6/15.4
Colistin	0.12	0.25	(100.0) ^b /0.0	100.0/0.0
Gentamicin	0.5	>16	84.6/15.4	84.6/15.4
Levofloxacin	0.06	>32	76.9/15.4	76.9/15.4
Meropenem	0.03	>32	84.6/15.4	84.6/15.4
Piperacillin/tazobactam	2	>128	84.6/15.4	76.9/23.1
<i>Klebsiella aerogenes</i> . (50)				
Ceftolozane/tazobactam	0.25	8	84.0/12.0	84.0/16.0
Amikacin	1	4	100.0/0.0	100.0/0.0
Cefepime	≤0.12	1	92.0/6.0	92.0/6.0
Ceftazidime	0.5	>32	66.0/32.0	64.0/34.0
Colistin	0.12	0.25	(96.0) ^b /4.0	96.0/4.0
Gentamicin	0.25	1	96.0/4.0	96.0/4.0
Levofloxacin	0.06	0.5	90.0/8.0	90.0/8.0
Meropenem	0.06	0.06	98.0/2.0	98.0/2.0
Piperacillin/tazobactam	4	64	72.0/6.0	64.0/36.0
<i>Enterobacter cloacae</i> species complex (152)				
Ceftolozane/tazobactam	0.25	32	77.0/19.1	77.0/23.0
Amikacin	2	4	98.0/1.3	97.4/2.6
Cefepime	≤0.12	>16	70.4/22.4	67.1/24.3
Ceftazidime	0.5	>32	57.2/40.8	54.6/42.8
Colistin	0.25	>8	(72.6) ^b / 27.4	72.6/27.4
Gentamicin	0.5	>8	78.9/21.1	78.3/21.7
Levofloxacin	0.06	>4	79.6/16.4	79.6/16.4

(Continued)

Table 3 (Continued).

Organism (No. Tested) Antimicrobial Agent	MIC (mg/L)		%S / %R	
	50%	90%	CLSI ^a	EUCAST ^a
Meropenem	0.03	0.5	92.1/7.9	92.1/7.9
Piperacillin/tazobactam	4	>64	69.7/17.8	66.4/33.6
Ceftazidime-nonsusceptible (>4 mg/L) <i>Enterobacter cloacae</i> species complex . (65)				
Ceftolozane/tazobactam	4	>32	46.2/44.6	46.2/53.8
Amikacin	2	8	95.4/3.1	93.8/6.2
Cefepime	16	>16	32.3/52.3	24.6/55.4
Colistin	0.25	>8	(88.9) ^b /11.1	88.9/11.1
Gentamicin	0.5	>8	53.8/46.2	52.3/47.7
Levofloxacin	0.5	>4	60.0/32.3	60.0/32.3
Meropenem	0.06	32	81.5/18.5	81.5/18.5
Piperacillin/tazobactam	64	>64	30.8/41.5	23.1/76.9
<i>Citrobacter</i> spp. (50)				
Ceftolozane/tazobactam	0.25	0.5	92.0 / 8.0	92.0/8.0
Amikacin	2	4	98.0/2.0	98.0/2.0
Cefepime	≤0.12	1	94.0/6.0	90.0/6.0
Ceftazidime	0.25	>32	82.0/16.0	80.0/18.0
Colistin	0.12	0.25	(100.0) ^b /0.0	100.0/0.0
Gentamicin	0.5	1	90.0/10.0	90.0/10.0
Levofloxacin	≤0.03	2	80.0/16.0	80.0/16.0
Meropenem	0.03	0.03	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	16	90.0/4.0	84.0/16.0
<i>Citrobacter koseri</i> (25)				
Ceftolozane/tazobactam	0.12	0.5	100.0 / 0.0	100.0/0.0
Amikacin	1	2	96.0/4.0	96.0/4.0
Cefepime	≤0.12	≤0.12	100.0 / 0.0	100.0 / 0.0
Ceftazidime	0.12	0.5	100.0/0.0	96.0/0.0
Colistin	0.12	0.12	(100.0) ^b /0.0	100.0 / 0.0
Gentamicin	0.25	0.5	96.0/4.0	96.0/4.0
Levofloxacin	≤0.03	0.12	95.0/4.0	96.0/4.0
Meropenem	≤0.015	0.03	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	4	100.0/0.0	96.0/4.0
<i>Citrobacter freundii</i> species complex (25)				
Ceftolozane/tazobactam	0.25	8	84.0/16.0	84.0/16.0
Amikacin	2	8	100.0 / 0.0	100.0/0.0
Cefepime	≤0.12	>16	88.0/12.0	80.0/12.0
Ceftazidime	0.5	>32	64.0/32.0	64.0/36.0
Colistin	0.25	0.25	(100.0) ^b /0.0	100.0 / 0.0
Gentamicin	0.5	>8	84.0/16.0	84.0/16.0
Levofloxacin	0.25	4	64.0/28.0	64.0/28.0
Meropenem	0.03	0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	32	80.0/8.0	72.0/28.0
<i>Serratia marcescens</i> (53)				
Ceftolozane/tazobactam	0.5	1	98.1/1.9	98.1/1.9
Amikacin	2	4	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.12	0.5	96.2/1.9	96.2/1.9
Ceftazidime	0.25	0.5	96.2/3.8	94.3/3.8
Colistin	>8	>8	(1.9) ^b /98.1	1.9/98.1

(Continued)

Table 3 (Continued).

Organism (No. Tested) Antimicrobial Agent	MIC (mg/L)		%S / %R	
	50%	90%	CLSI ^a	EUCAST ^a
Gentamicin	0.5	1	98.1/0.0	98.1/1.9
Levofloxacin	0.12	0.5	92.3/5.8	92.3/5.8
Meropenem	0.06	0.06	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	2	8	94.3/1.9	92.5/7.5
<i>Proteus mirabilis</i> (48)				
Ceftolozane/tazobactam	0.5	1	95.8/2.1	95.8/4.2
Amikacin	4	8	93.8/6.2	91.7/8.3
Cefepime	≤0.12	8	82.9/8.3	66.7/14.6
Ceftazidime	0.06	4	91.7/8.3	85.4/8.3
Colistin	>8	>8	(0.0) ^b /100.0	0.0/100.0
Gentamicin	1	>8	62.5/35.4	56.2/43.8
Levofloxacin	0.5	>4	50.0/37.5	50.0/37.5
Meropenem	0.06	0.12	97.9/2.1	97.9/2.1
Piperacillin/tazobactam	≤0.5	8	95.7/0.0	91.5/8.5
Indole-positive Proteae (25)				
Ceftolozane/tazobactam	0.25	0.5	100.0 / 0.0	100.0 / 0.0
Amikacin	2	4	100.0 / 0.0	100.0 / 0.0
Cefepime	≤0.12	4	88.0/8.0	88.0/4.0
Ceftazidime	0.25	1	92.0/4.0	92.0/8.0
Colistin	>8	>8	(0.0) ^b /100.0	0.0/100.0
Gentamicin	0.5	>8	84.0/12.0	76.0/24.0
Levofloxacin	0.12	2	60.0/16.0	60.0/16.0
Meropenem	0.06	0.12	100.0 / 0.0	100.0 / 0.0
Piperacillin/tazobactam	≤0.5	4	96.0/4.0	96.0/4.0

Notes: ^aCriteria published by CLSI²⁹ and EUCAST.³⁰ ^bIntermediate only, no susceptible category. ^cSusceptible, increased exposure.

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; CRE, carbapenem-resistant Enterobacterales; ESBL, extended-spectrum β-lactamase; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MDR, multidrug resistant; MIC, minimal inhibitory concentration; R, resistant; S, susceptible.

Table 4 Antimicrobial Activity of Ceftolozane/Tazobactam, Ceftazidime, Meropenem, and Piperacillin/Tazobactam Against Isolates of *P. aeruginosa* stratified by Country for Countries with 10 or More Isolates

Country (No. Tested)	% Susceptible (No. Susceptible) ^a			
	Ceftolozane/Tazobactam	Ceftazidime	Meropenem	Piperacillin/Tazobactam
Japan (19)	89.5 (17)	73.7 (14)	73.7 (14)	78.9 (15)
Korea (81)	95.1 (77)	72.8 (59)	70.4 (57)	67.9 (55)
Malaysia (72)	90.3 (65)	87.5 (63)	77.8 (56)	91.7 (66)
Philippines (68)	97.1 (66)	86.8 (59)	89.7 (61)	82.4 (56)
Singapore (19)	89.5 (17)	84.2 (16)	84.2 (16)	73.7 (14)
Taiwan (37)	97.3 (36)	89.2 (33)	70.3 (26)	78.4 (29)
Thailand (73)	80.8 (59)	72.6 (53)	64.4 (47)	78.1 (57)

Notes: ^aSusceptible based on criteria published by CLSI.²⁹ Vietnam not shown as it had 7 *P. aeruginosa* isolates.

Activities of Ceftolozane/Tazobactam and Comparators Against Enterobacterales

Ceftolozane/tazobactam (MIC_{50/90}, 0.25/16 mg/L) inhibited 86.8/86.8% of the 1662 Enterobacterales isolates tested at the CLSI/EUCAST susceptible breakpoints of $\leq 2/\leq 2$ mg/L, respectively (Tables 1 and 3). Enterobacterales isolates displayed susceptibility rates to other β -lactam agents ranging from 93.0/93.3% for meropenem, 81.5/77.7% for piperacillin/tazobactam, 66.0/64.5% for cefepime, and 65.3/60.9% for ceftazidime using CLSI/EUCAST breakpoints. Among the non- β -lactam agents, amikacin (MIC_{50/90}, 2/8 mg/L; 97.7/94.9% susceptible [CLSI/EUCAST]) was more active than colistin (MIC_{50/90}, 0.12/>8 mg/L; 87.6% susceptible [EUCAST]), gentamicin (MIC_{50/90}, 0.5/>8 mg/L; 76.7/75.9% susceptible [CLSI/EUCAST]), and levofloxacin (MIC_{50/90}, 0.5/>4 mg/L; 58.7/58.7% susceptible [CLSI/EUCAST]). Against 492 presumptive ESBL non-CRE phenotype Enterobacterales isolates, ceftolozane/tazobactam (MIC_{50/90}, 0.5/8 mg/L; 84.8/84.8% susceptible [CLSI/EUCAST]), meropenem (MIC_{50/90}, 0.03/0.12 mg/L; 99.2/100.0% susceptible [CLSI/EUCAST]), colistin (MIC_{50/90}, 0.12/0.25 mg/L; 94.3% susceptible [EUCAST]), amikacin (MIC_{50/90}, 2/8 mg/L; 96.7/91.5% susceptible [CLSI/EUCAST]), and piperacillin/tazobactam (MIC_{50/90}, 4/>64 mg/L; 75.1/66.1% susceptible [CLSI/EUCAST]) were the only agents to retain clinically useful activity (Table 3).

A total of 716 *E. coli* isolates were evaluated, 95.8/95.8% of which were susceptible to ceftolozane/tazobactam (MIC_{50/90}, 0.25/1 mg/L) by CLSI/EUCAST interpretive guidelines. Meropenem (MIC_{50/90}, $\leq 0.015/0.03$ mg/L; 98.6/98.6% susceptible [CLSI/EUCAST]), amikacin (MIC_{50/90}, 2/8 mg/L; 99.0/96.8% susceptible [CLSI/EUCAST]), colistin (MIC_{50/90}, 0.12/0.25 mg/L; 99.3% susceptible [EUCAST]), and piperacillin/tazobactam (MIC_{50/90}, 2/16 mg/L; 91.6/88.2% susceptible [CLSI/EUCAST]) showed good activity against *E. coli* (Table 3). Cefepime (MIC_{50/90}, $\leq 0.12/>16$ mg/L; 63.1/62.0% susceptible [CLSI/EUCAST]), ceftazidime (MIC_{50/90}, 0.25/>32 mg/L; 67.3/60.1% susceptible [CLSI/EUCAST]), gentamicin (MIC_{50/90}, 1/>8 mg/L; 70.5/69.8% susceptible [CLSI/EUCAST]), and levofloxacin (MIC_{50/90}, 1/>4 mg/L; 49.6/49.6% susceptible [CLSI/EUCAST]) showed decreased activity against *E. coli* isolates. Among presumptive ESBL non-CRE phenotype *E. coli* isolates, resistance rates to cefepime, ceftazidime, gentamicin, and levofloxacin were elevated (Table 3). Meropenem (MIC_{50/90}, 0.03/0.06 mg/L; 100.0/100.0% susceptible [CLSI/EUCAST]) and amikacin (MIC_{50/90}, 4/8 mg/L; 99.0/94.7% susceptible [CLSI/EUCAST]) retained potent activity against presumptive ESBL non-CRE phenotype strains of *E. coli*. Ceftolozane/tazobactam inhibited 93.7% of the presumptive ESBL non-CRE phenotype isolates of *E. coli* at ≤ 2 mg/L (Tables 1 and 3). Piperacillin/tazobactam was slightly less active (MIC_{50/90}, 4/32 mg/L; 88.0/80.1% susceptible [CLSI/EUCAST]) than ceftolozane/tazobactam against these strains of *E. coli*.

Ceftolozane/tazobactam showed moderate activity against isolates of *K. pneumoniae* (MIC_{50/90}, 0.25/>32 mg/L; 74.8/74.8% susceptible [CLSI/EUCAST]) and was slightly less active against presumptive ESBL non-CRE phenotype isolates (MIC_{50/90}, 2/>32 mg/L; 69.1/69.1% susceptible [CLSI/EUCAST]) (Tables 1 and 3). Among the β -lactam comparator agents tested, only meropenem was more active than ceftolozane/tazobactam against *Klebsiella* species, irrespective of the resistant phenotype (Table 3). Ceftolozane/tazobactam was also active against other frequently isolated Enterobacterales, including *Klebsiella oxytoca* (MIC_{50/90}, 0.25/>32 mg/L; 84.6/84.6% susceptible [CLSI/EUCAST]), *Klebsiella aerogenes* (MIC_{50/90}, 0.25/8 mg/L; 84.0/84.0% susceptible [CLSI/EUCAST]), *Enterobacter cloacae* species complex (MIC_{50/90}, 0.25/32 mg/L; 77.0/77.0% susceptible [CLSI/EUCAST]), *Citrobacter* spp. (MIC_{50/90}, 0.25/0.5 mg/L; 92.0/92.0% susceptible [CLSI/EUCAST]), *P. mirabilis* (MIC_{50/90}, 0.5/1 mg/L; 95.8/95.8% susceptible [CLSI/EUCAST]), indole-positive Proteae (MIC_{50/90}, 0.25/0.5 mg/L; 100.0/100.0% susceptible [CLSI/EUCAST]), and *Serratia marcescens* (MIC_{50/90}, 0.5/1 mg/L; 98.1/98.1% susceptible [CLSI/EUCAST]) (Tables 1 and 3). Ceftolozane/tazobactam (MIC_{50/90}, 4/>32 mg/L; 46.2/46.2% susceptible [CLSI/EUCAST]), cefepime (MIC_{50/90}, 16/>16 mg/L; 32.3/24.6% susceptible [CLSI/EUCAST]), and piperacillin/tazobactam (MIC_{50/90}, 64/>64 mg/L; 30.8/23.1% susceptible [CLSI/EUCAST]) all showed decreased activity against ceftazidime-nonsusceptible *E. cloacae* species complex (Table 3).

Previously in 1998–2010 and 2013–2015, we showed that, among isolates of *E. coli* and *K. pneumoniae*, the rates of presumptive ESBL and CRE phenotypes varied markedly among Asian countries.^{7,10,11,13,14,16} As seen in Table 2, resistance rates among these 2 species from 2016 to 2018 show continued variability among the Asian countries evaluated. The occurrence of *K. pneumoniae* isolates with a presumptive CRE phenotype ranged from 0.0% in Japan and Singapore to 55.3% in Vietnam and was 15.7% overall. The highest rates of presumptive ESBL non-CRE

phenotype *E. coli* were identified in isolates from Vietnam (65.4%) followed by Thailand (51.4%) and the lowest rates were in isolates from Singapore (30.0%). In contrast, the highest rates of presumptive ESBL non-CRE phenotype *K. pneumoniae* were associated with isolates from Korea (40.7%) while the lowest rates were in isolates from Vietnam (10.5%), Japan (6.7%), and Singapore (0.0%). Similar variability in resistance profiles was seen for ceftazidime-NS isolates of *Enterobacter* spp. and meropenem-NS isolates of *K. pneumoniae* (Table 2). These resistance rates are considerably higher than rates reported in 1998 to 2002,^{7,11} 2008,¹⁰ and 2013 to 2015.¹³

Discussion

Our study results extend those previously reported concerning the in vitro activity of ceftolozane/tazobactam against strains of Enterobacterales and *P. aeruginosa* in Asia.¹³ Ceftolozane/tazobactam was the most active of the tested β -lactam agents against *P. aeruginosa* and was second to meropenem against Enterobacterales. Ceftolozane/tazobactam retained activity against most presumptive ESBL non-CRE phenotype strains, second only to meropenem. Likewise, ceftolozane/tazobactam was more active than the other antipseudomonal β -lactam agents tested against strains of *P. aeruginosa* that were NS to ceftazidime, meropenem, and piperacillin/tazobactam as well as MDR strains. Among the non- β -lactam comparator agents, colistin and amikacin were the most active against Enterobacterales and *P. aeruginosa*, including the various resistant phenotypes. It should be noted that colistin and amikacin are nephrotoxic.³² In addition, colistin efficacy has been found to be poor when given systemically to patients with pneumonia.³³

Previously, Castanheira et al demonstrated a steady increase in the *E. coli* and *K. pneumoniae* ESBL prevalence rate in Asian countries from 1997 to 2016.¹ Notably, the resistance patterns for commonly used antimicrobials against Enterobacterales varied by geographical location and species characteristics.^{1,10,11,13} Our findings support and extend those observations. The rates of presumptive ESBL non-CRE phenotype *E. coli* and *K. pneumoniae* in the present study (42.3% and 28.7%, respectively) were comparable to or slightly higher than those reported by Pfaller et al for 2013 to 2015 (34.9% and 30.4%, respectively) and were higher than the presumptive ESBL non-CRE rates seen in the US and western Europe.^{1,7,8,10,11} Carbapenem resistance attributable to acquired carbapenemases remains relatively uncommon in Asia, comprising only 2% to 5% of Enterobacterales in 2004–2009,^{8,9} 3.6% in 2013–2015,¹³ and 6.8% in the present survey (2016–2018; Table 1). The majority of presumptive CRE phenotype isolates were accounted for by *K. pneumoniae*, with CRE rates of greater than 9% in 5 of the 8 Asian countries (range 0.0–55.3%; 15.7% overall) (Table 2). As previously noted, ceftolozane/tazobactam did not have activity against CRE.¹³

There are some limitations to this work that must be acknowledged. First, patient-level data is not collected in SENTRY Program. Second, no confirmatory testing was performed for either ESBL or CRE production. This is consistent with our previous publication concerning the activity of ceftolozane-tazobactam against Enterobacterales isolates from Asia.¹³ As such, we described these results as presumptive ESBL non-CRE phenotype and presumptive CRE phenotype strains. Third, we did not link the isolation of bacterial species and associated resistance profiles with patient presentation, treatment, or outcome. Fourth, susceptibility to ceftazidime/avibactam was not determined in this study. Fifth and finally, the SENTRY Program depends on the classification of isolates as originating from clinically significant healthcare-associated infections of specific body sites (e.g., bloodstream, respiratory specimens, urinary tract, skin and soft tissue specimens, and intra-abdominal abscesses) based on the judgement of the submitting laboratory.

In summary, these data for ceftolozane/tazobactam collected from 2016 to 2018 from 11 Asian medical centres demonstrate its sustained potency and spectrum against *P. aeruginosa* and Enterobacterales when compared to previous studies.^{13,23–26} These data suggest that ceftolozane/tazobactam may be an important treatment option for HAIs caused by wild-type and MDR strains of *P. aeruginosa*, including those resistant to ceftazidime or piperacillin/tazobactam as well as ESBL non-CR Enterobacterales.²⁰ Resistance rates among GNB from Asia are relatively high and have been increasing in recent years, emphasizing the need for resistance surveillance and antimicrobial stewardship in those countries.^{6,12}

Ethical Statement

Isolates were collected as part of the routine hospital laboratory procedure. No patient information was collected that could identify specific patients, only limited patient demographics were collected. Ethical approval not required.

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Disclosure

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