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The effect of ceftazidime/avibactam/aztreonam on clinical multidrug-resistant *P. aeruginosa* isolates from Germany

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Background

- The combination of ceftazidime (CTZ) and avibactam (AVI) exhibits potent activity against multi-drug resistant (MDR) Gram-negative bacteria.[1]
- In *Pseudomonas aeruginosa* this activity can be reduced due to altered membrane permeability, efflux pump mutations and presence of metallo-β-lactamases (MBLs).
- The combination of aztreonam (AZT) and AVI is suggested to be an effective alternative in the treatment of infections caused by MBL-producing *P. aeruginosa*.[2]
- The purpose of this study was to evaluate the effect of AVI in combination with CTZ and/or AZT in MDR *P. aeruginosa* isolates from hospitalized patients in Germany.

Methods

- Thirty-eight clinical *P. aeruginosa* isolates showing combined resistance to CTZ, imipenem and meropenem were selected from the strain collections of two multicentre surveillance studies conducted in 2018 and 2019/20.
- Carbapenemase genes were detected by PCR. Positive isolates were further investigated by whole-genome-sequencing at the German National Reference Centre for Gram-Negative Bacteria in Bochum.
- Susceptibility was tested by broth microdilution (CTZ ± AVI and AZT ± AVI) and agar dilution (ceftazidime/avibactam (CTV), AZT/AVI and CTV combined with AZT 8 or 16 mg/L).[3,4,5]
- Three representative MBL-producing isolates were further analysed using time-kill methodology. Drug concentrations applied were those corresponding to the area under the curve serum levels published by Montero et al.[6]: AZT 1,050 µg·h/mL corresponding to a dose of 2 g every 8 h, CTZ 800 µg·h/mL corresponding to a dose of 2 g every 8 h and AVI 147 µg·h /mL corresponding to a dose of 0.5 g every 8 h.

Results

- MIC distributions are shown in the Table.
- $MIC_{50/90}$ values for CTZ and AZT were each 32/64 mg/L. In combination with AVI the $MIC_{50/90}$s were reduced to 8/64 mg/L (CTZ) and 16/32 mg/L (AZT).
- Similar $MIC_{50/90}$ values were observed for the double combinations using agar dilution. In contrast, the triple combinations showed much lower $MIC_{50/90}$s of 0.125/4 mg/L (AZT 8 mg/L) and 0.06/0.06 mg/L (AZT 16 mg/L).

Table: MIC distribution, MIC_{50}- / MIC_{90}-values and number of susceptible (S;I) and resistant strains [%]

substance / combination		MIC (mg/L)												MIC_{50} (mg/L)	MIC_{90} (mg/L)	%S	%I	%R
		0.0625	0.125	0.25	0.5	1	2	4	8	16	32	64	**128**					
Ceftazidime MD	n	*0*	0	0	0	0	0	3	2	7	9	**17**		32	**64**	-	5	33
	cum-%	*0.0*	0.0	0.0	0.0	0.0	0.0	7.9	13.2	31.6	55.3	**100.0**				-	13.2	86.8
Ceftazidime / Avibactam (fix 4 mg/L) MD	n	*0*	0	0	0	0	4	9	11	6	3	**5**		8	**64**	24	-	14
	cum-%	*0.0*	0.0	0.0	0.0	0.0	10.5	34.2	63.2	78.9	86.8	**100.0**				63.2	-	36.8
Ceftazidime / Avibactam (4:1) AD	n	*0*	0	0	0	2	1	9	8	9	7	**2**		8	32	20	-	18
	cum-%	*0.0*	0.0	0.0	0.0	5.3	7.9	31.6	52.6	76.3	94.7	**100.0**				52.6	-	47.4
Aztreonam MD	n		*0*	0	0	0	0	0	4	9	15	9	**1**	32	64	-	13	25
	cum-%		*0.0*	0.0	0.0	0.0	0.0	0.0	10.5	34.2	73.7	97.4	**100.0**			-	34.2	65.8
Aztreonam / Avibactam (fix 4 mg/L) MD	n		*0*	0	0	2	0	2	11	9	12	2	**0**	16	32	no EUCAST breakpoints available		
	cum-%		*0.0*	0.0	0.0	5.3	5.3	10.5	39.5	63.2	94.7	100.0	**100.0**					
Aztreonam / Avibactam (4:1) AD	n		*0*	0	0	0	0	0	8	7	16	6	**1**	32	64			
	cum-%		*0.0*	0.0	0.0	0.0	0.0	0.0	21.1	39.5	81.6	97.4	**100.0**					
Ceftazidime / Avibactam (4:1) plus Aztreonam (fix 8 mg/L) AD	n	*15*	4	1	5	2	7	3	0	0	0	**1**		0.125	4			
	cum-%	*39.5*	50.0	52.6	65.8	71.1	89.5	97.4	97.4	97.4	97.4	**100.0**						
Ceftazidime / Avibactam (4:1) plus Aztreonam (fix 16 mg/L) AD	n	*36*	2	0	0	0	0	0	0	0	0	**0**		*0.0625*	*0.0625*			
	cum-%	*94.7*	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	**100.0**						

AD: Agar dilution; MD: Microbroth dilution; MIC, minimum inhibitory concentration; n, number of isolates; cum-%, cumulative percentage.
Numbers in bold include isolates with MIC > the highest concentration tested; numbers in italic include isolates with MIC < value shown.

- Eight MBL-encoding isolates were detected. The corresponding beta-lactamase (*bla*) genes were identified as bla_{GIM-1} (n=1), bla_{IMP-1} (n=1) and bla_{VIM-2} (n=6).
- Three VIM-2-encoding isolates (sequence types: ST-111/-233/-235) were further investigated by time-kill assay.
- When using the triple combination, a reduction of ≥ 3-log_{10} CFU/mL was observed for each strain within 24 h (Figure).

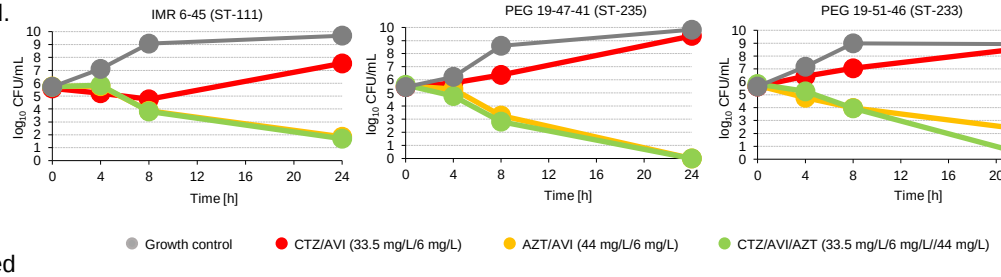

Figure: Time-kill assays of VIM-2-encoding *P. aeruginosa* isolates.

Conclusions

- There was no difference in the activity between CTV and AZT/AVI against MDR *P. aeruginosa* with combined resistance to ceftazidime and carbapenems.
- The combination of CTV/AZT was active against all clinical isolates and revealed a bactericidal effect after 24 h in VIM-2-producing strains of three widely distributed sequence types.

References

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