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New insights in therapeutic options against difficult-to-threat *Pseudomonas aeruginosa* (DTR-PA): *in vitro* activity of aztreonam in combination with avibactam, relebactam and in double β-lactams combinations with ceftazidime/avibactam and imipenem/relebactam.

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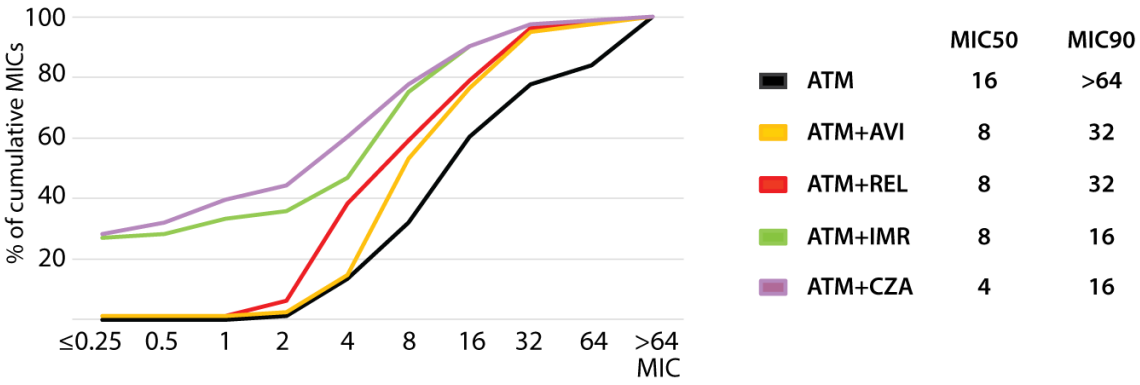
DTR-PA isolates exhibit nonsusceptibility to older-generation of β-lactam agents, including carbapenems and β-lactamase inhibitor combinations, and fluoroquinolones and are linked to poorer outcomes in severe infections. DTR-PA emergence may result from complex chromosomal resistance mechanisms or the acquisition of β-lactamases like ESBLs and metallo-β-lactamases (MBL). Aim: to compare the *in vitro* activities of aztreonam in combination with avibactam, relebactam, ceftazidime/avibactam, and imipenem/relebactam against DTR-PA.

The study included a panel of 81 DTR-PA clinical isolates (54 hospitals): 68 MBL producers (40 VIM, 6 VIM+PER, 2 VIM+GES, 10 IMP, 7 NDM, 3 SPM), and 13 carbapenemase nonproducers (4 GES, 4 PER, 1 CTX-M-15, 2 OXA-1-like, 1 CMY, 1 chromosomal-mediated resistance). DTR-PA isolates were cross-resistant to ceftazidime/avibactam and imipenem/relebactam. β-lactamases were characterized by PCR/sequencing and/or WGS. Susceptibility tests were conducted by agar dilution (CLSI), with avibactam and relebactam at final concentrations of 4mg/L, imipenem at 8 mg/L, and ceftazidime at 16 mg/L. The breakpoint for aztreonam alone, as per CLSI, was used for interpretation of the combinations tested (susceptible <= 8 mg/L). Potentiation was defined as a decrease in aztreonam MIC >= 2 dilutions.

The addition of inhibitors, alone or with a second β-lactam, reduced MIC50/90 compared to aztreonam from 16/>64 mg/L to 4-8/16-32 mg/L (Fig.1). Combinations with ceftazidime/avibactam or imipenem/relebactam demonstrated the highest activity, even more than both inhibitors without the β-lactam partner ($p<0.05$)(Fig.2). There was no notable distinction between ceftazidime/avibactam and imipenem/relebactam combinations ($p>0.05$) (Fig.2). Ceftazidime/avibactam plus aztreonam exhibited a more pronounced potentiation effect among MBLs, particularly VIM, whereas either ceftazidime/avibactam or imipenem/relebactam demonstrated this effect among ESBLs (Fig.3).

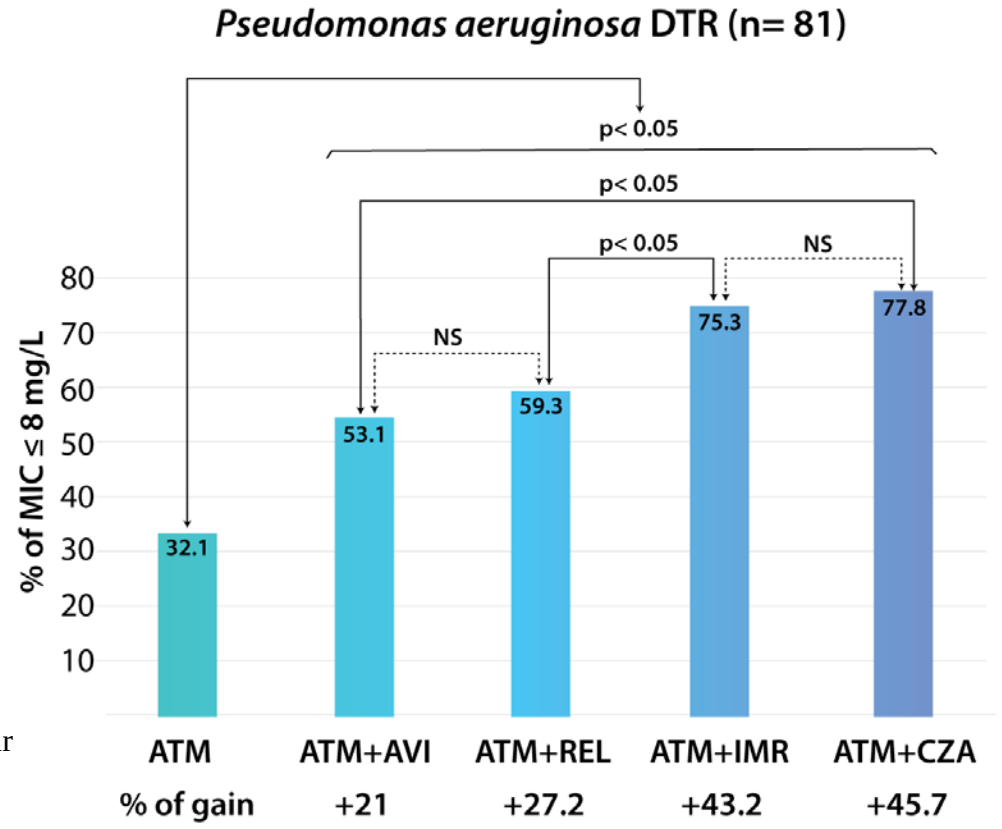
Aztreonam combinations exhibited promising *in vitro* activity against MBL and ESBL producers, providing potential treatment options. Combinations of aztreonam with ceftazidime/avibactam or imipenem/relebactam showed notable potentiation, particularly for VIM and ESBL, even at physiological concentrations. Thus, the inclusion of double β-lactam agents in the combination may offer additional benefits, usually not measured in routine laboratories. Further studies evaluating these combinations are warranted.

Figure 1.
Cumulative percentage of MICs (mg/L) for aztreonam and the indicated combinations. MIC50 and MIC90 (mg/L)



ATM: aztreonam; AVI: avibactam; REL: relebactam; CZA: ceftazidime + AVI; IMR: imipenem + REL

Figure 2.
In vitro restoration of suscetibility to aztreonam in the presence of different combinations of inhibitors



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ATM: aztreonam; AVI: avibactam; REL: relebactam; CZA: ceftazidime + AVI; IMR: imipenem + REL
NS: not significant difference (p> 0.05)

Figure 3.
In vitro activity of aztreonam and its combinations for DTR-PA according to the resistance mechanism involved.

DTR-PA Mechanism of resistance (n)	% of strains												
	ATM	**ATM + AVI**			**ATM + CZA**			**ATM + REL**			**ATM + IMR**		
	MIC <=8	MIC <=8	Gain	Pot.	MIC <=8	Gain	Pot.	MIC <=8	Gain	Pot.	MIC <=8	Gain	Pot.
All (81)	**32,1**	**53,1**	**21,0**	**18,5**	**77,8**	**45,7**	**60,5**	**59,3**	**27,2**	**21,0**	**75,3**	**43,2**	**42,0**
MBL Pos (68)	**38,2**	**54,4**	**16,2**	**14,7**	**75**	**36,8**	**54,4**	**63,2**	**25**	**17,6**	**70,6**	**32,4**	**30,9**
VIM (48)	45,8	60,4	14,6	16,7	85,4	39,6	72,9	70,8	25	18,8	79,2	33,3	43,8
IMP (10)	20	40	20	10	40	20	10	50	30	10	50	30	30
NDM (7)	0	28,9	28,9	14,3	42,9	42,9	14,3	42,9	42,9	14,3	42,9	42,9	14,3
SPM (3)	66	66	0	0	100	34	0	66	0	0	100	34	0
MBL Neg (13)	**0**	**46,2**	**46,2**	**38,5**	**92,3**	**92,3**	**92,3**	**38,5**	**38,5**	**38,5**	**100**	**100**	**100**
PER (4)	0	50	50	100	100	100	100	50	50	100	100	100	100
GES (4)	0	75	75	0	100	100	100	75	75	0	100	100	100

MIC in mg/L. Pos: positive. Neg: negative. ATM: aztreonam; AVI: avibactam; REL: relebactam. CZA: ceftazidime + AVI; IMR: imipenem + REL. Gain: differential increase in susceptibility obtained with the indicated combination with respect to aztreonam alone. Pot: potentiation, a decrease in aztreonam MIC >= 2 dilutions.