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Activity of Ceftolozane-Tazobactam Against Gram-Negative Isolates from Australia and New Zealand as part of the PACTS Surveillance 2016-2018

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ABSTRACT

Objectives: Ceftolozane-tazobactam (C-T) is an anti-pseudomonal cephalosporin combined with a well-described β-lactamase inhibitor. Ceftolozane-tazobactam has enhanced activity against *Pseudomonas aeruginosa,* and activity against Enterobacterales isolates that produce extended-spectrum β-lactamases (ESBLs) or AmpC cephalosporinases. In this study, we analysed the susceptibility of Gram-negative isolates to C-T and comparators collected in Australia and New Zealand from 2016 to 2018 as part of the Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) surveillance.

Methods: A total of 1693 nonduplicate Enterobacterales and 435 *P. aeruginosa* isolates were collected prospectively from hospitalized patients in six medical centres in Australia and two in New Zealand. Susceptibilities (S) to C-T and comparators were determined using broth microdilution. EUCAST breakpoints were used. Isolates with multi-drug resistant (MDR), extensively drug resistant (XDR), extended-spectrum β-lactamase non-carbapenem resistant (ESBL, non-CRE) phenotype, and CRE were analysed.

Results: For *P. aeruginosa*, 97.5% were S to C-T while 89.9% were S to meropenem. According to EUCAST criteria, 86.4% were susceptible-increased exposure to piperacillin-tazobactam. MDR and XDR *P. aeruginosa* isolates had 76.7% and 65.4% S to C-T, respectively; 34.9% and 19.2% S to meropenem, respectively; and 23.3% and 15.4% were susceptible-increased exposure to piperacillin-tazobactam, respectively. Meropenem (99.8% S), amikacin (99.1% S), and C-T (96.5% S) were the most active against Enterobacterales. Susceptibilities to C-T were 94.3% for ESBL, non-CRE phenotype, and 78.4% for MDR isolates. Only three CRE and five XDR isolates were identified.

Conclusions: These *in vitro* data indicate that C-T is a potent antimicrobial with activity against MDR and XDR *P. aeruginosa,* as well as ESBL, non-CRE phenotype isolates and MDR Enterobacterales.

1. Introduction

Antimicrobial resistance of Gram-negative organisms is a serious global public health issue according to the Centers for Disease Control and Prevention and the World Health Organization [1,2]. Prompt, appropriate antimicrobial treatment improves patient outcomes and reduces the economic impact to the health care system [3,4]. Several β-lactam/β-lactamase inhibitor combinations have been recently approved for clinical treatment of serious Gram-negative infections, including ceftolozane-tazobactam (C-T).

Ceftolozane-tazobactam is an antipseudomonal cephalosporin combined with a well-described β-lactamase inhibitor. This combination has enhanced activity against *Pseudomonas aeruginosa* as well as activity against Enterobacterales isolates producing extended-spectrum β-lactamases (ESBLs) or AmpC cephalosporinases [5]. Ceftolozane-tazobactam is approved in >70 countries to treat the following indications: complicated urinary tract in-

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fections, including pyelonephritis; complicated intra-abdominal infections in combination with metronidazole with a ceftolozane-tazobactam dose of 1.5 g every 8 h; and nosocomial pneumonia, including ventilator-associated pneumonia, with a ceftolozane-tazobactam a dose of 3.0 g every 8 h [6].

The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitored susceptibility to ceftolozane-tazobactam and comparators in Australia and New Zealand from 2011 to 2018. In the current study, we analysed the susceptibility of Gram-negative isolates to ceftolozane-tazobactam and comparators collected in Australia and New Zealand from 2016 to 2018.

2. Materials and methods

2.1. Organisms

A total of 1693 nonduplicate Enterobacterales and 435 *P. aeruginosa* isolates were collected prospectively from hospitalised patients in eight medical centres. Six centres in Australia submitted 1652 isolates and two centres in New Zealand submitted 476 isolates to the PACTS program from 2016 to 2018. PACTS is a subset of the SENTRY Antimicrobial Resistance Surveillance Program. Participating centres were asked to submit one isolate per patient per infection episode. Isolates were collected consecutively by infection type according to a common protocol, as described previously [7]. Only isolates determined to be significant by local criteria as the reported probable cause were submitted. Isolates were identified at each medical centre using the standard methods of the participating laboratory and then were confirmed by the central laboratory (JMI Laboratories, North Liberty, IA) using a matrix-assisted laser desorption ionization time-of-flight technology mass spectrometer (Bruker, Billerica, MA). Other biochemical methods were used when needed to differentiate specific species, such as *Escherichia coli* using spot indole and motility. Isolates from all infection types (bloodstream infections, pneumonia in hospitalised patients, intra-abdominal infections, skin and skin structure infections, and urinary tract infections) were analysed in this study.

2.2. Susceptibility testing

Minimum inhibitory concentrations (MICs) for all antibiotics were determined by JMI Laboratories using the reference broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI) standards [8]. All MIC testing for ceftolozane-tazobactam and piperacillin-tazobactam used a fixed tazobactam concentration of 4 mg/L. Quality control and interpretation of results were performed according to the CLSI M100 and the European Committee on Antimicrobial Testing (EUCAST) v. 12.0 [9,10]. All MIC values for American Type Culture Collection (ATCC) quality control strains were within the published ranges.

In version 10.0 of the EUCAST breakpoints, the Enterobacterales and *P. aeruginosa* breakpoints of several antimicrobial agents were changed to recategorize all isolates in the wild-type population as 'susceptible, increased exposure' [11]. 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 piperacillin-tazobactam, cefepime, ceftazidime, imipenem, aztreonam, and ciprofloxacin as well as previously imipenem-susceptible isolates of *Proteus* spp., *Providencia* spp., and *Morganella morganii* are shown as 'susceptible, increased exposure' in this study. In addition, CLSI removed the susceptible category for colistin, reporting only intermediate or resistant categories for Enterobacterales and *P. aeruginosa* [9].

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) isolates were categorized according to Magiorakos et al. [12]. Carbapenem-resistant Enterobacterales (CRE) were identified as having an MIC value >2 mg/L to doripenem, meropenem, or imipenem (an imipenem MIC was not applied for *Proteus* spp., *Providencia* spp., and *M. morganii*). *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca*, and *Proteus mirabilis* were grouped as 'ESBL phenotype' based on the CLSI screening criteria for potential ESBL production (i.e., an MIC of ≥2 mg/L for ceftazidime, ceftriaxone, or aztreonam as described by CLSI) [9]. Since carbapenemase-producing isolates may also appear to have an ESBL phenotype, non-carbapenem-resistant ESBL-screen-positive phenotype (ESBL, non-CRE) isolates were analysed separately. Resistance mechanisms were not molecularly characterised in this study.

3. Results and discussion

3.1. Organisms

The three most common Gram-negative isolates were *E. coli* (n = 868, 40.8%), followed by *P. aeruginosa* (n = 435, 20.4%) and *K. pneumoniae* (n = 275, 12.9%) in each of the infection types studied. *P. aeruginosa* was the most frequently isolated Gram-negative organism from pneumonia and skin and skin structure infections (37.0% and 41.3% of pneumonia and skin and soft tissue infection (SSTI), respectively), while *E. coli* was the most frequent Gram-negative isolate from the other three infection types.

3.2. Susceptibilities

The susceptibilities for *P. aeruginosa* or the Enterobacterales isolates tested against ceftolozane-tazobactam and comparators are shown in Tables. 1 and 2. The MIC distribution of ceftolozane-tazobactam for the organisms and organism groups in this study are shown in Table 3.

Ceftolozane-tazobactam was the β-lactam agent tested with the highest susceptibility rate (97.5%) against *P. aeruginosa* isolates (Table 1). The meropenem susceptibility rate was 89.9%; 86.4% of these isolates were susceptible-increased exposure to piperacillin-tazobactam according to EUCAST criteria Other active agents were colistin (99.3%) and amikacin (94.5%). Levofloxacin was the least active agent, with 80.0% classified as susceptible, increased exposure. Of 44 meropenem-nonsusceptible *P. aeruginosa* isolates, 79.5% were susceptible to ceftolozane-tazobactam. Of the 59 isolates resistant to piperacillin-tazobactam and 42 isolates resistant to ceftazidime, 81.4% and 73.8% were susceptible to ceftolozane-tazobactam, respectively. There were 26 (6.0%) XDR *P. aeruginosa* isolates, of which 65.4% were susceptible to ceftolozane-tazobactam. The XDR isolates had low levels of susceptibility to most of the comparators tested, including meropenem (19.2% susceptible) and piperacillin-tazobactam (5.4% susceptible, increased exposure). Colistin had the highest susceptibility against the resistant subgroups (88.5% susceptibility among XDR isolates [using EUCAST criteria, although it should be noted CLSI no longer recognises colistin-susceptible breakpoints for *P. aeruginosa*]).

The antimicrobials displaying the highest susceptibility rates to Enterobacterales were ceftolozane-tazobactam (96.5% susceptible), meropenem (99.8%), and amikacin (99.1%) (EUCAST criteria, Tables 2 and 3). The piperacillin-tazobactam susceptibility rate was 91.1% and levofloxacin susceptibility was 89.5%. Ceftolozane-tazobactam was active against 99.1% and 98.5% of the *E. coli* and *K. pneumoniae*, respectively (Tables 1 and 3). There were 176 (10.4%) ESBL-positive phenotype, non-CRE isolates, of which 143 (16.5%) were *E. coli*, 29 (10.5%) were *K. pneumoniae*, and 4 (4.8%) were *P. mirabilis*. Ceftolozane-tazobactam was active against 94.3% of the ESBL, non-CRE phenotype isolates while piperacillin-tazobactam susceptibility was 77.8% and meropenem susceptibility was 100%. By species, ceftolozane-tazobactam was active

Table 1
Antimicrobial activity of ceftolozane-tazobactam and comparator agents tested against 435 *Pseudomonas aeruginosa*

Organism/Antimicrobial agent	mg/L MIC_{50}	MIC_{90}	MIC range	CLSI[a] %S	%I	%R	EUCAST[a] %S	%S-IE	%R
All *P. aeruginosa* (n=435)									
Ceftolozane-tazobactam	0.5	1	0.06 to >32	97.5	1.4	1.1	97.5		2.5
Amikacin	4	8	≤0.25 to >32	94.5	2.1	3.4	94.5 [b]		5.5
Ceftazidime	2	8	0.25 to >32	90.3	1.8	7.8	[c]	90.3	9.7
Colistin	0.5	1	0.12 to >8	[d]	99.3	0.7	99.3		0.7
Levofloxacin	0.5	4	≤0.03 to >4	80.0	8.0	12.0	[c]	80.0	20.0
Meropenem	0.25	4	≤0.015 to >32	89.9	3.2	6.9	89.9 [e]	4.8	5.3
Piperacillin-tazobactam	4	32	≤0.5 to >64	86.4	7.8	5.8	[c]	86.4	13.6
Meropenem nonsusceptible (n=44)									
Ceftolozane-tazobactam	1	16	0.25 to >32	79.5	9.1	11.4	79.5		20.5
Amikacin	8	>32	2 to >32	65.9	6.8	27.3	65.9 [b]		34.1
Ceftazidime	8	>32	1 to >32	63.6	2.3	34.1	[c]	63.6	36.4
Colistin	0.5	1	0.12 to >8	[d]	93.2	6.8	93.2		6.8
Levofloxacin	2	>4	0.25 to >4	34.1	18.2	47.7	[c]	34.1	65.9
Meropenem	16	32	4 to >32	0.0	31.8	68.2	0.0 [e]	47.7	52.3
Piperacillin-tazobactam	16	>64	2 to >64	50.0	29.5	20.5	[c]	50.0	50.0
Piperacillin-tazobactam resistant (n=59)									
Ceftolozane-tazobactam	1	8	0.25 to >32	81.4	10.2	8.5	81.4		18.6
Amikacin	4	>32	1 to >32	79.7	5.1	15.3	79.7 [b]		20.3
Ceftazidime	32	>32	1 to >32	28.8	13.6	57.6	[c]	28.8	71.2
Colistin	0.5	1	0.12 to >8	[d]	96.6	3.4	96.6		3.4
Levofloxacin	1	>4	0.25 to >4	54.2	15.3	30.5	[c]	54.2	45.8
Meropenem	1	32	0.12 to >32	62.7	3.4	33.9	62.7 [e]	8.5	28.8
Piperacillin-tazobactam	64	>64	32 to >64	0.0	57.6	42.4	[c]	0.0	100.0
Ceftazidime resistant (n=42)									
Ceftolozane-tazobactam	2	16	0.5 to >32	73.8	14.3	11.9	73.8		26.2
Amikacin	8	>32	1 to >32	73.8	4.8	21.4	73.8 [b]		26.2
Ceftazidime	32	>32	16 to >32	0.0	19.0	81.0	[c]	0.0	100.0
Colistin	0.5	1	0.12 to >8	[d]	95.2	4.8	95.2		4.8
Levofloxacin	1	>4	0.25 to >4	57.1	14.3	28.6	[c]	57.1	42.9
Meropenem	1	32	0.12 to >32	61.9	4.8	33.3	61.9 [e]	9.5	28.6
Piperacillin-tazobactam	>64	>64	32 to >64	0.0	40.5	59.5	[c]	0.0	100.0
XDR (n=26)									
Ceftolozane-tazobactam	2	>32	0.25 to >32	65.4	15.4	19.2	65.4		34.6
Amikacin	32	>32	2 to >32	42.3	15.4	42.3	42.3 [b]		57.7
Ceftazidime	32	>32	1 to >32	30.8	3.8	65.4	[c]	30.8	69.2
Colistin	0.5	4	0.12 to >8	[d]	88.5	11.5	88.5		11.5
Levofloxacin	4	>4	0.5 to >4	7.7	23.1	69.2	[c]	7.7	92.3
Meropenem	16	32	0.25 to >32	19.2	7.7	73.1	19.2 [e]	15.4	65.4
Piperacillin-tazobactam	64	>64	2 to >64	15.4	46.2	38.5	[c]	15.4	84.6

[a] Criteria as published by CLSI (2022) and EUCAST (2022).
[b] For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with another active therapy.
[c] An arbitrary susceptible breakpoint of ≤0.001 mg/L and/or >50 mm has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination; instead, susceptible should be interpreted as susceptible-increased exposure.
[d] The colistin susceptible criteria was removed and isolates with MIC values ≤2 mg/L are classified as intermediate according to CLSI (2022).
[e] Using non-meningitis breakpoints.

against 94.4% of ESBL, non-CRE phenotype *E. coli*, whereas 82.5% were susceptible to piperacillin-tazobactam and 100.0% susceptible to meropenem. Among ESBL, non-CRE phenotype *K. pneumoniae*, 93.1% were susceptible to ceftolozane-tazobactam, 51.7% were susceptible to piperacillin-tazobactam, and 100.0% were susceptible to meropenem. With the 74 MDR Enterobacterales isolates, ceftolozane-tazobactam susceptibility was 78.4% (Tables 1 and 3) while susceptibility to meropenem was 95.9% and piperacillin-tazobactam was 50.0%. Only three (0.2%) CRE and five (0.3%) XDR isolates were identified (data not shown).

3.3. Conclusions

In this study, we examined the susceptibility of a collection of Gram-negative isolates from patients hospitalised in Australia and New Zealand during 2016 to 2018 to ceftolozane-tazobactam. This study updates the previous publication on ceftolozane-tazobactam activity against isolates collected from most of the same institutions during 2013 to 2015 [13]. Six of eight Australian sites and both New Zealand sites participated in at least five of the six years of the two studies. The activity of ceftolozane-tazobactam against the isolates in the earlier study was very similar to that observed in this study. For *P. aeruginosa*, ceftolozane-tazobactam was the most active ß-lactam tested in both periods. From 2013 to 2015, 95.7% of *P. aeruginosa* had MIC values ≤4 mg/L while from 2016 to 2018, 97.5% of *P. aeruginosa* were inhibited at the same values. The susceptibility of meropenem-nonsusceptible *P. aeruginosa* to ceftolozane-tazobactam increased slightly, with 79.5% of 44 isolates susceptible from 2016 to 2018, compared with 71.0% of 31 isolates from 2013 to 2015. Isolates resistant to ceftazidime or piperacillin-tazobactam followed a similar trend with slightly higher susceptibility to ceftolozane-tazobactam than in the previous study, with 73.8% vs. 70.8% for ceftazidime and 81.4% vs. 76.3% for piperacillin-tazobactam, respectively.

Ceftolozane-tazobactam also maintained activity against Enterobacterales: 97.7% exhibited ceftolozane-tazobactam MIC values ≤2 mg/L from 2013 to 2015 and 96.5% had MIC values at ≤2 mg/L from 2016 to 2018. Carbapenem-resistant Enterobacterales remained uncommon, with one isolate in the first analysis and three in the current time period. The largest difference between

Table 2
Antimicrobial activity of ceftolozane-tazobactam and comparator agents tested against Enterobacterales and resistant phenotypes (2016–2018)

Organism/Antimicrobial agent	mg/L MIC_{50}	MIC_{90}	MIC range	CLSI[a] %S	%I	%R	EUCAST[a] %S	%S-IE	%R
Enterobacterales (n=1693)									
Ceftolozane-tazobactam	0.25	0.5	0.03 to >32	96.5	0.8	2.7	96.5		3.5
Amikacin	2	4	≤0.25 to 32	99.9	0.1	0.0	99.1 [b]		0.9
Ceftazidime	0.25	8	≤0.015 to >32	88.4	2.1	9.5	85.6	2.8	11.6
Colistin	0.12	>8	≤0.06 to >8		85.5 [c]	14.5	85.5		14.5
Levofloxacin	0.06	1	≤0.03 to >4	89.5	1.8	8.8	89.5	1.7	8.8
Meropenem	0.03	0.06	≤0.015 to 4	99.7	0.1	0.2	99.8 [d]	0.2	0.0
Piperacillin-tazobactam	2	8	≤0.5 to >64	93.4	3.0	3.5	91.1		8.9
ESBL non-CRE (n=176)									
Ceftolozane-tazobactam	0.5	2	0.12 to >32	94.3	1.1	4.5	94.3		5.7
Amikacin	4	8	0.5 to 32	99.4	0.6	0.0	94.3 [b]		5.7
Ceftazidime	16	>32	0.25 to >32	30.7	18.2	51.1	9.1	21.6	69.3
Colistin	0.12	0.25	≤0.06 to >8		97.7 [c]	2.3	97.7		2.3
Levofloxacin	1	>4	≤0.03 to >4	44.9	7.4	47.7	44.9	7.4	47.7
Meropenem	0.03	0.06	≤0.015 to 0.5	100.0	0.0	0.0	100.0[d]	0.0	0.0
Piperacillin-tazobactam	4	32	0.12 to >128	83.5	9.7	6.8	77.8		22.2
MDR (n=74)									
Ceftolozane-tazobactam	0.5	>32	0.12 to >32	78.4	4.1	17.6	78.4		21.6
Amikacin	4	16	0.5 to 32	97.3	2.7	0.0	85.1 [b]		14.9
Ceftazidime	32	>32	0.06 to >32	16.2	14.9	68.9	6.8	9.5	83.8
Colistin	0.12	0.25	≤0.06 to >8		91.9[c]	8.1	91.9		8.1
Levofloxacin	>4	>4	0.06 to >4	18.9	10.8	70.3	18.9	10.8	70.3
Meropenem	0.03	0.5	≤0.015 to 4	93.2	2.7	4.1	95.9 [d]	4.1	0.0
Piperacillin-tazobactam	8	>64	0.25 to >64	54.1	27.0	18.9	50.0		50.0
E. coli (n=868)									
Ceftolozane-tazobactam	0.12	0.25	0.06 to >32	99.1	0.1	0.8	99.1		0.9
Amikacin	2	4	0.5 to 32	99.8	0.2	0.0	98.7 [b]		1.3
Ceftazidime	0.25	8	0.03 to >32	88.7	3.2	8.1	85.0	3.7	11.3
Colistin	0.12	0.25	≤0.06 to 4		99.8 [c]	0.2	99.8		0.2
Levofloxacin	≤0.03	>4	≤0.03 to >4	85.4	0.9	13.7	85.4	0.9	13.7
Meropenem	≤0.015	0.03	≤0.015 to 0.5	100.0	0.0	0.0	100.0 [d]		0.0
Piperacillin-tazobactam	2	4	≤0.5 to >128	96.1	1.8	2.1	94.6		5.4
ESBL, non-CRE (n=143)									
Ceftolozane-tazobactam	0.25	1	0.12 to >32	94.4	0.7	4.9	94.4		5.6
Amikacin	4	8	1 to 32	99.3	0.7	0.0	95.1 [b]		4.9
Ceftazidime	8	>32	0.25 to >32	31.5	19.6	49.0	9.1	22.4	68.5
Colistin	0.12	0.25	≤0.06 to 1		100.0 [c]	0.0	100.0		0.0
Levofloxacin	2	>4	≤0.03 to >4	46.2	3.5	50.3	46.2	3.5	50.3
Meropenem	0.03	0.06	≤0.015 to 0.5	100.0	0.0	0.0	100.0 [d]		0.0
Piperacillin-tazobactam	4	32	0.12 to >128	87.4	7.0	5.6	82.5		17.5
K. pneumoniae (n=275)									
Ceftolozane-tazobactam	0.25	1	0.03 to >32	98.5	0.4	1.1	98.5		1.5
Amikacin	1	2	≤0.25 to 16	100.0	0.0	0.0	99.3 [b]		0.7
Ceftazidime	0.25	2	≤0.015 to >32	92.0	1.1	6.9	89.8	2.2	8.0
Colistin	0.12	0.25	≤0.06 to 8		99.3 [c]	0.7	99.3		0.7
Levofloxacin	0.06	0.5	≤0.03 to >16	90.5	4.4	5.1	90.5	4.4	5.1
Meropenem	0.03	0.03	≤0.015 to 4	99.3	0.0	0.7	99.3 [d]	0.7	0.0
Piperacillin-tazobactam	2	8	≤0.5 to >64	95.3	2.9	1.8	91.3		8.7
ESBL, non-CRE (n=29)									
Ceftolozane-tazobactam	0.5	2	0.12 to >32	93.1	3.4	3.4	93.1		6.9
Amikacin	2	8	0.5 to 8	100.0	0.0	0.0	100.0 [b]		0.0
Ceftazidime	16	>32	0.25 to >32	31.0	10.3	58.6	10.3	20.7	69.0
Colistin	0.12	0.25	≤0.06 to 0.25		100.0 [c]	0.0	100.0		0.0
Levofloxacin	1	16	0.06 to >16	44.8	24.1	31.0	44.8	24.1	31.0
Meropenem	0.03	0.06	≤0.015 to 0.06	100.0	0.0	0.0	100.0 [d]		0.0
Piperacillin-tazobactam	8	128	2 to >128	62.1	24.1	13.8	51.7		48.3

ESBL, non-CRE, extended-spectrum β-lactamase not carbapenem resistant; I, intermediate; MDR, multi-drug resistant; MIC_{50}, minimal inhibitory concentration to inhibit growth of 50% of isolates; MIC_{90}, minimal inhibitory concentration to inhibit growth of 90% of isolates; R, resistant; S, susceptible; S-IE, susceptible-increased exposure.

[a] Criteria as published by CLSI (2022) and EUCAST (2022).

[b] For infections originating from the urinary tract. For systemic infections, aminoglycosides must be used in combination with another active therapy.

[c] The colistin susceptible criteria was removed and isolates with MIC values ≤ mg/L are classified as intermediate according to CLSI (2022).

[d] Using non-meningitis breakpoints. Organisms include: *Citrobacter amalonaticus* (1), *Citrobacter amalonaticus/farmeri* (4), *Citrobacter freundii* (2), *Citrobacter freundii species complex* (22), *Citrobacter koseri* (29), *Enterobacter asburiae* (1), *Enterobacter cancerogenus* (1), *Enterobacter cloacae* (56), *Enterobacter cloacae species complex* (84), *Escherichia coli* (868), *Hafnia alvei* (3), *Klebsiella aerogenes* (45), *Klebsiella oxytoca* (62), *Klebsiella pneumoniae* (275), *Klebsiella variicola* (11), *Morganella morganii* (37), *Pantoea agglomerans* (2), *Pantoea anthophila* (1), *Proteus mirabilis* (83), *Proteus penneri* (1), *Proteus vulgaris* (2), *Proteus vulgaris* group (7), *Providencia rettgeri* (3), *Providencia stuartii* (2), *Raoultella ornithinolytica* (2), *Salmonella enterica subsp. enterica serovar typhimurium* (1), *Serratia liquefaciens* (1), *Serratia marcescens* (81), unspeciated *Pantoea* (2), unspeciated *Providencia* (1), and *Yersinia enterocolitica* (3).

Table 3
Antimicrobial activity of ceftolozane-tazobactam tested against the main organisms and organism groups (Australia/New Zealand, 2016–2018)

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of:											
	≤0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]	MIC_{50}	MIC_{90}
Enterobacterales (1,693)	31	623	623	266	62	**28**	13	20	15	3	8	0.25	0.5
	1.9%	38.7%	75.5%	91.2%	94.9%	**96.5%**	97.3%	98.5%	99.4%	99.5%	100%		
MDR (74)	0	4	18	17	8	**11**	3	4	0	1	8	0.5	>32
	0.0%	5.4%	29.7%	52.7%	63.5%	**78.4%**	82.4%	87.8%	87.8%	89.2%	100%		
ESBL phenotype (178)	0	23	64	49	17	**13**	2	4	1	1	4	0.5	2
	0.0%	12.9%	48.9%	76.4%	86.0%	**93.3%**	94.4%	96.6%	97.2%	97.8%	100%		
Escherichia coli (868)	28	465	296	56	10	**5**	1	4	1	1	1	0.12	0.25
	3.2%	56.8%	90.9%	97.4%	98.5%	**99.1%**	99.2%	99.7%	99.8%	99.9%	100.0%		
ESBL (143)	0	22	56	42	10	**5**	1	4	1	1	1	0.25	1
	0.0%	15.4%	54.5%	83.9%	90.9%	**94.4%**	95.1%	97.9%	98.6%	99.3%	100.0%		
Klebsiella pneumoniae (275)	2	66	133	45	18	**6**	1	0	0	0	3	0.25	1
	1.1%	25.1%	73.5%	89.8%	96.4%	**98.5%**	98.9%	98.9%	98.9%	98.9%	100.0%		
ESBL (29)	0	1	8	6	6	**6**	1	0	0	0	1	0.5	2
	0.0%	3.4%	31.0%	51.7%	72.4%	**93.1%**	96.6%	96.6%	96.6%	96.6%	100.0%		
Enterobacter cloacae complex (141)	1	28	58	18	3	**7**	5	12	6	0	3	0.25	8
	0.7%	20.6%	61.7%	74.5%	76.6%	**81.6%**	85.1%	93.6%	97.9%	97.9%	100.0%		
Citrobacter spp. (58)	0	20	17	10	0	**0**	0	2	7	2		0.25	16
	0.0%	34.5%	63.8%	81.0%	81.0%	**81.0%**	81.0%	84.5%	96.6%	100.0%			
Pseudomonas aeruginosa (435)	1	4	40	282	76	18	**3**	6	2	0	3	0.5	1
	0.2%	1.1%	10.3%	75.2%	92.6%	96.8%	**97.5%**	98.9%	99.3%	99.3%	100.0%		
MDR (43)		0	1	3	15	11	**3**	5	2	0	3	2	16
		0.0%	2.3%	9.3%	44.2%	69.8%	**76.7%**	88.4%	93.0%	93.0%	100.0%		
XDR (26)		0	1	0	7	6	**3**	4	2	0	3	2	>32
		0.0%	3.8%	3.8%	30.8%	53.8%	**65.4%**	80.8%	88.5%	88.5%	100%		
Meropenem-NS (44)		0	1	11	15	5	**3**	4	2	0	3	1	16
		0.0%	2.3%	27.3%	61.4%	72.7%	**79.5%**	88.6%	93.2%	93.2%	100.0%		
Piperacillin-tazobactam-R (59)		0	2	9	20	14	**3**	6	2	0	3	1	8
		0.0%	3.4%	18.6%	52.5%	76.3%	**81.4%**	91.5%	94.9%	94.9%	100.0%		
Ceftazidime- R (42)			0	2	13	13	**3**	6	2	0	3	2	16
			0.0%	4.8%	35.7%	66.7%	**73.8%**	88.1%	92.9%	92.9%	100.0%		

[a] Greater than the highest concentration tested.EUCAST percent susceptible is indicated by the bold column (EUCAST v12.0, 2022).

the two studies was the increase of ESBL, non-CRE phenotype isolates in Australia and New Zealand; 176 (10.4%) were observed from 2016 to 2018 while only 67 (6.6%) were observed from 2013 to 2015. The increasing proportion of ESBL, non-CRE phenotype isolates was mostly due to *E. coli*, with 9.5% of *E. coli* previously classified as ESBL, non-CRE phenotype, and 16.5% currently classified as such. Despite the increase, ceftolozane-tazobactam remained active. Using the current EUCAST breakpoint of ≤2 mg/L, 97.0% of ESBL phenotype isolates from 2013 to 2015 and 94.3% from 2016 to 2018 were susceptible to ceftolozane-tazobactam.

Ceftolozane-tazobactam was first supplied in Australia in 2017, and at the time of writing it is not yet commercially available in New Zealand. Neither country has a centralised surveillance program that includes novel antimicrobials. The ESBL rate for *E. coli* reported here (16.5%) is somewhat higher than the third-generation cephalosporin resistance of 8 to 10% recently reported in the AURA 2021 report [14].

The main limitation of this study and the previous PACTS study is that the ESBL enzymes were not genetically characterised; therefore, we cannot determine which ESBL genotypes are most common or if there were changes over time in the prevalence of ESBLs circulating in Australia and New Zealand. As multilocus sequence typing was not performed, clonal spread cannot be determined. The small number of contributing laboratories, six in Australia and two in New Zealand, do not allow conclusions to be drawn regarding the overall prevalence of ESBL or CRE phenotypes in these countries. As most of the contributing medical centres participated throughout the duration of PACTS from 2013 until 2018, these data do suggest that an increase in the number of ESBL-producing *E. coli* occurred without a corresponding increase in CRE, similar to what was reported in AURA 2021 [14].

In conclusion, these *in vitro* data indicate that ceftolozane-tazobactam is a potent antimicrobial with activity against meropenem-nonsusceptible and XDR *P. aeruginosa*, as well as ESBL, non-CRE phenotype and MDR Enterobacterales. These data support consideration of ceftolozane-tazobactam for the treatment of infections caused by Gram-negative pathogens in Australia and New Zealand.

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Competing interests

W-T. C. and M.T. are employees of Merck & Co., Inc.

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Ethical approval

Not required

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