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Multi-Drug Resistant *Pseudomonas aeruginosa*, Co-Resistances in MYSTIC and SENTRY Programs

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ABSTRACT

Background: Emergence of multi-drug resistant (MDR) *Pseudomonas aeruginosa* (PSA) is a growing problem worldwide. It has been proposed that R to 1 broad-spectrum agent such as ciprofloxacin (CIP) could be associated with co-R to other antimicrobial classes. This report summarizes the effects of CIP susceptibility (S) by category when comparing S, intermediate (I) and R rates for selected carbapenems, cephalosporins, penicillin/ß-lactamase inhibitors and aminoglycosides.
Methods: A total of 1,111 (MYSTIC Programme [MP]; 1999 - 2002) and 5,191 (SENTRY Antimicrobial Surveillance Program [SP]; 1997 - 2001) PSA were tested using reference broth microdilution (BMD) methods as defined by NCCLS. Antimicrobials tested include: CIP, imipenem (IMP), meropenem (MERO), cefepime (CPM), ceftazidime (CAZ), piperacillin/tazobactam (P/T) and tobramycin (TOB). For each surveillance program, the PSA collections were separated into CIP categories according to the NCCLS criteria. The % S and R were then calculated for each of the comparator agents.
Results: Nearly identical results were observed in both global surveillance programs that showed linear increases in R rates for all antimicrobials as CIP categories moved from S to I to R. Examples are in the table.

	% R					
	CIP-S		CIP-I		CIP-R	
Antimicrobial	MP	SP	MP	SP	MP	SP
(n. MP/SP)	(835)	(3,977)	(53)	(310)	(223)	(904)
IMP	6	4	13	19	33	23
MERO	4	2	11	11	27	18
CPM	2	3	8	13	26	19
CAZ	5	8	8	23	34	34
P/T	4	6	13	19	35	31
TOB	2	2	6	11	27	27

The rank order of co-R rates (highest to lowest) was: CAZ = P/T > TOB = IMP > MERO = CPM.
Conclusions: The % R rate for non-quinolone class antimicrobials increased as the CIP MICs have increased. CIP-R predicts a high probability of co-R to other antimicrobial classes for PSA highest for CAZ and P/T; lowest for MERO and CPM. Due to the rise of MDR PSA, this finding will be important for clinicians when deciding on an antimicrobial therapy for patients requiring combination therapy for serious PSA infections.

INTRODUCTION

Resistance among Gram-negative bacilli has emerged as a serious therapeutic problem over the last decade as we have focused on the development of novel Gram-positive-active agents such as quinupristin/dalfopristin, linezolid and daptomycin. Most worrisome are the multidrug-resistant (MDR) strains of Gram-negative non-fermentative bacilli such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. These MDR-*P. aeruginosa* have been frequently described and novel resistance mechanisms have been characterized including:

1. Membrane protein deletions effecting drug transport;
2. Hyper-expression of native ß-lactamases or production of other inactivating enzymes;
3. Target mutations such as PBPs or in the QRDR etc.;
4. Production of novel ß-lactamases such as carbapenemases including metallo-ß-lactamases (IMP, VIM, SPM, GIM, etc.); and
5. Efflux pumps creating resistances to multiple antimicrobial classes.

Many experts in the fields of infectious disease and clinical microbiology have recognized that MDR-*P. aeruginosa* strains have varying probabilities of co-resistances among the possible therapeutic agents. In recent years, some classes such as the fluoroquinolones and cephalosporins have experienced escalated occurrences of co-resistance, yet other classes seem less compromised.

To assess the probabilities of co-resistances of fluoroquinolones and other antimicrobial classes in *P. aeruginosa*, the data bases of the MYSTIC Programme USA (1999 - 2002) and the SENTRY Antimicrobial Surveillance Program USA (1997 - 2001) were analyzed using six broad-spectrum anti-pseudomonal agents indexed by their resistance pattern to ciprofloxacin.

MATERIALS AND METHODS

Organisms. Clinical isolates of *P. aeruginosa* producing significant infections in two notable resistance surveillance programs were analyzed, all strains tested at JMI Laboratories (North Liberty, Iowa). A total of 1,111 strains were collected in the MYSTIC Program between 1999 - 2002 in the USA. Similarly, the SENTRY Program (USA, 1997 - 2001) tested 5,191 *P. aeruginosa* strains.

No duplicate strains were tested and clonal outbreak strains were omitted with only one strain being represented. NCCLS quality control strains *P. aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25922 and 35218 were tested concurrently with endpoint MIC values within published control parameters.

Susceptibility tests. All MIC tests were performed by reference broth microdilution methods (NCCLS, M7-A6, 2003) in panels prepared by TREK Diagnostics (Cleveland, OH). The broth was cation-adjusted Mueller-Hinton medium without supplements often used for fastidious species. The tested and analyzed anti-pseudomonal agents were: 1) ciprofloxacin; 2) cefepime; 3) ceftazidime; 4) imipenem; 5) meropenem; 6) piperacillin/tazobactam; and 7) tobramycin.

Susceptibility test categorical interpretations were those of the NCCLS M100-S14 (2004) using ciprofloxacin categories to index probabilities of co-resistance. Ciprofloxacin criteria were: susceptible at ≤ 1 µg/ml, intermediate at 2 µg/ml and resistant at ≥ 4 µg/ml. The tested agents represent the most frequently used anti-pseudomonal agents in North American hospitals.

RESULTS

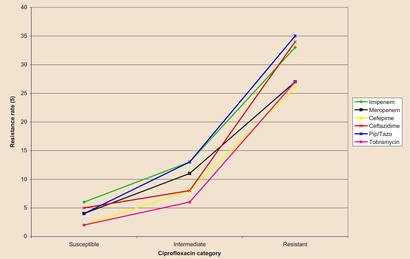
- Table 1 lists the susceptibility test results of the *P. aeruginosa* (1,111 strains) from the MYSTIC Programme. These isolates originated from a group of 15 USA hospitals, each using carbapenems routinely or as directed for elevated institutional resistance rates.

Table 1. Effects of ciprofloxacin susceptibility category on ß-lactam susceptibility patterns among 1,111 *P. aeruginosa* strains tested by reference MIC methods (MYSTIC Programme, 1999-2002).[a]

		MIC (µg/ml)		% by category	
Ciprofloxacin category	Antimicrobial agent	50%	90%	Susceptible	Resistant
Susceptible (835)					
	Ciprofloxacin	≤0.25	0.5	100.0	0.0
	Imipenem	1	4	91.0	5.7
	Meropenem	0.5	4	93.4	4.2
	Cefepime	4	8	92.6	1.8
	Ceftazidime	2	8	91.9	4.9
	Piperacillin/Tazobactam	8	32	96.3	3.7
	Tobramycin	≤1	≤1	98.1	1.6
Intermediate (53)					
	Ciprofloxacin	2	2	0.0	0.0
	Imipenem	2	16	75.5	13.2
	Meropenem	1	16	84.9	11.3
	Cefepime	8	16	79.2	7.5
	Ceftazidime	2	16	86.8	7.5
	Piperacillin/Tazobactam	8	128	86.8	13.2
	Tobramycin	≤1	2	94.3	5.7
Resistant (223)					
	Ciprofloxacin	>2	>2	0.0	100.0
	Imipenem	4	32	59.2	33.2
	Meropenem	2	32	59.6	26.5
	Cefepime	8	>16	51.1	25.6
	Ceftazidime	8	>16	55.6	34.1
	Piperacillin/Tazobactam	32	>128	65.0	35.0
	Tobramycin	≤1	>8	68.2	27.4

a. The overall ciprofloxacin susceptibility rate was 75.2% (resistance was 20.4%).

Figure 1. Mystic Programme (1,111 strains) comparisons of *P. aeruginosa* susceptibilities.



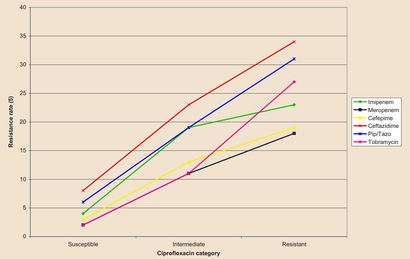
- The rank order of co-resistance probability among MYSTIC Programme *P. aeruginosa* isolates was (highest to lowest): piperacillin/tazobactam > ceftazidime > imipenem > tobramycin = meropenem > cefepime (Table 1; Figure 1). Rates of co-resistance for tobramycin, meropenem and cefepime were significantly lower ($p < 0.05$) when compared to the other three agents.

Table 2. Effects of ciprofloxacin susceptibility category on ß-lactam susceptibility patterns among 5,191 *P. aeruginosa* strains tested by reference MIC methods (SENTRY Program, 1997-2001).[a]

		MIC (µg/ml)		% by category	
Ciprofloxacin category	Antimicrobial agent	50%	90%	Susceptible	Resistant
Susceptible (3,977)					
	Ciprofloxacin	≤0.25	0.5	100.0	0.0
	Imipenem	1	4	92.8	4.1
	Meropenem	0.5	2	95.7	2.0
	Cefepime	2	8	91.3	3.1
	Ceftazidime	2	16	87.8	7.9
	Piperacillin/Tazobactam	4	32	94.4	5.6
	Tobramycin	0.5	1	97.2	2.2
Intermediate (310)					
	Ciprofloxacin	2	2	0.0	0.0
	Imipenem	2	>8	72.6	19.0
	Meropenem	1	>8	81.9	11.0
	Cefepime	8	>16	68.7	13.2
	Ceftazidime	4	>16	67.1	23.2
	Piperacillin/Tazobactam	8	>64	81.0	19.0
	Tobramycin	0.5	16	87.1	10.6
Resistant (904)					
	Ciprofloxacin	>2	>2	0.0	100.0
	Imipenem	2	>8	65.8	22.7
	Meropenem	2	>8	70.2	18.1
	Cefepime	8	>16	54.0	19.0
	Ceftazidime	8	>16	56.4	33.7
	Piperacillin/Tazobactam	16	>64	69.5	30.5
	Tobramycin	1	>16	70.0	26.7

a. The overall ciprofloxacin susceptibility rate was 76.6% (resistance was 17.4%).

Figure 2. SENTRY Program (5,191 strains) comparisons of *P. aeruginosa* susceptibilities.



- *P. aeruginosa* strains from MYSTIC Programme hospitals demonstrated progressively greater rates of co-resistance as the ciprofloxacin MICs increased from ≤ 1 µg/ml (susceptible) to ≥ 4 µg/ml (resistant). The increase in resistance for ciprofloxacin-intermediate strains compared to ciprofloxacin-susceptible isolates was markedly less than that observed for ciprofloxacin-resistant strains versus ciprofloxacin-intermediate isolates.

- Among SENTRY Program *P. aeruginosa* (5,191 strains), the co-resistance increases for each ciprofloxacin category was more linear (Figure 2). The rank order of co-resistances was also very similar as follows: ceftazidime > piperacillin/tazobactam > tobramycin > imipenem > cefepime > meropenem (Table 2). SENTRY Program isolates had a slight trend toward lower rates of MDR, attributed to the broader range of hospital types sampled, infection types and a wider mix of patient illness severity.

- Cefepime and meropenem consistently had the lowest likelihood of co-resistance in the *P. aeruginosa* strains in contrast to the most potent aminoglycoside, penicillin/ß-lactamase inhibitor combination, older carbapenem and ceftazidime (Tables 1 and 2; Figures 1 and 2).

CONCLUSIONS

- The probabilities of co-resistances can vary among *P. aeruginosa* and anti-pseudomonal agents because of:
  - local prevalence of resistance mechanisms (narrow or multiple)
  - characteristics of the utilized antimicrobials
  - selective anti-pseudomonal use in the clinical environment
- Two ß-lactams tested in two different surveillance programs (MYSTIC and SENTRY) had the lowest rates of co-resistances among the seven tested agents (ciprofloxacin analysis shown here). These agents were:
  - cefepime
  - meropenem
- Continued national and international surveillance should be a high priority to detect any changes in these established USA patterns of resistance, supplemented by locally derived antibiograms for empiric regimen choices.

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