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Mechanism-based-susceptibility testing (MBST) using disc diffusion assays (DDA) to Guide Treatment of Multidrug- and Extensively Drug Resistant *Pseudomonas aeruginosa* (MDR-XDR-*Pa*) in a Cystic Fibrosis (CF) Lung Transplant Recipient; are we ready for combination therapy vs. MDR-XDR-*Pa*?

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Background

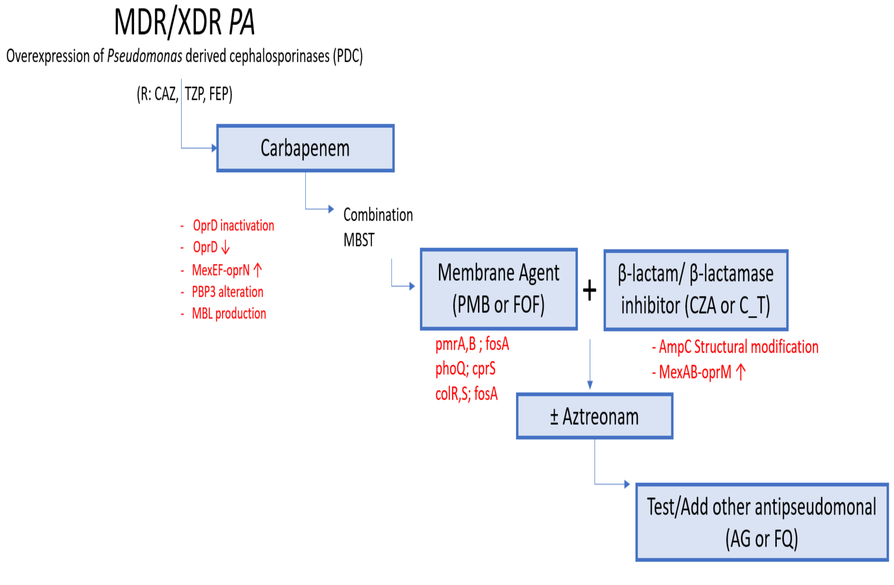
- The effective management of cystic fibrosis (CF) patients with recurrent pulmonary and sinus infections caused by MDR- and XDR-*Pa* are challenge due to the emergence of antibiotic resistance
- Combination of inhaled, and or oral and intravenous antimicrobial therapy for prolonged durations are often required
- We applied MBST with DDA to guide combination antibiotic therapy in an 18-year-old woman with CF that underwent bilateral lung transplantation
- We investigated if this approach can assist in choosing effective antibiotic regimens against XDR *pseudomonas aeruginosa*

Methods

- Consecutive MDR- and XDR-*Pa* respiratory isolates were collected
- Duration: December 2016 to March 2018 (pre and post lung transplant)
- Isolates were initially screened with Vitek and antibiotic commercial discs
- Further antibiotics were sequentially added to create double (DDD) or triple disc diffusion assays (TDD) based on resistance mechanisms
- Composites of anti-pseudomonal antibiotics, β-lactamase inhibitors, and cell membrane agents were utilized to achieve MBST
- Whole genome sequencing of isolates subsequently performed

Results

- During therapy, 1859 antibiotic-days were administered
- Isolates with varying AST patterns were found (Timeline)
- MBST with DDA revealed active combinations for resistant isolates
- Combinations led to a microbiological response allowing transplantation
- Regimens were also informed by allergies, clinical and radiologic findings



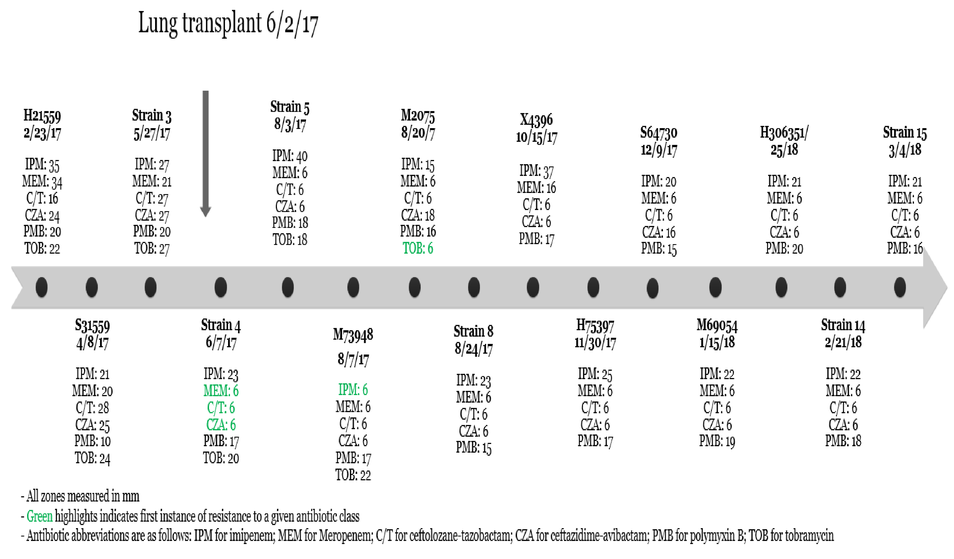
Results

Table: Antimicrobial combinations reflecting zones of inhibition by strain and date.

				Antibiotic Inactivation				Target Alteration		Combinations + inhibition zones (mm)		
Isolate ID	Date	MLST	Serotype	PDC	OXA	fosA	Aminoglycoside	Quinolone	Polymyxin	Combo 1	Combo 2	Combo 3
H21559	2/23/2017	2100	O6	PDC-73	OXA-59	✔	APH(3')	gyrA	basR/L71R, arnA, basS	CZA + TOB 35	PMB + IPM 38	FOF 40+
S31559	4/8/2017	2100	O6	PDC-79	OXA-50	✔	APH(3')	gyrA:T83I	basR/L71R, arnA, basS	CZA + TOB 31	FOF + CZA 35	PMB + C/T + MEM 39
S31559m	4/8/2017	463	O4	PDC-8	OXA-59	✔	APH(3')	—	basR/L71R, arnA, basS	C/T + IPM 34	CT + TOB 25	POL + IPM 30
M73948	8/7/2017	2100	O6	PDC-79	OXA-50	✔	APH(3')	gyrA:T83I	basR/L71R, arnA, basS	FOF + TZP 19	PMB + IPM 21	
M20735	8/20/2017	2100	O6	PDC-9	OXA-50	✔	APH(3')	—	basR/L71R, arnA, basS	FOF + TZP 32	FOF + CZA 26	CZA + TOB 22
X4396	10/15/2017	2100	O6	PDC-79	OXA-50	✔	APH(3')	gyrA:T83I	basR/L71R, arnA, basS	FOF + IPM 30	PMB + IPM 30	C/T + IPM 30
W79616	11/1/2017	2100	O6	PDC-9	OXA-50	✔	APH(3')	gyrA(D87N)	basR/L71R, arnA, basS	—	—	—
H75397	11/30/2017	2100	O6	PDC-79	OXA-50	—	APH(3')	gyrA:T83I	—	PMB+CIP 19	PMB + CZA + IPM 25	PMB + FOF + IPM 25
S64730	12/9/2017	2100	O6	PDC-9	OXA-50	✔	APH(3')	gyrA(D87N)	basR/L71R, arnA, basS	FOF + TZP 30	PMB + IPM 25	
M69054	1/15/2018	2100	O6	PDC-79	OXA-50	✔	APH(3')	gyrA:T83I	arnA	PMB + IPM 23		
H30635	1/24/2018	2100	O6	PDC-79	OXA-50	✔	APH(3')	gyrA:T83I	basR/L71R, arnA, basS	PMB + IPM 26		

FQ: fluoroquinolones; AG: aminoglycosides; MBL: Metallo-β-lactamase; CZA: ceftazidime-avibactam; C/T: ceftolozane-tazobactam; TOB: tobramycin; ATM: aztreonam; PMB: polymyxin B; FOF: fosfomycin; TZP: piperacillin-tazobactam; CIP: ciprofloxacin; IPM: imipenem; MEM: meropenem.

Timeline of *pseudomonas aeruginosa* isolates depicting emergence of antimicrobial resistance and results of single antibiotic disc diffusion



Conclusion

- Strains with evolving resistance profiles recapitulate the dynamic nature of respiratory infections in CF
- Double or triple DDAs identified potential treatment options e.g. vs. MDR-XDR *Pa*. MBST can support the management of challenging infections.
- Treatment of XDR *pseudomonas aeruginosa* is extremely challenging in immunosuppressed patients
- Antimicrobial options could be expanded with appropriate stewardship of testing multiple combinations based on the mechanisms of resistance and synergy.

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