Evaluation of *in Vitro* Susceptibility of Multidrug-resistant *Pseudomonas aeruginosa* isolates from Qatar to Ceftazidime/avibactam and Ceftolozane/tazobactam

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Introduction

The burden of multidrug-resistant *Pseudomonas aeruginosa* (MDR-PA) infections is a global healthcare challenge (1, 2). Surveillance monitoring in Qatar established significant prevalence of MDR-PA. Collected isolates were testes against alternative treatment options in particular, ceftazidime/avibactam (CZA) and ceftolozane/tazobactam (C/T), which have been approved for treatment of complicated Gram-negative infections (3).

Methods

A total of 205 MDR-PA isolates were collected between 2014-2015 from four hospitals in Qatar. The pathogens were isolated from: respiratory 44.9% (92), skin-soft tissues 26.3% (54), urine 23.4% (48), blood 3.4% (7) and other sites 2% (4). The activity spectrum of CZA and C/T were tested in vitro against MDR-PA using E-test according to international standard recommendations . MDR-PA were defined according to previously agreed consensus (4) .

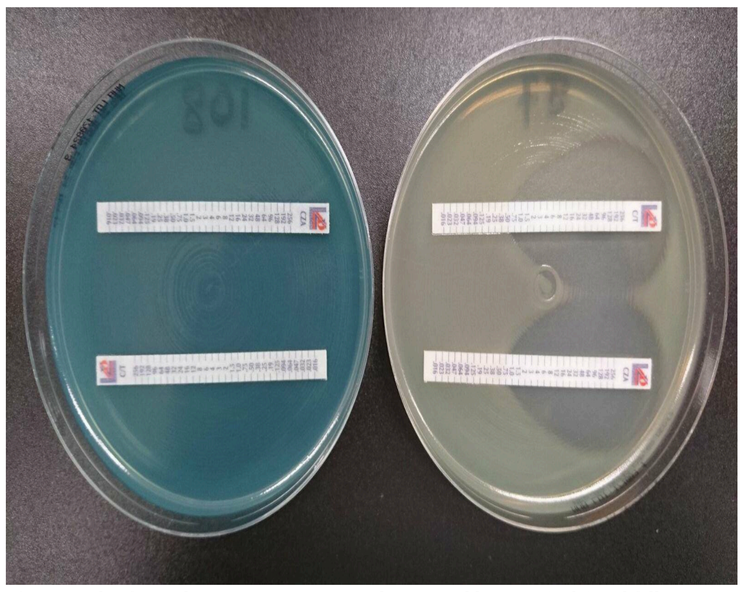
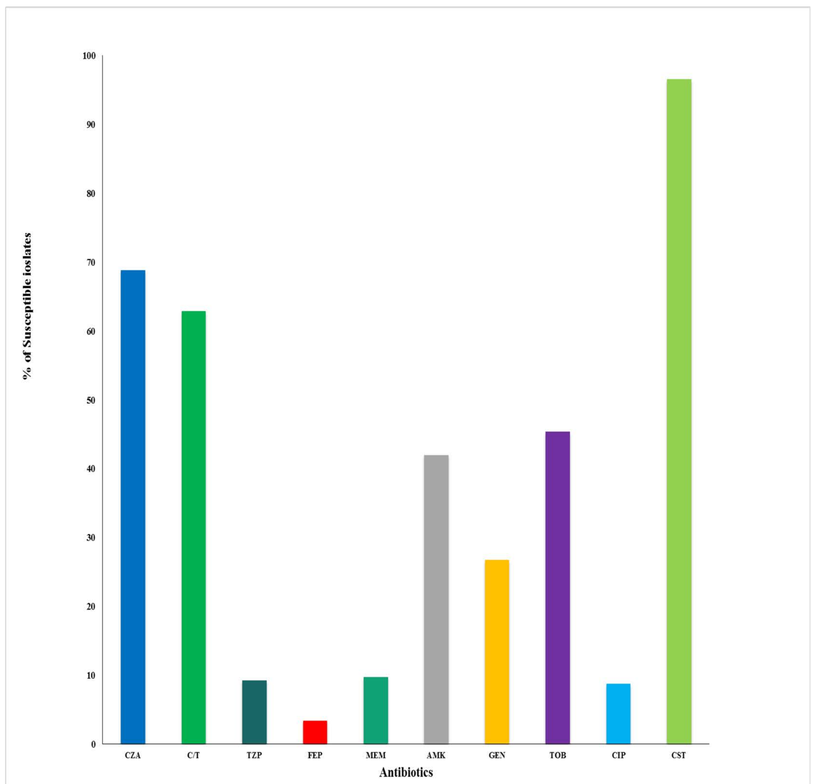


Figure 3. This figure depicts in vitro Etest results susceptible strain (right) and fully resistant strain (left). The different growth color is due to secretion of variety pigments including pyocyanin (blue-green) in the left, and pyoverdine (yellow-green and fluorescent) in the right.

Results

MDR-PA demonstrated favorable susceptibility to both CZA and C/T, at 68.8% (141/205) and 62.9% (129/205), respectively. Remarkably, 22.4% (46/205) of isolates were non-susceptible highlighting antimicrobial resistance endurance. Cumulative MIC 50/90 distribution to both CZA and C/T were, 4/64 µg/ml and 2/256 µg/ml, respectively.

When compared with eight other antibiotics, only colistin demonstrated higher susceptibility at 96.6%. The comparative results of phenotypically resistant of isolates to other antibiotics and CZA and C/T showed no significant correlation apart from fair agreement between C/T and CZA with amikacin (AMK) (0.37, p<0.001, k=0.27, p<0.001 respectively).



	CZA	C/T	TZP	FEP	MEM	AMK	GEN	TOB	CIP	CST
Susceptible no. (%)	141 (68.8)	129 (62.9)	19 (9.3)	7 (3.4)	20 (9.8)	86 (42)	55 (26.8)	93 (45.4)	18 (8.8)	198 (96.6)
Range	0.094-256	0.38-256	1-256	1.5-256	0.125-32	0.75-256	0.25-256	0.38-256	0.125-32	0.19-8
MIC50	4	2	256	64	32	32	48	24	32	1.5
MIC90	64	256	256	256	32	256	256	256	32	2

Figure 1. Susceptibility test of ceftazidime/avibactam, ceftolozane/tazobactam and their comparator agents against MDR-PA isolates in HMC, Qatar, during 2014 to 2015: CZA, ceftazidime-tazobactam; C/T, ceftolozane-tazobactam; TZP, piperacillin-tazobactam; FEP, cefepime; MEM, meropenem; AMK, amikacin; GEN, gentamicin; TOB, tobramycin; CIP, ciprofloxacin; CST, colistin

Table 1: Cumulative MIC distribution for Ceftazidime/Avibactam, Ceftolozane/Tazobactam and comparator agents against MDR-PA isolates from HMC, Qatar, in 2014 to 2015.

	No. (cumulative %) of isolates inhibited at an MIC (µg/ml))																			MIC50	MIC90
Antibiotic	≤0.75	1	1.5	2	3	4	6	8	12	16	24	32	48	64	96	128	192	256			
CZA	9 (4.4)	6 (7.3)	11 (12.7)	24 (24.4)	27 (37.6)	29 (51.7)	24 (63.4)	11 (68.8)	10 (73.7)	8 (77.6)	7 (81)	6 (83.9)	7 (87.3)	4 (89.3)	4 (91.2)	3 (92.7)	0 (92.7)	15 (100)		4	64
C/T	40 (19.5)	39 (38.5)	18 (47.3)	13 (53.7)	7 (57.1)	12 (62.9)	5 (65.4)	3 (66.8)	3 (68.3)	5 (70.7)	5 (73.2)	2 (74.1)	1 (74.6)	2 (75.6)	0 (75.6)	0 (75.60	0 (75.6)	50 (100)		2	256
FEB	0 (0)	0 (0)	1 (0.5)	1 (1)	0 (1)	1 (1.5)	0 (1.5)	4 (3.4)	13 (9.8)	16 (17.6)	19 (26.8)	18 (35.6)	17 (44)	13 (50.2)	8 (54.1)	8 (58)	8 (62)	78 (100)		64	256
GM	7 (3.4)	7 (6.8)	8 (10.7)	10 (15.6)	13 (22)	9 (26.3)	12 (32.2)	17 (40.5)	1 (41)	6 (44)	6 (46.8)	4 (48.8)	5 (51.2)	2 (52.2)	0 (52.2)	0 (52.2)	3 (53.7)	95 (100)		48	256
PIP/TAZ	0 (0)	2 (1)	0 (1)	1 (1.5)	0 (1.5)	1 (2)	3 (3.4)	3 (4.9)	3 (6.3)	7 (9.8)	10 (14.1)	12 (20)	12 (26.3)	12 (32.2)	9 (36.6)	4 (38.5)	8 (42.9)	118 (100)		256	256
AK	1 (0.5)	1 (1)	2 (2)	2 (2.9)	8 (6.8)	12 (12.7)	8 (16.7)	19 (25.9)	15 (33.2)	16 (41)	13 (47.3)	8 (51.2)	9 (55.6)	6 (58.5)	8 (62.4)	8 (66.3)	2 (67.3)	67 (100)		32	256
TOB	13 (6.3)	20 (16.1)	27 (29.3)	18 (38)	7 (41.4)	7 (44.9)	2 (45.9)	0 (45.9)	4 (47.8)	1 (48.3)	12 (54.1)	13 (60.5)	9 (64.9)	5 (67.3)	4 (69.3)	5 (71.7)	1 (72.2)	57 (100)		24	256
CS	43 (21)	38 (39)	82 (79.5)	35 (96.6)	3 (98)	2 (99)	1 (99.5)	1 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)		1.5	2
MER	8 (3.9)	1 (4.4)	5 (6.8)	6 (9.8)	4 (11.7)	4 (13.7)	4 (15.6)	9 (20)	4 (22)	3 (23.4)	1 (23.9)	156 (100)	NA	NA	NA	NA	NA	NA		32	32
CIP	12 (5.9)	5 (8.3)	5 (10.7)	7 (14.1)	9 (18.5)	14 (25.4)	6 (28.3)	6 (31.2)	6 (34.1)	2 (35.1)	3 (36.6)	130 (100)	NA	NA	NA	NA	NA	NA		32	32

- Green: Susceptible
- Blue: Intermediate
- Red: Resistance

Conclusion :

Although the study results demonstrated lower than expected in vitro susceptibility of CZA and C/T against MDR-PA isolates in Qatar compared to other regions probably because of accumulated resistance; it paved the way for potential future role of CZA and C/T in the management of MDR-PA infections.

The novel antibiotics will be recommended as alternatives to complement existing options hindered by their recognized limitations.

References

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