Original Article

In vitro potency of antipseudomonal β-lactams against blood and respiratory isolates of *P. aeruginosa* collected from US hospitals

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Background: Challenges due to multidrug resistant (MDR) Gram-negative bacterial pathogens such as *P. aeruginosa* (PSA) are increasing globally. Suboptimal antimicrobial therapy of infections caused by PSA is associated with increased morbidity and mortality. As a result, antimicrobial susceptibility (%S) studies are pivotal to identifying trends in antimicrobial resistance that inform decisions regarding choice of antimicrobial therapy. This study assessed the *in vitro* potency of 7 antipseudomonal agents including ceftolozane/tazobactam (C/T) against PSA collected from numerous sites across the US.

Methods: Multiple US hospitals provided non-duplicate respiratory and blood isolates of PSA for potency testing. MICs against PSA were determined using broth microdilution methods according to CLSI for 7 antimicrobials with antipseudomonal activity: aztreonam (ATM), cefepime (FEP), ceftazidime (CAZ), C/T, imipenem (IPM), meropenem (MEM) and piperacillin/tazobactam (TZP). %S was defined per CLSI or FDA breakpoint criteria.

Results: Thirty-five hospitals geographically spread across the US provided a total of 1,209 PSA isolates. Of the antibiotics assessed, %S to C/T was the highest at 95% with an MIC_{50} of 0.5 mg/L and MIC_{90} of 2 mg/L. In comparison, other %S (MIC_{50}/MIC_{90}) was as follows: ATM 66% (8/32); FEP 76% (4/32); CAZ 78% (4/64); IPM 68% (2/16); MEM 74% (0.5/16); and TZP 73% (8/128).

Conclusions: For this geographically diverse PSA population, C/T demonstrated the highest overall susceptibility (95%). Other antipseudomonal agents inclusive of the carbapenems displayed susceptibilities of 66–78%. In the era of escalating PSA resistance to the β-lactams, the potency of C/T may represent an important clinical option.

Keywords: Antipseudomonal; β-lactams; empiric therapy; *Pseudomonas aeruginosa*; resistance

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Introduction

Pseudomonas aeruginosa is an opportunistic pathogen associated with a variety of infections ranging from simple folliculitis to sever septic shocks depending on the host immune status and severity of any underlying conditions present. As a result of its ability to adapt to variable environmental conditions as well as develop biofilms, *P. aeruginosa* is capable of avoiding innate immune clearance mechanisms and thus has enhanced pathogenicity (1). Moreover, *P. aeruginosa* flourish under selective antimicrobial pressure, are intrinsically resistance to many classes of antimicrobials and are capable of acquiring additional resistance genes from other organisms. These characteristics combined with the

organisms' ability to develop resistance using a variety of mechanisms makes *P. aeruginosa* a formidable pathogen in the clinical arena (1,2).

The corner stone of *P. aeruginosa* therapy most often involves the administration of a β-lactam antimicrobial; however, escalating resistance within this class has eroded the treatment armamentarium. In December 2014, ceftolozane/tazobactam (C/T) a β-lactam/β-lactamase inhibitor combination with antipseudomonal activity including multi-drug resistant (MDR) isolates was approved by the FDA to treat complicated urinary tract infections (cUTI) and intra-abdominal infections (IAI) (3). Recently, a phase III multicenter clinical trail completed enrollment of 726 patients with ventilated nosocomial pneumonia to assess C/T efficacy and safety in comparison with meropenem (clinicaltrials.gov, NCT 02070757).

In the current era of rapidly evolving antimicrobial resistance, studies assessing the potency of available antimicrobials are fundamental to informing decisions regarding the most appropriate choice of therapy (4,5). As well as, focused effort on using the source of isolates (i.e., respiratory versus blood) as a guide to select proper empiric therapy is an increasing demand. Thus, we assessed the *in vitro* potency of 7 antipseudomonal agents including C/T against *P. aeruginosa* collected from numerous hospitals across the US.

Methods

Consecutive non-duplicate, non-urine, respiratory or blood isolates of *P. aeruginosa* were obtained from adult inpatients as part of their routine medical management. Isolates were collected from 35 different hospitals across the United States, in 2017 and 2018. Organisms were identified at each participating site using methods normally employed by their laboratories and were transferred onto trypticase soy agar slants for shipping.

Once received at the central processing laboratory (Center for Anti-Infective Research and Development, Hartford Hospital, Hartford, CT, USA) isolates were transferred onto trypticase soy agar plates containing 5% sheep blood for minimum inhibitory concentration (MIC) determination. The MIC determinations for the following agents: aztreonam (ATM), C/T, cefepime (FEP), ceftazidime (CAZ), imipenem (IPM), meropenem (MEM) and piperacillin/tazobactam (TZP) were undertaken using Clinical Laboratory Standards Institute (CLSI) broth microdilution methods (6).

Merck Pharmaceuticals provided C/T, all others antibiotics were purchased from Sigma (St. Louis, MO, USA). MIC trays were prepared using the Biomek 3000 (Beckman Instruments, Inc., Fullerton, CA, USA). As recommended by CLSI, *K. pneumoniae* 700603 and *P. aeruginosa* 27853 were utilized as quality control (QC) strains; all QC values were within CLSI acceptable ranges (6). Colony counts were performed on each isolate to verify the correct inoculum. The CLSI interpretative susceptibility criteria were utilized for each agent. *P. aeruginosa* were classified as carbapenem non-susceptible if isolates were non-susceptible to IPM or MEM with MIC >2 mg/L. Additionally, isolates were defined as multidrug resistant (MDR) if they displayed resistance to 3 or more classes as represented by the following phenotypic resistance profiles: CIP (MIC ≥4 mg/L), IPM (MIC ≥8 mg/L), CAZ (MIC ≥32 mg/L), TZP (MIC ≥128 mg/L), and TOB (MIC ≥16 mg/L) (6).

Results

A total of 1,209 *P. aeruginosa* isolates were collected and tested. Antipseudomonal potency of assessed agents is presented in *Table 1*. The MIC for which 50% and 90% of isolates were inhibited ($MIC_{50/90}$) by C/T was 0.5/2 mg/L, MEM 0.5/16 mg/L, and IPM 2/16 mg/L. The MIC distribution for all agents is displayed in *Figure 1*, among this population of *P. aeruginosa*; C/T exhibited the highest activity with 95% susceptibility, followed by CAZ (78%) and FEP (76%). All other antipseudomonal agents, consisting of representative examples across classes, demonstrated a range of 66–74% susceptibility (*Table 1*).

Based on location, around half (55.2%) of isolates tested were collected from patients outside the ICU. Similar %S were found in isolates collected inside and outside the ICU with C/T exhibiting the highest susceptibility in both settings. However, based on source of isolates tested, the majority of samples were from respiratory sources in both ICU and non-ICU setting. Isolates from blood samples were found more susceptible compared with isolates from respiratory samples. Additionally, isolates collected from blood samples outside ICU exhibited reduced susceptibilities compared with blood samples collected inside ICU (*Table 1*).

Overall, carbapenem non-susceptibility defined by IPM or MEM MIC of >2 mg/L was 35% (n=423) in the current *P. aeruginosa* population. Among carbapenem non-susceptible isolates, C/T showed the highest susceptibility

Table 1 Susceptibility of *P. aeruginosa* to antipseudomonal agents tested

Variables	N (%) of isolates	ATM		C/T		FEP		CAZ		IPM		MEM		TZP	
		$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S
Total isolates collected from patients	1,209 (100)	8/32	66	0.5/2	95	4/32	76	4/64	78	2/16	68	0.5/16	74	8/128	73
Isolates based on location															
ICU*	541 (44.7)	8/64	66	1/2	95	4/32	75	4/64	77	2/16	67	1/16	72	8/256	70
Respiratory	436 (36.1)	8/64	63	1/4	94	4/32	71	4/64	75	2/32	63	1/16	69	8/256	68
Blood	104 (8.6)	8/32	75	0.5/1	99	4/8	90	2/16	88	2/16	83	0.5/8	88	8/64	80
Non-ICU	668 (55.3)	8/32	66	0.5/2	96	4/32	78	2/32	79	2/16	68	0.5/16	75	8/128	76
Respiratory	474 (39.2)	8/64	64	1/4	95	4/32	73	4/64	74	2/16	67	0.5/16	73	8/256	72
Blood	194 (16.0)	8/32	72	0.5/2	98	2/16	89	2/8	90	1/16	71	0.5/8	81	8/32	87
Isolates based on source															
Blood	298 (24.6)	8/32	73	0.5/2	98	2/16	89	2/16	89	2/16	75	0.5/8	83	8/32	84
ICU	104 (8.6)	8/32	75	0.5/1	99	4/8	90	2/16	88	2/16	83	0.5/8	88	8/64	80
Non-ICU	194 (16.0)	8/32	72	0.5/2	98	2/16	89	2/8	90	1/16	71	0.5/8	81	8/32	87
Respiratory	910 (75.3)	8/64	64	1/4	95	4/32	72	4/64	74	2/16	65	1/16	71	8/256	70
ICU	436 (36.1)	8/64	63	1/4	94	4/32	71	4/64	75	2/32	63	1/16	69	8/256	68
Non-ICU	474 (39.2)	8/64	64	1/4	95	4/32	73	4/64	74	2/16	67	0.5/16	73	8/256	72

*, total number of isolates 1,208 (one patient in ICU was missing source of sample). ATM, aztreonam; C/T, ceftolozane/tazobactam; FEP, cefepime; CAZ, ceftazidime; IPM, imipenem; MEM, meropenem; TZP, piperacillin/tazobactam; MIC, minimum inhibitory concentration; %S, percent susceptibility; ICU, intensive care unit.

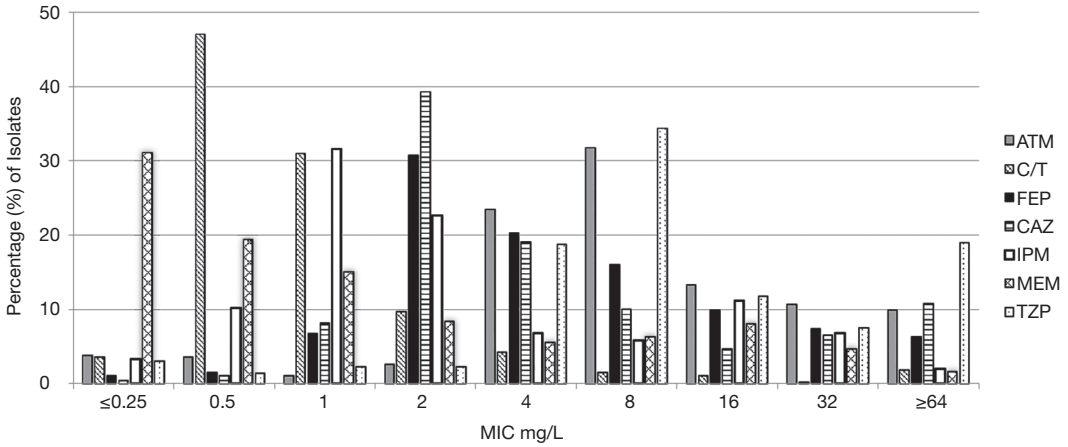

Figure 1 MIC distribution of aztreonam (ATM), ceftolozane/tazobactam (C/T), cefepime (FEP), ceftazidime (CAZ), imipenem (IPM), meropenem (MEM) and piperacillin/tazobactam (TZP) against *P. aeruginosa*.

exhibiting 89% followed by CAZ 60% and all other agents were below 54% susceptibility (*Table 2*). Among the assessed *P. aeruginosa* population, 322 isolates were TZP NS; C/T was found to have 85% susceptible with 17–39% for the remaining antipseudomonal agents tested (*Table 2*). Thirteen percent of isolates (n=153) were defined as MDR by reference broth microdilution methods. The degree of susceptibility among these MDR isolates for C/T was 74% whereas that of the other agents tested ranges from 5–12% (*Table 2*).

Susceptibilities varied by resistance status to 1 or more antipseudomonal versus isolates resistant to all antipseudomonal agents. *P. aeruginosa* resistant to 1 or more composed 54% and presented 92% susceptibility to C/T followed by 59% and 56% for CAZ and FEP, respectively. Similar to that observed in MDR subset, *P. aeruginosa* non-susceptible to all antipseudomonal retained 75% susceptibility to C/T. Isolates that demonstrated non-susceptibility to C/T (n=55) displayed low susceptibility rates ranging from 7–25% for the other antipseudomonal agents. Susceptibility and MIC distribution over the 9 U.S. census divisions were assessed. In all U.S. census divisions, susceptibility rates were ≥93% and ranging from 93–99% (*Table 3*).

Discussion

Based on MIC_{90} observed in this study, C/T was at least 3 folds more active than other antipseudomonal agents tested, while its overall susceptibility was 95% in this population of *P. aeruginosa*. These data are in line with a previous surveillance program done by our group in 2015 where 1,257 *P. aeruginosa* were tested and reported C/T MIC_{90} was 2 mg/L, and 97% susceptibility, followed by CAZ (77%) and MEM (76%) (7). Additionally, a surveillance study testing 3,815 *P. aeruginosa* isolates from 32 U.S. hospitals between 2012–2015 reported 97% C/T susceptibility and $MIC_{50/90}$ of 0.5/2 mg/L (8). Similarly, a recent surveillance study in 2017 with 1909 *P. aeruginosa* isolates collected from 70 U.S. medical centers and tested using broth micro-dilution found C/T the most active compound with 97.5% susceptibility rates (9). Moreover, a surveillance study conducted between 2007–2016 among *P. aeruginosa* collected from patients in ICU reported 97.5%S to C/T followed by 96.1%S to amikacin (10).

Quarter of *P. aeruginosa* population observed herein was from blood source, with higher susceptibilities in comparison to respiratory isolates. However, as 75% of isolates in this study were from respiratory samples and susceptibilities among these isolates are reduced in comparison with isolates from blood samples, studies similar to ASPECT-NP (clinicaltrials.gov, NCT 02070757) are needed to focus more efforts on considering source of isolates in selecting the most appropriate therapy.

Albeit the majority of isolates were collected outside ICU (55.2%), these organisms were more susceptible than those collected inside ICU. Our findings are in line with a previous study that reported 65% of *P. aeruginosa* were collected outside ICU with higher susceptibility observed in isolates collected outside ICU (11). These observations are of paramount importance in clinical settings, as understanding susceptibility of *P. aeruginosa* based on source

Table 2 Potency of antipseudomonal agents in the presence of various phenotypic resistance profiles.

Phenotype profile	% susceptibility							
	N [%]	ATM	C/T	FEP	CAZ	IPM	MEM	TZP
NS to ATM	410 [34]	–	88	44	49	46	45	35
NS to C/T	55 [5]	11	–	9	7	25	22	15
NS to CAZ	267 [22]	21	81	20	–	39	41	14
NS to FEP	287 [24]	20	83	–	25	38	35	19
NS to IPM	392 [32]	44	90	54	59	–	27	49
NS to MEM	316 [26]	28	86	41	50	10	–	36
NS to TZP	322 [27]	17	85	28	29	39	38	-
NS to carbapenems[a]	432 [36]	41	89	54	60	7	25	48
MDR	153 [13]	12	74	6	10	5	6	8
NS to 1 or more agent[b]	648 [54]	37	92	56	59	40	51	50
NS to all agents[c]	118 [10]	–	75	–	–	–	–	–

Aztreonam (ATM), ceftolozane/tazobactam (C/T), cefepime (FEP), ceftazidime (CAZ), imipenem (IPM), meropenem (MEM) and piperacillin/tazobactam (TZP) against *P. aeruginosa*. [a], carbapenem non-susceptibility defined as non-susceptible to IPM or MEM with MIC of >2 mg/L; [b], antipseudomonal agents tested in this study (ATM, C/T, FEP, CAZ, IPM, MEM, and TZP); [c], antipseudomonal agents tested in this study other than the compound of interest (ATM, FEP, CAZ, IPM, MEM, and TZP). MDR, multidrug resistant; MIC, minimum inhibitory concentration; NS, non-susceptible.

Table 3 Ceftolozane-tazobactam MIC distributions and susceptibility in U.S. census divisions

U.S. census regions[a]	No. of isolates at MIC (g/mL) of									Total No.	% susceptible
	0.125	0.25	0.5	1	2	4	8	16	≥32		
1. East North Central		4	57	40	11	5	1	1	3	122	96
2. East South Central			31	39	9	3	2	1		85	96
3. Middle Atlantic		5	49	21	2			1	2	80	96
4. Mountain		12	93	46	20	8	1	5	6	191	94
5. New England		2	43	31	13	4	4	1	1	99	94
6. Pacific	2	4	66	41	14	5	1	2	6	141	94
7. South Atlantic	1	4	116	76	24	15	5	1	2	244	97
8. West North Central		1	47	33	10	8	4		4	107	93
9. West South Central	1	6	71	43	15	3		1		140	99

[a], states in each U.S. Census Bureau division are: 1, Indiana, Illinois, and Ohio; 2, Kentucky, Mississippi, and Tennessee; 3, New York, and Pennsylvania; 4, Arizona, New Mexico, Utah, and Nevada; 5, Connecticut, Massachusetts, and Rhode Island; 6, California, and Washington; 7, Florida, Georgia, Maryland, North Carolina, South Carolina, and Virginia; 8, Iowa, Missouri, and Minnesota; 9, Oklahoma, and Texas. MIC, minimum inhibitory concentration.

and location of these isolates can guide providers to select the most appropriate empiric therapy in high-risk patients. Especially that *P. aeruginosa* was often thought of as an ICU pathogen; however, the prevalence of this pathogen is increasing outside the ICU (11).

While an overall basal assessment of potency is required for the total isolates collected, subset analysis looking at target phenotypic profiles where a novel compound of

interest may be used in clinical settings is of increased relevance. Since *P. aeruginosa* are commonly resistance to 1 or more of the conventional β-lactams this phenotypic profile appears as a reasonable target to assess the potency of new therapies. In a recent study of 309 *P. aeruginosa* was resistant to 1 or more antipseudomonal β-lactams, 72.5% of the isolates were C/T susceptible (12). In our current population, 648 (54%) of the isolates were non-susceptible to 1 or more and 118 (10%) were non-susceptible to all antipseudomonal antibiotics. Despite varying phenotypic profiles to individual β-lactams, C/T demonstrated 81–90% susceptibility, which diminished to 74% and 75% when considering the MDR and NS to all agents, respectively. Similar to our previous observation, this current *in vitro* assessment of *P. aeruginosa* reveals that resistant to 1 β-lactam does not translate to resistance to the entire class and thus the testing of novel therapies in the wake of resistance to conventional agents may often yield viable treatment options (13). In infections suspected to be caused by resistant *P.* aeruginosa, combination therapy is the most common strategy in clinical settings. Although synergistic interactions are not confirmed to be superior over monotherapy against *P.* aeruginosa in clinical studies, combination therapy increases the probability of providing appropriate initial therapy by having at least one active agent against the suspected pathogen especially in cases where susceptibilities are not known (5).

Some variations in susceptibility rates to C/T were observed between U.S. census divisions. However, the overall susceptibility rates to C/T were high, ranging from 93–99% (*Table 3*). These observations are in line with a previous study that reported C/T susceptibility rates ranging 94–99% (8). However, these observations suggest the growing need of regional resistance rates surveillance studies.

In an attempt to initiate early appropriate therapy in the at-risk patient, data derived in the current study highlights the need for routine susceptibility testing of C/T in institutions where >20% of the *P.* aeruginosa are non-susceptibility to conventional β-lactams, while reflective testing schemes may be suitable in institutions with lower resistance.

Conclusions

In this *P. aeruginosa* population, C/T demonstrated the highest overall susceptibility (95%), while, other antipseudomonal agents including carbapenems displayed susceptibilities ranging from 66–78%. In the era of escalating *P. aeruginosa* resistance to conventionally utilized β-lactams, the enhanced potency of newer novel therapies should be considered in an attempt optimize both clinical and microbiologic outcomes.

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Footnote

Conflicts of Interest: DP Nicolau has acted as a consultant

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