In Vitro Susceptibility of Amikacin against Gram-Negative Respiratory and Blood Isolates from US Hospitals

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INTRODUCTION

Nosocomial pneumonia caused by *P. aeruginosa* continues to pose significant challenges in US hospitals due to increasing antimicrobial resistance. Yet more challenging is delivering effective antibiotic concentrations to the lung as many parenteral therapies have poor penetration including amikacin.

To overcome this challenge, the administration of amikacin by inhalation (Amikacin Inhale, BAY41-6551) is currently under phase III study as an adjunctive therapy to IV antibiotics for the treatment of Gram-negative pneumonia in intubated and mechanical ventilated patients.

Our objective was to define the potency of amikacin against a US collection of *P. aeruginosa* nosocomial isolates and relate these data to achievable lung concentrations.

METHODS

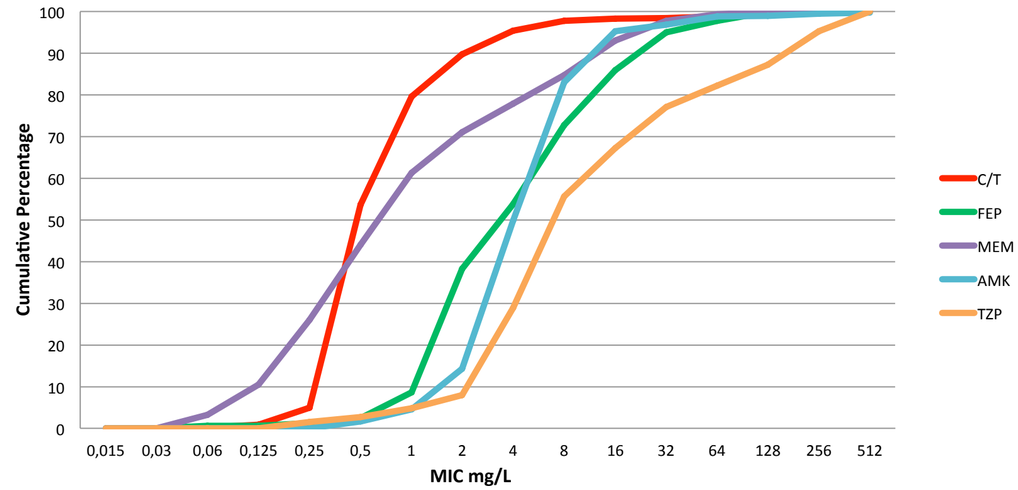
- 50 US hospitals provided non-duplicate nosocomial blood and respiratory isolates of *P. aeruginosa* (n=815) from adult inpatients from June 2013 to July 2014.
- MICs were determined using CLSI defined broth microdilution methods for ceftolozane/tazobactam, cefepime, ciprofloxacin, aztreonam, piperacillin/tazobactam, meropenem, tobramycin and amikacin.
- CLSI and FDA breakpoints were used to define susceptibility.[1]
- *P. aeruginosa* were identified as multidrug resistant (MDR) if they displayed resistance to 3 or more classes of anitbitics.[2]

Table 1. MIC profile of AMK and comparators for isolates of *P. aeruginosa*

Isolates	Anitmicrobial agent	Range	Modal	MIC_{50}	MIC_{90}	%S
All isolates	C/T	≤0.06->64	0.5	0.5	4	95
n=815	FEP	≤0.06->64	2	4	32	73
	CIP	≤0.015->16	0.125	0.25	16	68
	ATM	≤0.06->64	4	8	32	67
	TZP	≤0.25->256	8	8	256	67
	MEM	≤0.06->64	0.5	1	16	71
	TOB	≤0.06->64	0.5	1	8	90
	AMK	≤0.5->64	4	8	16	95
MDR+ isolates	C/T	0.5->64	1	2	32	78
n=116	FEP	2->64	32	32	128	13
	CIP	2->64	32	16	32	11
	ATM	0.25->64	128	32	128	19
	TZP	4->256	256	256	512	6
	MEM	0.25->64	16	16	64	17
	TOB	0.125->64	1	4	128	52
	AMK	0.5->64	8	8	32	87
MEM-R isolates	C/T	0.25->64	1	1	8	89
n=236	FEP	1->64	16	16	64	42
	CIP	0.06->16	32	4	32	35
	ATM	0.25->64	32	16	64	35
	TZP	4->256	32	32	512	36
	MEM	4->64	16	16	32	0
	TOB	≤0.06->64	1	1	64	74
	AMK	0.5->64	8	8	16	91
FEP-R isolates	C/T	0.25->64	1	2	8	85
n=222	FEP	16->64	16	32	64	0
	CIP	0.06->16	32	4	32	39
	ATM	0.25->64	32	32	128	23
	TZP	1->256	256	128	512	20
	MEM	≤0.06->64	16	8	32	38
	TOB	0.25->64	1	1	64	76
	AMK	0.5->64	8	8	32	89
TZP-R isolates	C/T	0.25->64	1	2	8	88
n=267	FEP	1->64	16	16	64	34
	CIP	≤0.015->16	32	2	32	46
	ATM	0.25->64	32	32	128	27
	TZP	32->256	32	128	512	0
	MEM	0.125->64	16	4	32	44
	TOB	0.25->64	1	1	64	78
	AMK	0.5->64	8	8	16	91

ceftolozane/tazobactam (C/T), cefepime (FEP), ciprofloxacin (CIP), piperacillin/tazobactam (TZP), meropenem (MEM), tobramycin (TOB,) and amikacin (AMK)

Figure 1. MIC distribution of *P. aeruginosa* (n=815) for amikacin, ceftolozane/tazobactam, cefepime, piperacillin/tazobactam and meropenem.



RESULTS

- The range of MICs, mode, MIC_{50}, $MIC_{90,}$ and susceptibility (%S) for *P. aeruginosa* are shown in Table 1.
  - Ceftolozane/tazobactam, amikacin, and tobramycin retained highest potency (90-95%).
  - Piperacillin/tazobactam and aztreonam, ciprofloxacin were among the least potent (67-68%).
  - Despite β-lactam non-susceptibility and MDR classification, amikacin displayed $MIC_{90} \leq 32$ mg/L.
- Figure 1 display the MIC distributions of *P. aeruginosa.*
  - The MIC_{90} of ceftolozane/tazobactam was 2-6 fold lower than other agents.
  - Overall 99% of isolates had an amikacin MIC of ≤ 64 mg/L.

CONCLUSIONS

In this study we defined the phenotypic profile of amikacin for blood and respiratory nosocomial isolates implicated in ICU based pulmonary infections.

When considering the MIC_{90}, only ceftolozane/tazobactam, tobramycin and amikacin had values at or below their respective breakpoints.

Despite resistance to other β-lactams, amikacin maintained high susceptibility.

For amikacin 95% of organisms had a MIC of ≤16 mg/L, moreover nearly all (99%) organisms have MICs ≤64 mg/L which is well below the achievable lung concentrations of approximately 5000 mg/L with the administration of Amikacin Inhale.

These data highlight the enhanced potency of amikacin and suggest that the achievable lung concentrations after inhalation will exceed the MICs typically observed for *P. aeruginosa* in the hospital setting

1.Clinical and Laboratory Standards Institute. 2014. Performance standards for antimicrobial susceptibility testing; twenty-fourth informational supplement. CLSI document M100-S24 U. Clinical and Laboratory Standards Institute, Wayne, PA.

2. Bulik CC, Christensen H, Nicolau DP. *In vitro* potency of CXA-101, a novel cephalosporin, against *Pseudomonas aeruginosa* displaying various resistance phenotypes, including multidrug resistance. Antimicrob Agents Chemother. 2010;54(1):557-9.