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Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2014-2016) Gram-Negative Organisms Collected from Latin American Medical Centres

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Revised Abstract

Background: Ceftolozane-tazobactam (C-T) was approved by the US FDA (2014) and EMA (2015) to treat complicated urinary tract infections, acute pyelonephritis, and complicated intra-abdominal infections. The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) is a global surveillance program that monitors resistance to C-T in gram-negative isolates.

Methods: Gram-negative bacilli (GNB), including 1,957 *Enterobacteriaceae* (ENT) and 498 *Pseudomonas aeruginosa* (PSA), were collected during 2014-2016 from 17 Latin American hospitals in 11 countries (including 4 sites in Brazil) and tested against C-T, amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), levofloxacin (LVX), meropenem (MER), and piperacillin-tazobactam (TZP) using CLSI broth microdilution methodology. Data were stratified by country and various resistant subsets. EUCAST (2017) interpretive criteria were used.

Results: C-T inhibited 84.8% of ENT at the susceptibility (S) breakpoint of ≤1 mg/L ($MIC_{50/90}$, 0.25/8 mg/L). Susceptibility to other drugs ranged from 59.8% (LVX) to 94.8% (MER; Table). C-T S varied somewhat by country, being lowest in Brazil and Colombia (78.7%) and highest in Guatemala (98.3%). An extended-spectrum β-lactamase (ESBL) non-CRE phenotype was found in 27.6% of the ENT isolates, and of these, 76.5% were S to C-T ($MIC_{50/90}$, 0.5/16 mg/L). CRE isolates comprised 5.0% of the ENT set, and S rates were ≤1.0% for all β-lactams tested, 52.6% for AMK, and 57.7% for COL. For multidrug-resistant (MDR) isolates (32.3% of ENT), AMK (79.0%S), COL (77.7%S), and MER (84.0%S) were the most active, 58.4% were S to C-T ($MIC_{50/90}$, 1/>32 mg/L) and all remaining comparators were ≤40.9%S. C-T was active against 91.2% of the PSA at ≤4 mg/L ($MIC_{50/90}$, 0.5/4 mg/L), while S to other antimicrobials ranged from 64.7% (LVX) to 99.0% (COL; Table). Susceptibility to C-T varied somewhat by country, from a low of 68.2% (Peru) to a maximum of 100.0% (Costa Rica, Ecuador, Guatemala); S for Brazil was 95.2%. Against MDR PSA (29.5%), COL (97.3%S) and C-T (70.1%S; $MIC_{50/90}$, 2/>32 mg/L) were the most active antimicrobials. In contrast, 55.1% were S to AMK and all remaining drugs were ≤42.2%S. Susceptibility to C-T for MER-nonsusceptible (NS), extensively drug-resistant (XDR), and CAZ-NS PSA was similar to the MDR subset at 71.5%, 56.0%, and 60.2%, respectively.

Conclusions: C-T demonstrated potent activity against a large collection of contemporary GNB isolates from Latin America, and this activity was similar among the participating countries for ENT and PSA. AMK and MER were more active than C-T against ESBL (non-CRE) and all ENT tested. For PSA (including MDR), C-T was more active than all comparators except COL.

		% susceptible [EUCAST (2017)]							
Organism/subset	N	C-T	CAZ	FEP	MER	TZP	AMK	COL	LVX
ENT	1,957	84.8	62.9	64.8	94.8	77.9	92.8	81.6	59.8
ESBL non-CRE	541	76.5	7.0	6.9	99.1	57.8	90.0	94.4	22.8
MDR	632	58.4	11.2	10.3	84.0	40.9	79.0	77.7	15.8
PSA	498	91.2	79.3	81.3	73.9	79.1	84.7	99.0	64.7
MDR	147	70.1	42.2	40.8	23.1	40.8	55.1	97.3	14.3
XDR	84	56.0	17.9	13.1	10.7	17.9	40.5	98.8	0.0
CAZ-NS	103	60.2	0.0	28.2	33.0	21.4	58.3	99.0	27.2
MER-NS	130	71.5	46.9	43.8	0.0	44.6	61.5	99.2	20.8

Introduction

- Ceftolozane-tazobactam (C-T) is an antimicrobial combination the United States Food and Drug Administration (US FDA; 2014) and European Medicines Agency (EMA; 2015) approved to treat complicated urinary tract infections, acute pyelonephritis, and complicated intra-abdominal infections[1,2]
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) is a global surveillance program that monitors resistance to C-T in gram-negative isolates
- Here we report on the antimicrobial activity of C-T and comparators against gram-negative clinical isolates collected from Latin American medical centres during 2014 through 2016

Materials and Methods

- A total of 2,831 gram-negative bacilli (GNB), including 1,957 *Enterobacteriaceae* (ENT) and 498 *Pseudomonas aeruginosa* (PSA), were collected in 2014 through 2016 from 17 Latin American hospitals located in 11 countries (including 4 sites in Brazil) and tested for antimicrobial susceptibility to ceftolozane-tazobactam (C-T) using CLSI broth microdilution methodology[3,4] in a central monitoring laboratory (JMI Laboratories)
  - For C-T MIC testing, tazobactam was used at a fixed concentration of 4 mg/L
- Other antibiotics tested included amikacin (AMK), cefepime (FEP), ceftazidime (CAZ), colistin (COL), levofloxacin (LVX), meropenem (MER), and piperacillin-tazobactam (TZP)
- Phenotypic classes analyzed:
  - Carbapenem-resistant ENT (CRE)
    - Resistant to doripenem, imipenem, and/or meropenem
  - Extended-spectrum β-lactamase (ESBL) non-CRE *Enterobacteriaceae*
    - ESBL criteria from CLSI M100-S27[4] were used for classification, except that carbapenemase-resistant isolates (which might otherwise be classified as ESBL) were excluded from these analyses
  - Ceftazidime-nonsusceptible (CAZ-NS) PSA: MIC >8 mg/L
  - Meropenem-nonsusceptible (MER-NS) PSA: MIC >2 mg/L
  - Multidrug-resistant (MDR) ENT and PSA
    - Nonsusceptible (NS; EUCAST breakpoints) to at least 3 antimicrobial classes[5]
  - Extensively drug-resistant (XDR) PSA
    - Susceptible (S) to 2 or fewer antimicrobial classes[5]
- EUCAST (2017) clinical breakpoints for C-T[6]
  - *Enterobacteriaceae* susceptible (S) / resistant (R) breakpoints were ≤1 / >1 mg/L
  - *P. aeruginosa* S / R breakpoints were ≤4 / >4 mg/L
- CLSI (2017) clinical breakpoints for C-T[4]
  - *Enterobacteriaceae* S / R breakpoints were ≤2 / ≥8 mg/L
  - *P. aeruginosa* S / R breakpoints were ≤4 / ≥16 mg/L

Results

- The number of ENT and PSA isolates from each country, as well as the relative percentages of each analyzed phenotypic subclass of isolates, are shown in Table 1
  - The fraction of each subclass varied by country (eg, CRE ranged from 0% in Costa Rica, Guatemala, Panama, and Peru to 11.2% in Brazil)
- The MIC distributions for C-T against ENT and the 4 most commonly isolated GNB species are shown in Table 2
- The antimicrobial activity of C-T and comparators for major ENT species and *P. aeruginosa* is summarized in Tables 3 and 4, respectively
- The C-T %S values for ENT and PSA isolates from each Latin American country that participated in the study are shown in Figure 1
- ***Enterobacteriaceae***: C-T inhibited 84.8% of all ENT at the susceptible breakpoint of ≤1 mg/L ($MIC_{50/90}$, 0.25/8 mg/L); only AMK (92.8%S) and MER (94.8%S) were slightly more active than C-T (Table 3)
  - C-T %S varied somewhat by country, being lowest in Brazil and Colombia (78.7%) and highest in Guatemala (98.3%) (Figure 1)
  - Against the 3 most prevalent ENT species, C-T activity was greatest against *E. coli* ($MIC_{50/90}$, 0.25/0.5 mg/L; 96.4%S) and somewhat lower against *K. pneumoniae* ($MIC_{50/90}$, 0.5/>32 mg/L; 69.7%S) and *Enterobacter cloacae* species complex ($MIC_{50/90}$, 0.25/16 mg/L; 76.7%S; Table 3)
  - A total of 541 ENT isolates had an ESBL non-CRE phenotype (C-T $MIC_{50/90}$, 0.5/16 mg/L; 76.5%S) and was 90.0%S to AMK, 6.9%S to FEP, 7.0%S to CAZ, 94.4%S to COL, 22.8%S to LVX, 99.1%S to MER, and 57.8%S to TZP
  - For 632 (32.3%) MDR isolates, AMK (79.0%S), COL (77.7%S), and MER (84.0%S) were the most active, while 58.4% were S to C-T, and the remaining comparators were ≤40.9%S
  - A total of 97 (5.0%) isolates were CRE, and ≤1.0% were S to any β-lactam tested, 52.6% were S to AMK, and 57.7% were S to COL
- ***P. aeruginosa***: C-T inhibited 91.2% of the PSA isolates at the EUCAST S breakpoint of ≤4 mg/L ($MIC_{50/90}$, 0.5/4 mg/L) and was the most active antimicrobial tested against these organisms, except for COL (99.0%S) (Table 4)
  - Although the results for countries with small numbers of tested isolates must be interpreted with caution, the susceptibility to C-T varied somewhat by nation, from a low of 68.2% (Peru) to a maximum of 100.0% (Costa Rica, Ecuador, Guatemala); S for Brazil was 95.2% (Figure 1)
  - A total of 147 PSA were MDR (29.5%). The most active drugs against MDR PSA were COL (97.3%S) and C-T (70.1%S); 55.1% were S to AMK, and the remaining drugs were ≤42.2%S
  - Susceptibility to C-T for MER-NS, CAZ-NS, and extensively drug-resistant (XDR) PSA was similar to or slightly lower than the MDR subset at 71.5%, 60.2%, and 56.0%, respectively
  - Forty of 498 *P. aeruginosa* (8.0%) isolates were resistant to MER (MIC range, 8–32 mg/L) but susceptible to CAZ (MIC range, 2–8 mg/L; data not shown). This unusual resistance phenotype was observed in 8 nations, including Brazil [number of isolates (n) = 17; 11.6%], Argentina (n = 6; 6.3%), Mexico (n = 5; 6.4%), Venezuela (n = 5; 10.4%), and Peru (n = 3; 13.6%). C-T (MIC_{50}, 1 mg/L) was 4-fold more potent than CAZ (MIC_{50}, 4 mg/L) against such isolates, with only 2 *P. aeruginosa* isolates, which were collected from Argentina and Venezuela, resistant to C-T

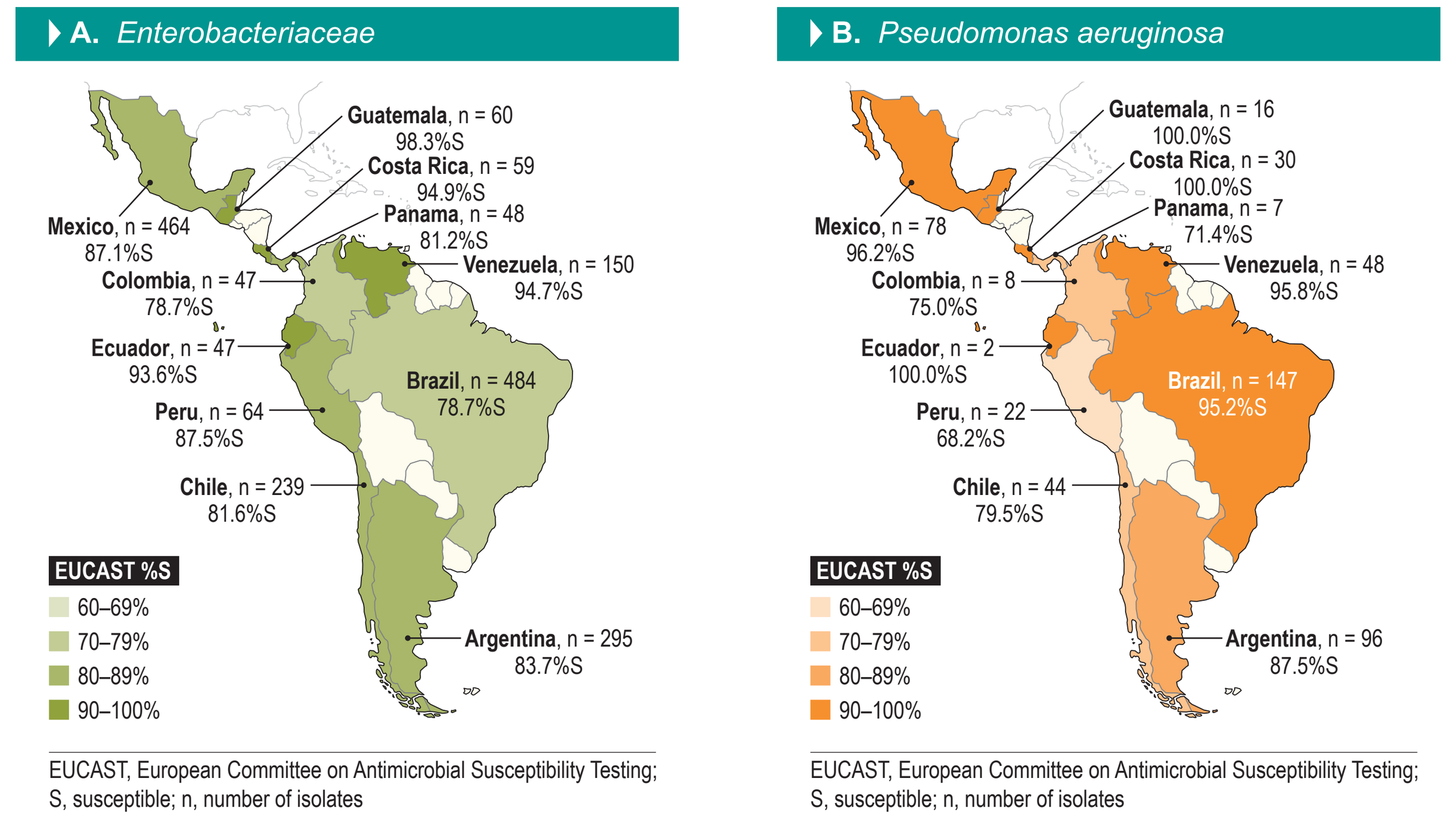
Table 1 Frequencies of tested *Enterobacteriaceae* and *P. aeruginosa* phenotypic classes from Latin America

	Enterobacteriaceae				*P. aeruginosa*				
Country	No.	%ESBL non-CRE	%CRE	%MDR	No.	%MER-NS	%CAZ-NS	%MDR	%XDR
Argentina	295	19.0%	5.1%	30.8%	96	30.2%	31.3%	35.4%	27.1%
Brazil	484	16.5%	11.2%	29.5%	147	25.2%	15.6%	32.0%	12.9%
Chile	239	28.5%	0.8%	29.3%	44	36.4%	43.2%	43.2%	31.8%
Colombia	47	19.1%	4.3%	21.3%	8	50.0%	37.5%	50.0%	50.0%
Costa Rica	59	25.4%	0.0%	15.3%	30	16.7%	6.7%	10.0%	10.0%
Ecuador	47	25.5%	2.1%	27.7%	2	0.0%	0.0%	0.0%	0.0%
Guatemala	60	26.7%	0.0%	23.3%	16	6.3%	0.0%	6.3%	0.0%
Mexico	464	40.5%	4.3%	39.7%	78	17.9%	11.5%	19.2%	5.1%
Panama	48	39.6%	0.0%	52.1%	7	28.6%	28.6%	28.6%	28.6%
Peru	64	60.9%	0.0%	48.4%	22	40.9%	45.5%	50.0%	40.9%
Venezuela	150	26.0%	2.0%	28.0%	48	27.1%	10.4%	22.9%	6.3%
All	**1,957**	**27.6%**	**5.0%**	**32.3%**	**498**	**26.1%**	**20.7%**	**29.5%**	**16.9%**

Table 2 Antimicrobial activity of ceftolozane-tazobactam tested against the main organisms and organism groups of isolates (mg/L)

Organism / organism group	No. of isolates at MIC in mg/L (cumulative %)												MIC_{50}	MIC_{90}
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>		
Enterobacteriaceae (1,957)	0 (0.0)	36 (1.8)	526 (28.7)	599 (59.3)	353 (77.4)	146 (84.8)	57 (87.7)	39 (89.7)	29 (91.2)	22 (92.3)	30 (93.9)	120 (100.0)	0.25	8
ESBL non-CRE (541)	0 (0.0)	1 (0.2)	22 (4.3)	137 (29.6)	164 (59.9)	90 (76.5)	40 (83.9)	18 (87.2)	12 (89.5)	9 (91.1)	10 (93.0)	38 (100.0)	0.5	16
MDR (632)	0 (0.0)	1 (0.2)	17 (2.8)	110 (20.3)	151 (44.1)	90 (58.4)	44 (65.3)	31 (70.3)	21 (73.6)	18 (76.4)	30 (81.2)	119 (100.0)	1	>32
CRE (97)							0 (0.0)	1 (1.0)	2 (3.1)	7 (10.3)	16 (26.8)	71 (100.0)	>32	>32
Escherichia coli (777)	0 (0.0)	24 (3.1)	317 (43.9)	250 (76.1)	117 (91.1)	41 (96.4)	14 (98.2)	2 (98.5)	2 (98.7)	5 (99.4)	1 (99.5)	4 (100.0)	0.25	0.5
ESBL non-CRE (273)		0 (0.0)	16 (5.9)	85 (37.0)	104 (75.1)	41 (90.1)	14 (95.2)	2 (96.0)	2 (96.7)	5 (98.5)	1 (98.9)	3 (100.0)	0.5	1
MDR (191)		0 (0.0)	13 (6.8)	53 (34.6)	71 (71.7)	30 (87.4)	12 (93.7)	2 (94.8)	0 (94.8)	5 (97.4)	1 (97.9)	4 (100.0)	0.5	2
Klebsiella pneumoniae (587)	0 (0.0)	10 (1.7)	110 (20.4)	161 (47.9)	74 (60.5)	54 (69.7)	22 (73.4)	11 (75.3)	12 (77.3)	10 (79.0)	23 (83.0)	100 (100.0)	0.5	>32
ESBL non-CRE (234)	0 (0.0)	1 (0.4)	5 (2.6)	40 (19.7)	54 (42.7)	45 (62.0)	21 (70.9)	11 (75.6)	10 (79.9)	3 (81.2)	9 (85.0)	35 (100.0)	1	>32
MDR (288)	0 (0.0)	1 (0.3)	3 (1.4)	31 (12.2)	46 (28.1)	35 (40.3)	18 (46.5)	10 (50.0)	12 (54.2)	9 (57.3)	23 (65.3)	100 (100.0)	4	>32
Enterobacter cloacae species complex (202)		0 (0.0)	40 (19.8)	67 (53.0)	35 (70.3)	13 (76.7)	8 (80.7)	9 (85.1)	8 (89.1)	6 (92.1)	5 (94.6)	11 (100.0)	0.25	16
Non-CRE (198)		0 (0.0)	40 (20.2)	67 (54.0)	35 (71.7)	13 (78.3)	8 (82.3)	9 (86.9)	8 (90.9)	6 (93.9)	3 (95.5)	9 (100.0)	0.25	8
MDR (58)			0 (0.0)	2 (3.4)	13 (25.9)	9 (41.4)	6 (51.7)	6 (62.1)	4 (69.0)	3 (74.1)	5 (82.8)	10 (100.0)	2	>32
Pseudomonas aeruginosa (498)	0 (0.0)	2 (0.4)	6 (1.6)	64 (14.5)	260 (66.7)	79 (82.5)	27 (88.0)	16 (91.2)	8 (92.8)	7 (94.2)	4 (95.0)	25 (100.0)	0.5	4
Meropenem-nonsusceptible (130)	0 (0.0)	1 (0.8)	0 (0.8)	5 (4.6)	34 (30.8)	28 (52.3)	12 (61.5)	13 (71.5)	5 (75.4)	7 (80.8)	3 (83.1)	22 (100.0)	1	>32
Ceftazidime-nonsusceptible (103)				0 (0.0)	5 (4.9)	26 (30.1)	20 (49.5)	11 (60.2)	7 (67.0)	6 (72.8)	3 (75.7)	25 (100.0)	4	>32
MDR (147)			0 (0.0)	3 (2.0)	27 (20.4)	38 (46.3)	19 (59.2)	16 (70.1)	8 (75.5)	7 (80.3)	4 (83.0)	25 (100.0)	2	>32
XDR (84)				0 (0.0)	2 (2.4)	21 (27.4)	13 (42.9)	11 (56.0)	5 (61.9)	7 (70.2)	2 (72.6)	23 (100.0)	4	>32

Figure 1 Activity of ceftolozane-tazobactam versus ENT and PSA in each participating Latin American nation



The figure displays the number of isolates and percent susceptibility values for ceftolozane-tazobactam [%S; EUCAST (2017)] for each of the 11 Latin American countries participating in the study.

Table 3 Activity of ceftolozane-tazobactam and comparator antimicrobial agents when tested against *Enterobacteriaceae* from Latin America

Group / antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
Enterobacteriaceae (n = 1,957)						
Ceftolozane-tazobactam	0.25	8	87.7	10.3	84.8	15.2
Amikacin	2	8	96.2	2.4	92.8	3.8
Cefepime	≤0.5	>16	66.2	29.9 [b]	64.8	32.0
Ceftazidime	0.25	>16	67.4	29.2	62.9	32.6
Colistin	≤0.5	>8			81.6	18.4
Levofloxacin	0.25	>4	66.1	31.4	59.8	36.1
Meropenem	0.03	0.12	94.2	5.2	94.8	4.2
Piperacillin-tazobactam	2	>64	83.0	10.9	77.9	17.0
ESBL non-CRE *Enterobacteriaceae* (n = 541)						
Ceftolozane-tazobactam	0.5	16	83.9	12.8	76.5	23.5
Amikacin	4	8	97.4	1.3	90.0	2.6
Cefepime	>16	>16	10.2	80.5 [b]	6.9	85.9
Ceftazidime	16	>16	18.5	70.8	7.0	81.5
Colistin	≤0.5	≤0.5			94.4	5.6
Levofloxacin	>4	>4	31.5	64.6	22.8	71.3
Meropenem	0.03	0.06	97.2	0.9	99.1	0.0
Piperacillin-tazobactam	8	>64	70.9	15.7	57.8	29.1
MDR *Enterobacteriaceae* (n = 632)						
Ceftolozane-tazobactam	1	>32	65.3	29.7	58.4	41.6
Amikacin	4	32	88.8	7.1	79.0	11.2
Cefepime	>16	>16	13.0	78.2 [b]	10.3	83.0
Ceftazidime	>16	>16	19.3	73.9	11.2	80.7
Colistin	≤0.5	>8			77.7	22.3
Levofloxacin	>4	>4	28.2	68.4	15.8	76.9
Meropenem	0.03	32	82.1	16.0	84.0	13.1
Piperacillin-tazobactam	16	>64	54.8	30.7	40.9	45.2
CRE *Enterobacteriaceae* (n = 97)						
Ceftolozane-tazobactam	>32	>32	0.0	99.0	0.0	100.0
Amikacin	8	>32	59.8	28.9	52.6	40.2
Cefepime	>16	>16	0.0	100.0 [b]	0.0	100.0
Ceftazidime	>16	>16	0.0	100.0	0.0	100.0
Colistin	≤0.5	>8			57.7	42.3
Levofloxacin	>4	>4	9.3	86.6	3.1	92.8
Meropenem	>32	>32	0.0	99.0	1.0	85.6
Piperacillin-tazobactam	>64	>64	0.0	99.0	0.0	100.0
Escherichia coli (n = 777)						
Ceftolozane-tazobactam	0.25	0.5	98.2	1.5	96.4	3.6
Amikacin	2	8	99.1	0.6	96.3	0.9
Cefepime	≤0.5	>16	68.2	28.4 [b]	66.9	30.0
Ceftazidime	0.25	>16	71.2	24.6	66.9	28.8
Colistin	≤0.5	≤0.5			99.0	1.0
Levofloxacin	0.5	>4	54.3	42.9	51.6	46.3
Meropenem	≤0.015	0.03	99.9	0.1	99.9	0.1
Piperacillin-tazobactam	2	16	92.8	2.8	87.3	7.2
ESBL non-CRE *E. coli* (n = 273)						
Ceftolozane-tazobactam	0.5	1	95.2	4.0	90.1	9.9
Amikacin	4	8	98.5	1.5	92.3	1.5
Cefepime	>16	>16	10.7	80.5 [b]	7.4	85.3
Ceftazidime	16	>16	18.3	69.6	6.2	81.7
Colistin	≤0.5	≤0.5			98.9	1.1
Levofloxacin	>4	>4	20.1	76.9	17.6	80.6
Meropenem	≤0.015	0.03	100.0	0.0	100.0	0.0
Piperacillin-tazobactam	8	32	85.7	5.1	72.5	14.3
MDR *E. coli* (n = 191)						
Ceftolozane-tazobactam	0.5	2	93.7	5.2	87.4	12.6
Amikacin	4	16	96.9	2.1	86.4	3.1
Cefepime	>16	>16	12.1	81.1 [b]	8.4	84.2
Ceftazidime	16	>16	17.8	73.3	11.0	82.2
Colistin	≤0.5	≤0.5			97.4	2.6
Levofloxacin	>4	>4	6.8	91.6	2.1	94.2
Meropenem	≤0.015	0.06	99.5	0.5	99.5	0.5
Piperacillin-tazobactam	8	64	77.0	9.4	56.5	23.0
Klebsiella pneumoniae (n = 587)						
Ceftolozane-tazobactam	0.5	>32	73.4	24.7	69.7	30.3
Amikacin	2	16	92.0	5.3	88.2	8.0
Cefepime	8	>16	48.3	48.5 [b]	47.3	50.9
Ceftazidime	8	>16	49.9	46.3	46.2	50.1
Colistin	≤0.5	1			91.4	8.6
Levofloxacin	0.5	>4	60.2	36.9	52.0	42.0
Meropenem	0.03	32	82.5	15.7	84.3	12.9
Piperacillin-tazobactam	8	>64	64.8	26.6	58.2	35.2
ESBL non-CRE *K. pneumoniae* (n = 234)						
Ceftolozane-tazobactam	1	>32	70.9	24.4	62.0	38.0
Amikacin	2	16	96.2	1.3	89.7	3.8
Cefepime	>16	>16	7.7	84.1 [b]	5.2	90.1
Ceftazidime	>16	>16	12.0	78.6	2.6	88.0
Colistin	≤0.5	1			96.1	3.9
Levofloxacin	>4	>4	42.1	53.2	27.0	62.7
Meropenem	0.03	1	93.6	2.1	97.9	0.0
Piperacillin-tazobactam	16	>64	53.2	27.9	38.6	46.8
MDR *K. pneumoniae* (n = 288)						
Ceftolozane-tazobactam	4	>32	46.5	50.0	40.3	59.7
Amikacin	4	>32	84.4	10.4	77.1	15.6
Cefepime	>16	>16	1.7	92.0 [b]	1.0	96.5
Ceftazidime	>16	>16	7.3	86.8	2.4	92.7
Colistin	≤0.5	>8			83.2	16.8
Levofloxacin	>4	>4	26.0	69.4	14.6	77.4
Meropenem	0.06	>32	64.2	31.9	68.1	26.4
Piperacillin-tazobactam	>64	>64	33.8	51.2	22.3	66.2
Enterobacter cloacae species complex (n = 202)						
Ceftolozane-tazobactam	0.25	16	80.7	14.9	76.7	23.3
Amikacin	1	4	96.0	2.5	93.6	4.0
Cefepime	≤0.5	>16	72.6	21.4 [b]	69.2	23.9
Ceftazidime	0.5	>16	64.9	32.7	57.9	35.1
Colistin	≤0.5	>8			79.3	20.7
Levofloxacin	≤0.12	>4	84.7	13.4	78.2	18.8
Meropenem	0.03	0.12	97.5	2.0	98.0	1.5
Piperacillin-tazobactam	2	>64	79.2	10.4	73.8	20.8

[a] Criteria as published by CLSI[4] and EUCAST[6]
[b] Intermediate interpreted as susceptible-dose dependent

Table 4 Activity of ceftolozane-tazobactam and comparator antimicrobial agents when tested against *Pseudomonas aeruginosa* from Latin America

Group / antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %R
P. aeruginosa (n = 498)						
Ceftolozane-tazobactam	0.5	4	91.2	7.2	91.2	8.8
Amikacin	4	32	87.8	8.6	84.7	12.2
Cefepime	2	>16	81.3	10.8	81.3	18.7
Ceftazidime	2	>16	79.3	15.1	79.3	20.7
Colistin	1	2	99.0	1.0	99.0	1.0
Levofloxacin	0.5	>4	73.1	21.7	64.7	35.3
Meropenem	0.5	16	73.9	19.5	73.9	13.3
Piperacillin-tazobactam	4	64	79.1	9.2	79.1	20.9
Meropenem-nonsusceptible *P. aeruginosa* (n = 130)						
Ceftolozane-tazobactam	1	>32	71.5	24.6	71.5	28.5
Amikacin	8	>32	67.7	23.8	61.5	32.3
Cefepime	16	>16	43.8	34.6	43.8	56.2
Ceftazidime	16	>16	46.9	38.5	46.9	53.1
Colistin	1	2	99.2	0.8	99.2	0.8
Levofloxacin	>4	>4	34.6	54.6	20.8	79.2
Meropenem	16	>32	0.0	74.6	0.0	50.8
Piperacillin-tazobactam	32	>64	44.6	23.1	44.6	55.4
Ceftazidime-nonsusceptible *P. aeruginosa* (n = 103)						
Ceftolozane-tazobactam	4	>32	60.2	33.0	60.2	39.8
Amikacin	8	>32	64.1	26.2	58.3	35.9
Cefepime	16	>16	28.2	46.6	28.2	71.8
Ceftazidime	>16	>16	0.0	72.8	0.0	100.0
Colistin	1	2	99.0	1.0	99.0	1.0
Levofloxacin	>4	>4	35.0	57.3	27.2	72.8
Meropenem	8	>32	33.0	55.3	33.0	40.8
Piperacillin-tazobactam	64	>64	21.4	40.8	21.4	78.6
MDR *P. aeruginosa* (n = 147)						
Ceftolozane-tazobactam	2	>32	70.1	24.5	70.1	29.9
Amikacin	8	>32	63.3	26.5	55.1	36.7
Cefepime	16	>16	40.8	36.7	40.8	59.2
Ceftazidime	16	>16	42.2	43.5	42.2	57.8
Colistin	1	2	97.3	2.7	97.3	2.7
Levofloxacin	>4	>4	29.9	59.9	14.3	85.7
Meropenem	8	>32	23.1	62.6	23.1	44.9
Piperacillin-tazobactam	32	>64	40.8	27.9	40.8	59.2
XDR *P. aeruginosa* (n = 84)						
Ceftolozane-tazobactam	4	>32	56.0	38.1	56.0	44.0
Amikacin	32	>32	48.8	36.9	40.5	51.2
Cefepime	>16	>16	13.1	57.1	13.1	86.9
Ceftazidime	>16	>16	17.9	61.9	17.9	82.1
Colistin	1	2	98.8	1.2	98.8	1.2
Levofloxacin	>4	>4	11.9	78.6	0.0	100.0
Meropenem	16	>32	10.7	77.4	10.7	59.5
Piperacillin-tazobactam	64	>64	17.9	36.9	17.9	82.1

[a] Criteria as published by CLSI[4] and EUCAST[6]

Conclusions

- C-T demonstrated potent activity against a large collection of contemporary gram-negative isolates from Latin America (PACTS 2014-2016)
- Against *Enterobacteriaceae*, C-T exhibited $MIC_{50/90}$ values of 0.25/8 mg/L (84.8%S). Of the tested antimicrobials, only AMK and MER were more active than C-T
  - Among carbapenem-susceptible ENT isolates with an ESBL phenotype (ESBL non-CRE), 76.5% were susceptible to C-T
- For *P. aeruginosa* (including MDR, XDR, CAZ-NS, and MER-NS) isolates, C-T was the most active β-lactam tested
  - Among the non-β-lactams tested, only COL was more active than C-T
- C-T appears to represent a valuable treatment option for gram-negative infections, including those caused by various resistant organism groups

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