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Antimicrobial Activity of Ceftolozane-Tazobactam Tested against Contemporary (2014-2016) *Pseudomonas aeruginosa* Isolates with Various Resistant Phenotypes from US Hospitals

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Introduction

- Ceftolozane-tazobactam (C-T) is a combination of a novel antipseudomonal cephalosporin and a well-described β-lactamase inhibitor
  - C-T retains activity against most *Pseudomonas aeruginosa* with derepressed AmpC or up-regulated efflux, including ceftazidime-, cefepime-, or meropenem-resistant strains
- C-T was approved by the United States (US) Food and Drug Administration in 2014 for complicated urinary tract infections, including acute pyelonephritis and complicated intra-abdominal infections (in combination with metronidazole) at a dose of 1.5 g (1 g C + 0.5 g T) q8h
- C-T is currently in a clinical trial for treatment of hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia (3 g [2 g C + 1 g T] q8h)
- The Program to Assess Ceftolozane-Tazobactam Susceptibility (PACTS) monitors C-T resistance to gram-negative (GN) isolates worldwide
- In this study, we tested recent *P. aeruginosa* isolates collected from US hospitalized patients in all 9 US census divisions
  - Activities of C-T and 7 other agents were compared

Materials and Methods

- A total of 2,656 *P. aeruginosa* (PSA) isolates were collected from patients in 30 US hospitals throughout the 9 US census divisions in 2014-2016 and were tested for susceptibility (S) to C-T by CLSI broth microdilution methodology at JMI Laboratories (North Liberty, Iowa, USA)
  - Only 1 isolate per patient per infection episode was collected
  - The most frequent infection type was pneumonia (56.0%) followed by skin and skin structure infections (18.5%) and bloodstream infections (12.8%)
- Other antibiotics tested included amikacin, cefepime (FEP), ceftazidime (CAZ), colistin (COL), meropenem (MER), levofloxacin, and piperacillin-tazobactam (TZP)
- Resistant phenotypes analyzed were: CAZ+FEP nonsusceptible (CAZ+FEP-NS), MER-NS, TZP-NS, CAZ+FEP+TZP+MER-NS (beta-lactam [BL]-NS), and COL-NS according to CLSI criteria
- Multidrug resistant (MDR) and extensively drug R (XDR) phenotypes were defined according to Magiorakos et al (2012)
- CLSI (2017) and EUCAST (2017) interpretive criteria were used
- The US divisions were: 1) New England, 2) Middle Atlantic, 3) East North Central, 4) West North Central, 5) South Atlantic, 6) East South Central, 7) West South Central, 8) Mountain, and 9) Pacific

Results

- For all PSA isolates, 97.7% were S to C-T (Table 1)
  - C-T was more active than other comparators, except COL (99.4%S)
- The C-T MIC distributions and $MIC_{50/90}$ of all isolates tested against the resistant phenotypes are shown in Table 2
  - A total of 16 (0.6%) isolates were COL-NS (Table 2) and 93.8% were S to C-T
  - 165 (6.2%) isolates were BL-NS of which 72.1% were S to C-T
  - 248 (9.3%) were XDR isolates (79.8%S to C-T)
  - 546 (20.6%) were MDR isolates (89.2%S to C-T)
- The %S to C-T for various resistance phenotypes for each division are shown in Figure 1
- The %S for C-T by division ranged from 99.7% (West North Central) to 93.0% (Pacific) for all PSA
  - The West North Central division and East South Central had the highest %S to C-T for all resistant phenotypes, including isolates resistant to other 4 beta-lactam agents tested (CAZ, FEP, MER, and TZP) where 90.9% and 95.0% were S to C-T
  - The Pacific division had the lowest %S to C-T for the resistant phenotypes

Conclusions

- Against PSA, C-T demonstrated potent activity versus isolates with various resistant phenotypes, including BL-NS, COL-NS, MDR, and XDR isolates
- Divisions varied for C-T %S
- C-T was the most active beta-lactam tested and had activity second only to COL among all antimicrobials tested
- These results demonstrate that C-T is an important treatment for PSA infections in the US

Acknowledgements

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References

Clinical and Laboratory Standards Institute (2017). *M100-S27. Performance standards for antimicrobial susceptibility testing: 27th informational supplement.* Wayne, PA: CLSI.

EUCAST (2017). Breakpoint tables for interpretation of MICs and zone diameters. Version 7.0, January 2017. Available at http://www.eucast.org/clinical_breakpoints/. Accessed January 2017.

Magiorakos, A. P., A. Srinivasan, R. B. Carey, Y. Carmeli, M. E. Falagas, C. G. Giske, S. Harbarth, J. F. Hindler, G. Kahlmeter, B. Olsson-Liljequist, D. L. Paterson, L. B. Rice, J. Stelling, M. J. Struelens, A. Vatopoulos, J. T. Weber, and D. L. Monnet. "Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance." (2012) *Clin Microbiol Infect* **18**(3): 268-281.

Table 1 Activity of ceftolozane-tazobactam and comparator antimicrobial agents when tested against 2,656 PSA isolates

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI			EUCAST		
			%S	%I	%R	%S	%I	%R
Ceftolozane-tazobactam	0.5	2	97.7	1	1.3	97.7		2.3
Amikacin	4	8	96.5	1.2	2.2	92.2	4.3	3.5
Cefepime	2	16	87.4	8.6	4	87.4		12.6
Ceftazidime	2	32	85.4	4.5	10.1	85.4		14.6
Colistin	1	2	99.4		0.6	99.4		0.6
Levofloxacin	0.5	>4	76.3	7	16.7	67.1		32.9
Meropenem	0.5	8	81	5.7	13.3	81	12.1	6.9
Piperacillin-tazobactam	4	64	81.9	9.8	8.3	81.9		18.1

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

Organism / organism group (no. of isolates)	No. of isolates at MIC (µg/mL; cumulative %)													MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>		
PSA (2,656)	0 0.0	1 <0.1	4 0.2	24 1.1	393 15.9	1446 70.3	502 89.2	144 94.7	81 97.7	27 98.7	6 98.9	5 99.1	23 100.0	0.5	2
TZP-NS PSA (480)				0 0.0	3 0.6	72 15.6	162 49.4	108 71.9	80 88.5	24 93.5	5 94.6	3 95.2	23 100.0	2	8
CAZ- or FEP-NS PSA (474)				0 0.0	2 0.4	43 9.5	165 44.3	122 70.0	81 87.1	27 92.8	6 94.1	5 95.1	23 100.0	2	8
CAZ+FEP-NS (248)					0 0	3 1.2	46 19.8	67 46.8	75 77.0	26 87.5	6 89.9	3 91.1	22 100.0	4	32
MER-NS PSA (504)				0 0.0	10 2.0	138 29.4	173 63.7	77 79.0	51 89.1	22 93.5	6 94.6	5 95.6	22 100.0	1	8
COL-NS PSA (16)					0 0.0	9 56.2	4 81.2	2 93.8	0 93.8	0 93.8	1 100.0			0.5	2
MDR PSA (546)				0 0.0	12 2.2	118 23.8	201 60.6	100 78.9	56 89.2	25 93.8	6 94.9	5 95.8	23 100.0	1	8
XDR PSA (248)				0 0.0	1 0.4	9 4.0	90 40.3	54 62.1	44 79.8	19 87.5	6 89.9	3 91.1	22 100.0	2	32
BL-NS PSA (165)					0 0.0	2 1.2	32 20.6	40 44.8	45 72.1	19 83.6	5 86.7	1 87.3	21 100.0	4	>32

Susceptible breakpoint for C-T (CLSI) is ≤4 µg/mL.

Figure 1 Percent susceptibility of C-T against various resistant phenotypes (NS to TZP, MER, CAZ+FEP, and BLs) by US division