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Antibiotic resistance in a collection of *Pseudomonas aeruginosa* isolated from Cystic Fibrosis patients through Europe (Belgium, France, Germany and United Kingdom)

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Abstract

Cystic fibrosis (CF) is the most common life – limiting disease in NW European populations. The primary cause of death in CF patients is the progressive lung disease mainly caused by chronic and recurrent bacterial infections, especially caused by *Pseudomonas aeruginosa*. Here we evaluated the activity of different classes of antibiotics against *Pseudomonas aeruginosa* isolates collected from CF patients in 4 CF centres across Europe. We found that colistin is the most active agent against this collection (often used as last-resort antibiotic), followed by tobramycin and meropenem. The resistance rates to the other main antipseudomonal agents are worryingly high.

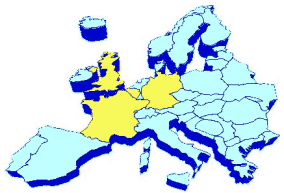
Background

Cystic fibrosis (CF) is an automosal recessive genetic disease, affecting mainly NW European populations and characterized by overproduction of sticky, thick mucus in many organs such as the lung, pancreas and gastrointestinal tract. This offers an ideal environment in the lung for proliferation of opportunistic pathogens.

Pseudomonas aeruginosa is the most common micro-organism causing chronic respiratory tract infections in CF patients older than 25 years (1). These patients, therefore, require repeated and prolonged antibiotic treatments with anti-pseudomonal drugs. If effective, these treatments contribute to increasing life expectancy and maintaining a acceptable quality of life. Antibiotics belonging to the classes of β-lactams, aminoglycosides, fluoroquinolones and polymyxins (the latter as last-resort antibiotics) are used to treat pseudomonal infections.

Objectives

Our aim was to determine MIC distributions and resistance rates to major antipseudomonal antibiotics against isolates collected from CF patients in 4 centers through Europe.



Materials & Methods

Bacterial isolates: 342 *P. aeruginosa* isolates were collected in 4 Cystic Fibrosis centers from different countries (*Hôpital des enfants malades Reine Fabiola/Erasme*; Belgium, n = 91; *Hôpital Jean Minjoz*, Besançon, France; n = 81; University Hospital of Münster, n = 71, Germany; Queen's; University of Belfast, UK, n=99).

Susceptibility testing: Minimal Inhibitory Concentrations (MIC) were determined by microdilution in cation-adjusted Mueller-Hinton broth following CLSI recommendations, with P.a. ATCC 27853 used as quality control strain. Susceptibility was assessed according to The European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretive criteria (2).

Analysis of cross resistance: This was assessed using quantile density contour analysis (QDCI; 0.1 to 0.9) using JMP software v10.0.2

Results

Table 1: MIC distributions and percentage of susceptibility/resistance based on EUCAST breakpoints

Antibiotic	MIC distribution (mg/L)				% Susceptible isolates[a]	% Resistant isolates[a]
	min	max	MIC_{50}	MIC_{90}		
Amikacin [AMK]	1	>512	32	128	25	54
Tobramycin [TOB]	0.064	>512	2	16	73	26
Piperacillin-tazobactam [TZP]	0.5	>512	64	512	31	69
Ceftazidime [CAZ]	0.5	>512	32	512	36	64
Meropenem [MEM]	0.016	256	2	32	48	18
Ciprofloxacin [CIP]	0.016	64	1	8	32	51
Colistin [CST]	0.125	>512	1-2	4	93	7

[a] EUCAST breakpoints : AMK S≤ 8 - R>16; TOB S≤ 4 - R>4; CAZ S≤ 8 - R>8; MEM S≤ 2 - R>8; TZP S≤16 - R >16; CIP S≤ 0.5 - R>1; CST S≤ 4 - R>4.

Table 2: Percentage of cross resistance among tested antibiotics

TOB	TZP	CAZ	MEM	CIP	CST	Antibiotics
25	44	42	15	35	6	AMK
	23	22	8	20	4	TOB
		62	17	40	6	TZP
			16	39	6	CAZ
				16	3	MEM
					4	CIP

Figure 2: Correlation between MICs of individual isolates for (a) AMK vs TOB, (b) MEM vs CST, (c) MEM vs CAZ and (d) MEM vs TZP using quantile density contour analysis.

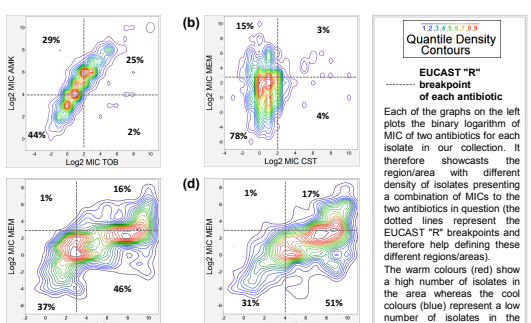
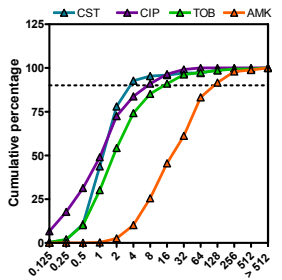
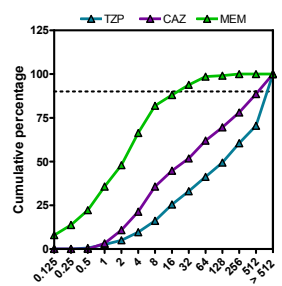


Figure 1: MIC distributions of AMK, TOB, CIP and CST *(top)* and β-lactams : CAZ, MEM and TZP *(bottom)*





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- More than half of the isolates were resistant to amikacin, ceftazidime, piperacillin-tazobactam, and ciprofloxacin, 20-25 % to tobramycin and meropenem, and only 7 % to colistin (which appears as a last-resort antibiotic).
- Cross-resistance was rare with colistin, 26 % among aminoglycosides, 18-62 % among β-lactams, and 35-44 % among drugs from different classes with high resistance rates (CIP, TZP, CAZ, AMK).
- Among aminoglycosides, tobramycin appears more active than amikacin, most probably due to the high expression of the efflux pump MexXY-OprM reported for isolates from CF patients (3).
- Among β-lactams, meropenem is most active, probably because carbapenems are stable to most prevalent β-lactamases (4).

Conclusions

- Resistance and cross-resistance rates are worryingly high in this collection, most probably related to frequent antibiotic usage in the corresponding patients' population, with best options remaining tobramycin, meropenem, and, if needed, colistin.
- High concentrations at the infection site are therefore required to reach pharmacodynamic target and inhaled formulations may prove a useful strategy in this context.

References

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