Comparison of Ceftolozane/Tazobactam, Ceftazidime/Avibactam, and Meropenem/Vaborbactam Activity Against *P. aeruginosa:* A Multicenter Evaluation

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INTRODUCTION

- Recent data have shown high rates of resistance and co-resistance of *P. aeruginosa* to traditional first-line β-lactam antibiotics (piperacillin/tazobactam, ceftazidime, cefepime, and meropenem), with < 45% susceptibility to the others when resistance to one agent is present, driving a large medical need for newer agents.
- We compared the in vitro activity of newer Gram-negative antibiotics ceftolozane/tazobactam, ceftazidime/avibactam, and meropenem/vaborbactam against a global collection of PsA isolates.

METHODS

SMART Surveillance Program:

- The Study for Monitoring Antimicrobial Resistance Trends (SMART) represents our company's commitment to monitor the in vitro susceptibility of clinical bacterial isolates to antimicrobials in intra-abdominal, respiratory, urinary tract, and bloodstream infections globally, and has been ongoing since 2002.
- Currently, the global antimicrobial surveillance program includes gram-negative clinical isolates collected from medical centers located in the United States, Canada, Latin America, Europe, Asia/South Pacific and the Middle East/Africa.
- Each participating hospital was asked to submit up to 100 consecutive clinically relevant gram-negative bacilli (one isolate per patient episode) from lower respiratory tract specimens, up to 50 isolates from urinary tract specimens, up to 50 isolates from intra-abdominal specimens, and up to 50 isolates from bloodstream specimens.

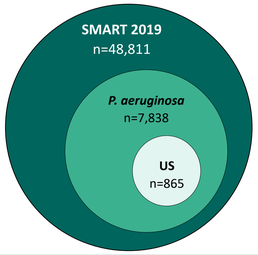
Clinical Isolates:

- *P. aeruginosa* isolates submitted from US hospitals in 2019 were included in this study (see also Figure 1).

Testing:

- Isolates collected as part of the SMART program from US medical centers were sent to IHMA's U.S. laboratory in Schaumburg, Illinois for testing
- Susceptibility testing (MIC, µg/ml) was performed by broth microdilution, with susceptibility determined by CLSI breakpoints except for MV where EUCAST breakpoints were applied due to CLSI offering no susceptibility breakpoint criteria.
- Susceptibility defined breakpoints (µg/ml) were: ceftolozane/tazobactam MIC ≤4; ceftazidime/ avibactam MIC ≤8; meropenem/vaborbactam MIC ≤8; piperacillin/ tazobactam MIC ≤16; meropenem MIC ≤2; ceftazidime MIC ≤8; cefepime ≤8

Figure 1. Source of clinical isolates



RESULTS

- 865 clinical *P. aeruginosa* isolates (one unique initial isolate per patient) were submitted from 21 US medical centers in 2019.
- The phenotypic β-lactam susceptibility profile in this population was piperacillin/tazobactam (79%), ceftazidime (82%), cefepime (83%), and meropenem (78%).
- Table 1 provides the comparative susceptibility rates. Co-resistance between commonly prescribed first line β-lactam antibiotics was common.
- Ceftolozane/tazobactam, ceftazidime/avibactam and meropenem/vaborbactam were more active than traditional β-lactams, with ceftolozane/tazobactam having higher in vitro activity regardless of phenotype, followed by ceftazidime/avibactam and then meropenem/vaborbactam (Table 1 and Figure 2)

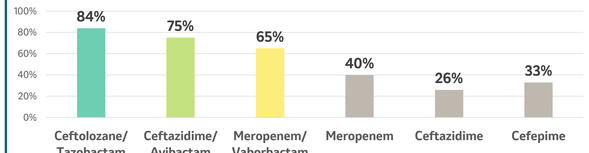
Table 1. Probability of Coverage of *P. aeruginosa* when NS or R to a Given First Line β-lactam Antibiotic (2019 US SMART Data): All *P. aeruginosa*

Susceptibility Phenotype	C/T n (%)	CZA n (%)	MVB n (%)	TZP n (%)	MEM n (%)	CAZ n (%)	FEP n (%)
All *P. aeruginosa* (n=865)	832 (96%)	818 (95%)	789 (91%)	687 (79%)	674 (78%)	709 (82%)	722 (83%)
Piperacillin/Tazobactam NS (n=178)	150 (84%)	134 (75%)	116 (65%)	0	72 (40%)	46 (26%)	59 (33%)
Meropenem NS (n=191)	166 (87%)	154 (81%)	115 (60%)	85 (45%)	0	106 (55%)	101 (53%)
Ceftazidime NS (n=156)	123 (79%)	109 (70%)	104 (67%)	24 (15%)	71 (46%)	0	38 (24%)
Cefepime NS (n=143)	112 (78%)	97 (68%)	88 (62%)	24 (17%)	53 (37%)	25 (17%)	0
Piperacillin/Tazobactam R (n=95)	73 (78%)	60 (63%)	61 (64%)	0	35 (37%)	3 (3%)	6 (6%)
Meropenem R (n=137)	116 (85%)	103 (75%)	61 (45%)	47 (34%)	0	60 (44%)	57 (42%)
Ceftazidime R (n=117)	85 (73%)	74 (63%)	80 (68%)	9 (8%)	52 (44%)	0	15 (13%)
Cefepime R (n=66)	39 (59%)	30 (45%)	35 (53%)	8 (12%)	22 (33%)	3 (5%)	0

Abbreviations: C/T, ceftolozane/tazobactam; CZA, ceftazidime/avibactam; MVB, meropenem/vaborbactam; TZP, piperacillin/tazobactam; MEM, meropenem; CAZ, ceftazidime; FEP, cefepime; NS, non-susceptible; R, resistant
Non-susceptible (NS) definitions were: piperacillin/tazobactam MIC ≥32; meropenem MIC ≥4; ceftazidime MIC ≥16; cefepime MIC ≥16
Resistant (R) definitions were: piperacillin/tazobactam MIC ≥128; meropenem MIC ≥8; ceftazidime MIC ≥32, cefepime MIC ≥32

Figure 2. % Susceptibility vs Piperacillin/Tazobactam NS *P. aeruginosa*

(2019 US SMART Data, n=178)



C-T vs C-A, Chi-square p = 0.0348; Fisher's exact test p = 0.0473
C-T vs M-V, Chi-square p < 0.0001; Fisher's exact test p < 0.0001

- 71% were isolated from patients with respiratory tract infections (Figure 3), and 32% of the isolates were obtained from patients residing in an intensive care unit (ICU)
- Similar trends in susceptibility were observed for the respiratory tract infection (Table 2 and Figure 4) and ICU (Table 3 and Figure 5) subsets

Figure 3. *P. aeruginosa* Site of Infection (2019 US SMART Data)

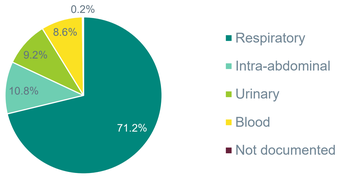
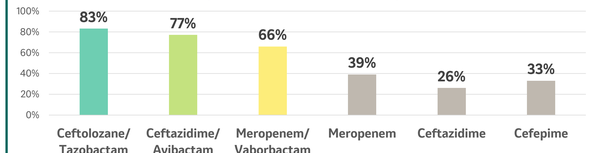


Table 2. Probability of Coverage of *P. aeruginosa* when NS or R to a Given First Line β-lactam Antibiotic (2019 US SMART Data): Respiratory Infection Subset

Susceptibility Phenotype	C/T n (%)	CZA n (%)	MVB n (%)	TZP n (%)	MEM n (%)	CAZ n (%)	FEP n (%)
All *P. aeruginosa* (n=616)	588 (95%)	582 (95%)	559 (91%)	482 (78%)	464 (75%)	494 (80%)	505 (82%)
Piperacillin/Tazobactam NS (n=134)	111 (83%)	103 (77%)	89 (66%)	0	52 (39%)	35 (26%)	44 (33%)
Meropenem NS (n=152)	131 (86%)	125 (82%)	95 (63%)	70 (46%)	0	85 (56%)	83 (55%)
Ceftazidime NS (n=122)	94 (77%)	88 (72%)	84 (69%)	23 (19%)	55 (45%)	0	31 (21%)
Cefepime NS (n=111)	84 (76%)	78 (70%)	71 (64%)	21 (19%)	42 (38%)	20 (18%)	0
Pip/Tazo R (n=70)	52 (74%)	47 (67%)	47 (67%)	0	25 (36%)	3 (4%)	5 (7%)
Meropenem R (n=110)	92 (84%)	85 (77%)	53 (48%)	39 (35%)	0	49 (45%)	48 (44%)
Ceftazidime R (n=92)	64 (70%)	61 (66%)	64 (70%)	9 (10%)	40 (44%)	0	12 (13%)
Cefepime R (n=49)	26 (53%)	25 (51%)	27 (55%)	7 (14%)	16 (33%)	1 (2%)	0

Figure 4. % S vs TZP-NS *P. aeruginosa:* Respiratory Infection Subset

(2019 US SMART Data, n=178)



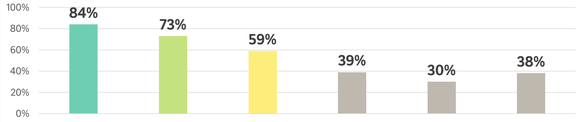
C-T vs C-A, Chi-square p = 0.2231; Fisher's exact test p = 0.2864
C-T vs M-V, Chi-square p = 0.0020; Fisher's exact test p = 0.0030

Table 3. Probability of Coverage of *P. aeruginosa* when NS or R to a Given First Line β-lactam Antibiotic (2019 US SMART Data): Intensive Care Unit (ICU) Subset

Susceptibility Phenotype	C/T n (%)	CZA n (%)	MVB n (%)	TZP n (%)	MEM n (%)	CAZ n (%)	FEP n (%)
All *P. aeruginosa* (n=279)	268 (96%)	262 (94%)	249 (89%)	215 (77%)	212 (76%)	226 (81%)	235 (84%)
Piperacillin/Tazobactam NS (n=64)	54 (84%)	47 (73%)	38 (59%)	0	25 (39%)	19 (30%)	24 (38%)
Meropenem NS (n=67)	58 (87%)	53 (79%)	37 (55%)	28 (42%)	0	40 (60%)	37 (55%)
Ceftazidime NS (n=53)	42 (79%)	36 (68%)	35 (66%)	8 (15%)	26 (49%)	0	14 (26%)
Cefepime NS (n=44)	33 (75%)	27 (61%)	23 (52%)	4 (9%)	14 (32%)	5 (11%)	0
Pip/Tazo R (n=31)	22 (71%)	18 (58%)	20 (65%)	0	12 (39%)	1 (3%)	2 (6%)
Meropenem R (n=49)	43 (88%)	38 (78%)	19 (39%)	16 (33%)	0	26 (53%)	23 (47%)
Ceftazidime R (n=42)	31 (74%)	26 (62%)	28 (67%)	4 (10%)	19 (45%)	0	6 (17$)
Cefepime R (n=21)	10 (48%)	8 (38%)	10 (48%)	3 (14%)	5 (24%)	1 (5%)	0

Figure 5. % S vs TZP-NS *P. aeruginosa:* ICU Subset

(2019 US SMART Data, n=178)



C-T vs C-A, Chi-square p = 0.1294; Fisher's exact test p = 0.1931
C-T vs M-V, Chi-square p = 0.0017; Fisher's exact test p = 0.0029

STUDY LIMITATIONS

- While the phenotypic profile of *P. aeruginosa* is easily determined for ceftolozane/tazobactam, ceftazidime/avibactam and meropenem/vaborbactam, the exact resistance mechanism(s) responsible for the NS of any given isolate remains elusive. Nevertheless, to our knowledge, this is the largest multicenter head to head comparison of the activities of ceftolozane/tazobactam, ceftazidime/avibactam and meropenem/vaborbactam among *P. aeruginosa* with varying resistant phenotypes, infection types and settings of care.

CONCLUSIONS

- Among the newer agents, ceftolozane/tazobactam demonstrated the most reliable in vitro activity against *P. aeruginosa* with resistance to traditional first-line β-lactams.
- Further studies are needed to translate the potential clinical relevance of these findings in different practice settings with varying rates of antimicrobial resistance among *P. aeruginosa*.

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References: [1]Grupper M et al. Antimicrob Agents Chemother 2017; 61(10):e00875-17. Moise P et al. Critical Care 2020; 24(Suppl 1):P425.

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