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Activity of Ceftolozane/Tazobactam against Gram-Negative Isolates from Lower Respiratory Tract Infections – SMART United States 2018

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Introduction

Ceftolozane / tazobactam (C/T) is an anti-pseudomonal cephalosporin combined with a β-lactamase inhibitor. C/T has been approved by the United States Food & Drug Administration (FDA) and the European Medicines Agency (EMA) for complicated urinary tract infections, complicated intraabdominal infections, and hospital-acquired and ventilator - associated bacterial pneumonia. Using isolates collected in the United States as part of the global Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program, we evaluated the activity of C/T and comparators against gram-negative pathogens collected from patients with lower respiratory tract infections (LRTI).

Methods

In 2018, 24 hospitals in the United States each collected up to 100 consecutive aerobic or facultatively anaerobic gram-negative bacilli from LRTI, for a total of 1792 isolates. MICs were determined using CLSI broth microdilution and interpreted with CLSI breakpoints [1, 2]. C/T-nonsusceptible (NS) Enterobacterales and *Pseudomonas aeruginosa* isolates were screened by PCR and sequencing for genes encoding β-lactamases [3].

Figure 1. Species distribution (n, %) among collected gram-negative isolates (n=1792) from patients with LRTI

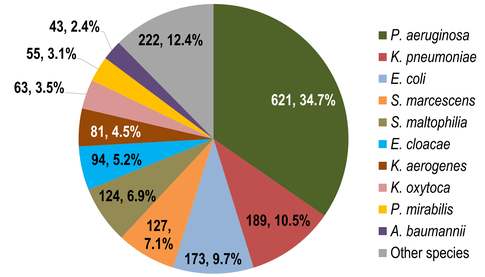
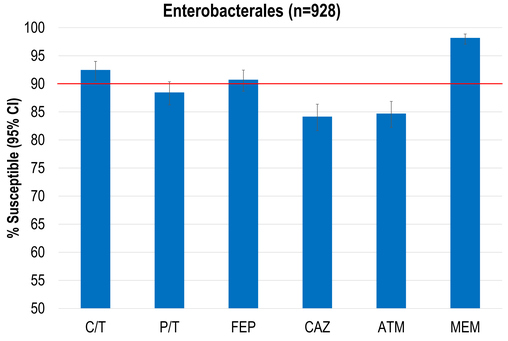


Figure 2. Susceptibility to C/T and β-lactam comparators of all Enterobacterales combined



C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; MEM, meropenem; CI, confidence interval.

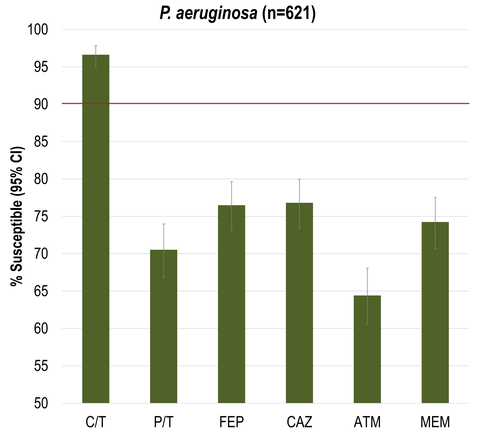
Table 1. Susceptibility to C/T and β-lactam comparators of the most common Enterobacterales species

Species	n	% Susceptible					
		C/T	P/T	FEP	CAZ	ATM	MEM
K. pneumoniae	189	89.9	82.5	78.8	75.7	77.8	95.2
E. coli	173	98.3	92.5	89.0	85.6	85.0	100
S. marcescens	127	96.1	93.7	96.9	95.3	92.9	96.1
E. cloacae	94	85.1	86.2	90.4	76.6	77.7	98.9

C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; MEM, meropenem

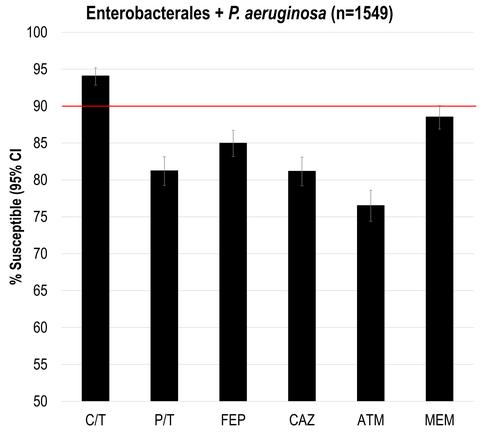
Results

Figure 3. Susceptibility to C/T and β-lactam comparators of *P. aeruginosa*



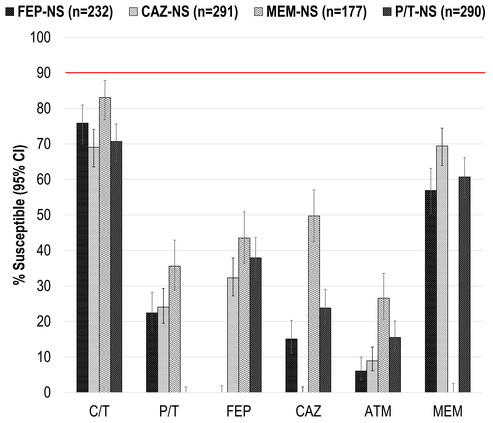
C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; MEM, meropenem; CI, confidence interval

Figure 4. Susceptibility to C/T and β-lactam comparators of Enterobacterales and *P. aeruginosa* combined



C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; MEM, meropenem; CI, confidence interval

Figure 5. Susceptibility to C/T and β-lactam comparators of nonsusceptible phenotypes of Enterobacterales and *P. aeruginosa* combined



C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; MEM, meropenem; CI, confidence interval

Table 2. Acquired β-lactamases detected in molecularly characterized C/T-nonsusceptible Enterobacterales and *P. aeruginosa* isolates[a, b]

Genotype	n (%)	
	Enterobacterales (n=67)	*P. aeruginosa* (n=21)
KPC ± ESBL ± AmpC	13 (19.4%)	
IMP		1 (4.8%)
AmpC ± ESBL	1 (1.5%)	
ESBL only	11 (16.4%)	
None detected	42 (62.7%)[c]	20 (95.2%)[d]

[a]Original spectrum β-lactamases (e.g., TEM-1, SHV-1) and intrinsic AmpC β-lactamases common to *P. aeruginosa* and some Enterobacterales species such as Enterobacter are not included in this analysis.
[b]Three C/T-NS Enterobacterales isolates were not molecularly characterized.
[c]Among the 42 Enterobacterales isolates in which no acquired β-lactamases were detected, 39 (92.9%) were species with intrinsic AmpC.
[d]Other resistance mechanisms such as AmpC subtypes with mutations in the Ω-loop or in amino acids that interact with it, or undetected β-lactamases may be involved [4].
ESBL, extended-spectrum β-lactamase.

Results Summary

- Among all gram-negative pathogens collected from patients with LRTI, the 3 most common species were *P. aeruginosa*, *K. pneumoniae*, and *E. coli* (Figure 1). Enterobacterales and *P. aeruginosa* combined comprised 86% of all collected gram-negative isolates from LRTI.
- C/T was active against 92.5% of all Enterobacterales isolates combined. Among the comparator β-lactams, only meropenem showed higher activity (Figure 2).
- C/T was active against 85-98% of the 4 most common Enterobacterales species (Table 1).
- Among *P. aeruginosa* isolates, susceptibility to C/T was 96.6%, 20-32 percentage points higher than to the tested comparator β-lactams (Figure 3).
- C/T was active against 94.1% of all Enterobacterales and *P. aeruginosa* combined, 6-18 percentage points higher than the other tested comparator agents (Figure 4).
- Among subsets of Enterobacterales and *P. aeruginosa* isolates that were nonsusceptible to commonly used β-lactams, including meropenem, C/T maintained activity against 69-83% of isolates (Figure 5).
- Among molecularly characterized C/T-NS Enterobacterales isolates, 19% carried KPC, 16% carried ESBL, and 58% were species with intrinsic AmpC in which no acquired β-lactamases were detected. Among 21 molecularly characterized C/T-NS *P. aeruginosa*, one isolate carried an IMP-type metallo-β-lactamase, and in the remaining isolates no acquired β-lactamases were detected (Table 2).

Conclusions

With its broad coverage of Enterobacterales and *P. aeruginosa*, C/T can provide an important empiric therapy option for patients with LRTI in the United States, including those with infections caused by meropenem-nonsusceptible isolates.

References:

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