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In Vitro Activity of Ceftolozane/Tazobactam against Enterobacterales and *Pseudomonas aeruginosa* Isolates from Geriatric Patients in the Asia/Pacific region – SMART 2016-2018

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Introduction

Ceftolozane/tazobactam (C/T) is an antipseudomonal cephalosporin combined with a β-lactamase inhibitor approved by the United States FDA and the European Medicines Agency (EMA) for complicated urinary tract and intraabdominal infections, and hospital-acquired and ventilator - associated bacterial pneumonia. We evaluated the activity of C/T against isolates collected from patients ≥65 years old as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program in the Asia/Pacific region.

Methods

In 2016-2018, 50 clinical laboratories in Australia, Hong Kong, Malaysia, New Zealand, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam each collected up to 250 consecutive aerobic or facultatively anaerobic gram-negative pathogens per year. Susceptibility was determined using CLSI broth microdilution and breakpoints (1, 2]. C/T-nonsusceptible (NS) Enterobacterales and *P. aeruginosa* isolates were screened by PCR and sequenced for genes encoding β-lactamases (except isolates from Vietnam 2017 and one Vietnam site in 2018, Enterobacterales from one site in Taiwan in 2018, and a small number of other isolates that were not available for molecular characterization) [3].

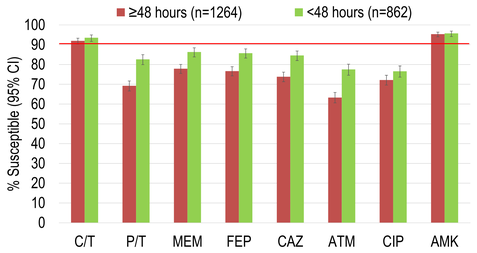
A total of 2126 *P. aeruginosa* isolates (68.7% from patients with lower respiratory tract infections, 12.6% from intraabdominal infections, 15.1% from urinary tract infections, 3.0% from bloodstream infection, and 0.8% for which the source was not specified) and 8645 Enterobacterales isolates (29.9%, 27.6%, 32.4%, 9.5%, and 0.6%, respectively) from patients ≥65 years old were analyzed.

Table 1. Susceptibility of *P. aeruginosa*, Enterobacterales, and the 5 most common Enterobacterales species[a]

	% Susceptible							
Phenotype	C/T	P/T	MEM	FEP	CAZ	ATM	CIP	AMK
All *P. aeruginosa* (2126)	92.6	74.7	81.3	80.3	78.2	69.1	73.9	95.5
P/T-NS (539)	72.7	0.0	47.9	31.5	22.8	13.7	42.3	85.3
MEM-NS (398)	68.1	29.4	0.0	38.9	40.7	25.4	32.4	80.4
FEP-NS (418)	64.4	11.7	41.9	0.0	16.0	10.8	34.9	79.9
CAZ-NS (464)	67.2	10.3	49.1	24.4	0.0	13.8	41.6	82.8
All Enterobacterales (8645)	88.4	83.8	96.7	73.6	70.5	69.7	58.3	97.9
E. coli (3890)	94.9	90.5	99.1	69.0	71.0	67.1	49.5	99.3
K. pneumoniae (2579)	79.9	73.9	92.0	68.0	63.6	65.9	55.8	95.8
E. cloacae (381)	66.1	63.5	95.3	71.9	53.8	56.7	74.5	98.7
P. mirabilis (325)	98.8	99.1	99.7	91.1	96.9	96.6	69.5	96.3
S. marcescens (241)	93.0	91.7	97.5	90.5	90.5	90.5	77.6	97.5

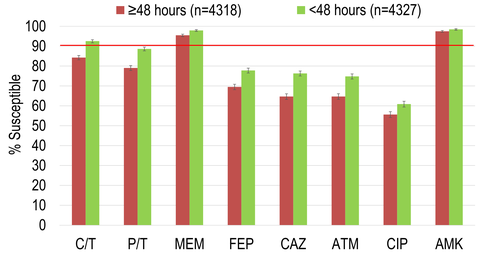
[a]Results for colistin are not shown because Enterobacterales are no longer considered susceptible to colistin per 2020 CLSI guidelines.
C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin.

Figure 1. Susceptibility of *P. aeruginosa* isolates stratified by length of hospital stay at the time of specimen collection[a]



[a]Results for colistin are not shown because P. aeruginosa isolates are no longer considered susceptible to colistin per 2020 CLSI guidelines.
C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin

Figure 2. Susceptibility of Enterobacterales isolates stratified by length of hospital stay at the time of specimen collection[a]



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Results

Figure 3. Species distribution among collected Enterobacterales isolates stratified by length of hospital stay at time of specimen collection

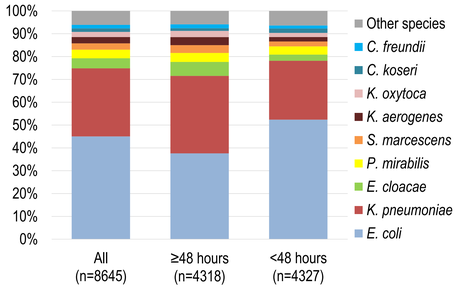
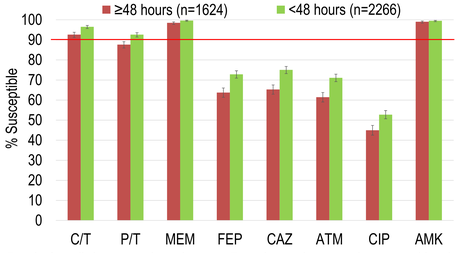
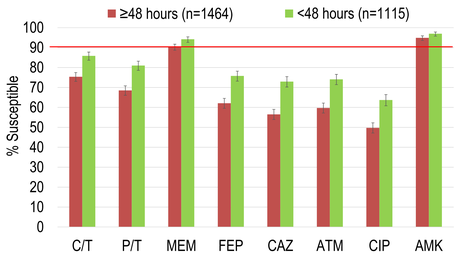


Figure 4. Susceptibility of *E. coli* isolates stratified by length of hospital stay at the time of specimen collection[a]



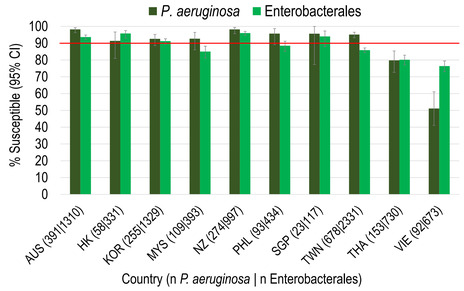
[a]Results for colistin are not shown because Enterobacterales are no longer considered susceptible to colistin per 2020 CLSI guidelines.
C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin

Figure 5. Susceptibility of *K. pneumoniae* stratified by length of hospital stay at the time of specimen collection[a]



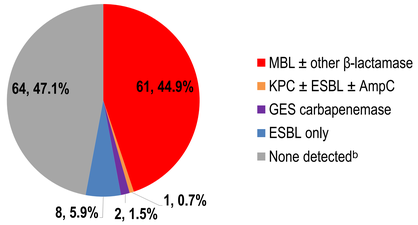
[a]Results for colistin are not shown because Enterobacterales are no longer considered susceptible to colistin per 2020 CLSI guidelines.
C/T, ceftolozane/tazobactam; P/T, piperacillin/tazobactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin

Figure 6. Susceptibility to C/T of *P. aeruginosa* and Enterobacterales isolates stratified by country



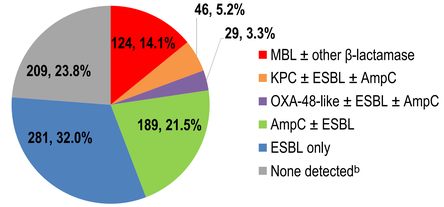
AUS, Australia; HK, Hong Kong; KOR, South Korea; MYS, Malaysia; NZ, New Zealand; PHL, Philippines; SGP, Singapore; TWN, Taiwan; THA, Thailand; VIE, Vietnam.

Figure 7. Acquired β-lactamases detected in 136 molecularly characterized C/T-nonsusceptible *P. aeruginosa* isolates (n, %)[a]



[a]Intrinsic AmpC β-lactamases common to *P. aeruginosa* are not included in this analysis.
[b]Among isolates for which no acquired β-lactamases were detected, 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].

Figure 8. Acquired β-lactamases detected in 878 molecularly characterized C/T-nonsusceptible Enterobacterales isolates (n, %)[a]



[a]Original spectrum β-lactamases (e.g., TEM-1, SHV-1) and intrinsic AmpC β-lactamases common to some Enterobacterales species such as *Enterobacter* are not included in this analysis.
[b]Among the 209 Enterobacterales isolates with no detected acquired β-lactamases, 187 (89.5%) were species with intrinsic AmpC.

Results Summary

- C/T was active against 92.6% of *P. aeruginosa* isolates, 11-24 percentage points higher than the tested comparator β-lactams and against 88.4% of Enterobacterales, 5-19 percentage points higher than the comparator β-lactams except meropenem (Table 1).
- C/T maintained activity against 64-73% of *P. aeruginosa* isolates that were NS to commonly used β-lactams (Table 1).
- Susceptibility of *P. aeruginosa* to all studied agents was lower for isolates collected ≥48h than <48h post-admission but the difference was small for C/T and amikacin. C/T was active against >91% of *P. aeruginosa* in both strata, 7-29 percentage points higher than all comparators except amikacin (Figure 1).
- C/T maintained activity against 84% of all Enterobacterales collected ≥48h post-admission, 4-32 percentage points higher than the comparators except meropenem and amikacin (Figure 2).
- Lower susceptibility of Enterobacterales collected ≥48h post-admission can be explained in part by a larger proportion of *K. pneumoniae* and smaller proportion of *E. coli* (Figure 3). However, *E. coli* and *K. pneumoniae* also showed lower susceptibility in the ≥48h stratum (Figures 4 and 5).
- C/T was active against >91% of *P. aeruginosa* and ≥85% of Enterobacterales isolates in all countries except Thailand and Vietnam (Figure 6), where the prevalence of carbapenemase-positive isolates, particularly those carrying metallo-β-lactamases, is high [5]. C/T is not active against carbapenemase-producers.
- Among molecularly characterized C/T-NS *P. aeruginosa* and Enterobacterales isolates, 47% and 23%, respectively, carried carbapenemases (Figures 7 and 8).

Conclusions

Among isolates collected from patients ≥65 years old in the Asia/Pacific region, susceptibility of *P. aeruginosa* and Enterobacterales to C/T was >91% and >84%, respectively, even among isolate collected ≥48 hours post-admission, which showed higher resistance than those collected <48h. C/T is a potential new treatment option for older patients with infections caused by *P. aeruginosa* and Enterobacterales in Asia/Pacific.

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