# The peculiarities of *Pseudomonas aeruginosa* resistance to antibiotics and prevalence of serogroups

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Key words: Pseudomonas aeruginosa; resistance; antibiotics; serogroups.

**Summary.** Pseudomonas aeruginosa is one of the most common nonfermenting aerobic gramnegative microorganisms identified in clinical specimens of hospitalized patients. The emergence of multidrug-resistant (MDR) Pseudomonas aeruginosa strains is a growing concern in hospitalacquired infections. Typing of strains is important for identifying the sources of infection as well as prevention of cross-infections and monitoring of the efficacy of antimicrobial therapy. The aim of this study was to evaluate the antimicrobial resistance and prevalence of Pseudomonas aeruginosa serogroups isolated at Kaunas University of Medicine Hospital, Lithuania.

Material and methods. Minimum inhibitory concentrations of piperacillin, cefoperazone, ceftazidime, cefotaxime, cefepime, imipenem, meropenem, gentamicin, amikacin, tobramycin, and ciprofloxacin for 609 Pseudomonas aeruginosa strains isolated from various clinical specimens between November 2001 and November 2002 were determined by the microdilution method in Mueller–Hinton agar using interpretative guidelines of National Committee for Clinical Laboratory Standards. Serogroups of Pseudomonas aeruginosa strains were identified using serums of Seiken Co. Ltd (Tokyo, Japan), containing antibodies against antigens of Pseudomonas aeruginosa O-group.

Results. Pseudomonas aeruginosa strains were the most sensitive to ceftazidime (78.9%), imipenem (73.6%), meropenem (70.9%) and the most resistant to gentamicin (54.1%) and ciprofloxacin (52.5%). Multidrug-resistant strains made up 9.85% of all Pseudomonas aeruginosa strains investigated. Multidrug-resistant Pseudomonas aeruginosa strains were 1.5–3.5 times more resistant to antibiotics compared to non-multidrug-resistant strains, except to amikacin: multidrug-resistant strains were more sensitive (81.7%) than non-multidrug-resistant Pseudomonas aeruginosa strains (61.0%). Pseudomonas aeruginosa serogroups O:E and O:B were the most common serogroups (34.7% and 29.0%, respectively) followed by serogroups O:I (11.4%) and O:A (10.1%). Pseudomonas aeruginosa serogroup O:E strains were the most prevalent among multidrug-resistant strains (48.3%).

Conclusions. The results of our study show that serogroup O:E was the most prevalent serogroup of Pseudomonas aeruginosa in our hospital, and its resistance to antibiotics was the highest.

#### Background

In the second half of the last century, *Pseudomonas aeruginosa* has become an important hospital pathogen. This microorganism is prevalent in the hospital environment. *P. aeruginosa* is a commensal bacterium of normal human microflora, which is found on skin surfaces, in nostril, in upper respiratory tract. It colonizes the intestine of up to 40% of healthy people (1). This percentage increases among hospitalized patients proportionally with increasing duration of hospitalization (2, 3). That is why it is one of the most common microorganisms, obtained from clinical research material and causing hospital-acquired infections (HAI). According to the data of Center for Disease Control (USA), *P. aeruginosa* is the fifth most common pathogen among hospital microorganisms and causes 10% of all HAI (1, 4). For the treatment of HAI caused by *P. aeruginosa*, combinations of antibiotics are used. It is very important to know the trends of resistance of bacteria for the right choice of antibiotics for combined therapy (5, 6). Furthermore, *P. aeruginosa* needs minimal nutritional conditions for reproduction. Microorganisms growing in such an environment are much more viable than microorganisms growing in the envi-

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ronment where is no lack of nutrition (1, 2). Biological characteristics of *P. aeruginosa* strains, determining the resistance to external factors and quick progress of resistance to antibiotics and ability to spread in the environment, create conditions for multidrug-resistant (MDR) *P. aeruginosa* strains to survive, reproduce, and spread in the hospital. The current study investigated the antimicrobial resistance and prevalence of serogroups of *P. aeruginosa* isolated in Kaunas University of Medicine Hospital (KUMH), Lithuania.

# Material and methods

*P. aeruginosa* strains isolated from hospitalized patients at KUMH were collected at the Laboratories of Microbiology of KUMH and Kaunas University of Medicine, Lithuania, from November 15, 2001, to November 15, 2002. We excluded isolates collected within 2 days when they came from the same specimen source of the same patient. Isolates of *P. aeruginosa* were defined as being multidrug-resistant (MDR) phenotypes if they were resistant to more than two classes of antibiotics: cephalosporins (ceftazidime), aminoglycosides (gentamicin, amikacin), carbapenems (imipenem, meropenem), fluoroquinolones (ciprofloxacin). Finally, 609 *P. aeruginosa* strains were obtained: 549 *P. aeruginosa* strains and 60 MDR strains.

*Antibiotics*. The following antibiotics – carbenicillin, piperacillin, cefoperazone, ceftazidime, cefotaxime, cefepime, imipenem, meropenem, gentamicin, amikacin, tobramycin, and ciprofloxacin – were obtained as standard powders of known potency from their respective manufactures.

Bacteria and susceptibility testing. Clinical isolates of *P. aeruginosa* (n=609) initially were identified using routine methods: colonial/microscopic morphology and enzymatic characteristics. Minimum inhibitory concentrations (MICs) were determined by a microdilution method of the antimicrobial agent in Mueller-Hinton agar (Mueller-Hinton II Agar, BBL, Cockeysville, USA) according to the recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) (7). Inocula with a turbidity of a 0.5 McFarland standard were prepared from overnight cultures by suppressing the growth of bacteria in sterile Mueller-Hinton agar. Final inocula contained 10<sup>4</sup> CFU/spot. Plates were incubated overnight at 35°C. MIC was defined as the lowest concentration of an antimicrobial that inhibited the growth of microorganism. Breakpoints were those approved by the NCCLS (7). Reference P. aeruginosa strain ATCC 27853 was used for quality control.

*Establishment of the serogroups*. Serogroups of *P. aeruginosa* strains were identified using serums of Seiken Co. Ltd (Tokyo, Japan), containing antibodies against antigens of *P. aeruginosa* O-group. Live cells of *P. aeruginosa* were used. Agglutination, emerging as a consequence of antibody-antigen interaction, was evaluated macroscopically. If the reaction was weak or unclear, the test was repeated heating the cells of bacteria up to 120°C for 90 min. The principle of letter coding was applied, corresponding Lanyi and Bergan principle of digital coding (8).

Statistical analysis. Statistical analysis was performed using specialized program package SPSS (Statistical Package for Social Science, Microsoft Inc., USA, version 10.0 for Windows). A P value less than 0.05 was considered statistically significant. Evaluating the independence of two indications, criterion  $\chi^2$  was used.

# Results

During 2001–2002, 609 *P. aeruginosa* strains were obtained in KUMH units. More than half (59.0%) of *P. aeruginosa* recovered from clinical specimens of patients hospitalized in surgery units, 30.0% – in intensive care units, and 11.0% – therapy units. The low respiratory tract (36.4%) and pleura secret (23.4%) were the most frequent sources of this bacterium, followed by urine (7.8%), burn wounds (6.9%), wounds (6.6%), and other (18.9%) (P<0.05).

Table 1 presents the resistance of *P. aeruginosa* strains to penicillins, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones. From cephalosporins investigated, *P. aeruginosa* strains were the most sensitive to ceftazidime (78.9%); about half of *P. aeruginosa* strains were sensitive to other cephalosporins: cefoperazone (50.3%), cefotaxime (44.6%), and cefepime (60.8%). Strains were sensitive to carbapenems as well – to imipenem (73.6%) and meropenem (70.9%). *P. aeruginosa* strains were the most resistant to gentamicin among all aminoglycosides investigated (54.1%). More than half (52.5%) of *P. aeruginosa* were resistant to ciprofloxacin.

MDR strains made up 9.85% of *P. aeruginosa* investigated. More than half (61.7%) of MDR *P. aeruginosa* strains were detected in surgery units, 18.3% – in intensive care units, and 20.6% – in therapy units. The most common source of MDR strains was pleura secret (25.0%) and low respiratory tract (20.0%) followed by urine (15.0%), burn wounds (11.7%), wounds (6.7%), and other (21.6%) (P<0.05).

MDR strains were considerably more resistant to antibiotics than non-MDR *P. aeruginosa* strains. MDR strains were statistically significantly more resistant to cephalosporins: cefoperazone (58.3% vs. 34.1%, P<0.001), ceftazidime (45.0% vs. 12.8%, P<0.001), cefotaxime (68.3% vs. 23.3%, P<0.001), cefepime (58.3% vs. 20.2%, P<0.001); carbapenems: imipenem (73.3% vs. 23.9%, P<0.001), meropenem (25.0% vs. 11.3%, P<0.001); aminoglycosides: gentamicin (76.7% vs. 54.1%, P<0.001), tobramycin (60.0% vs. 31.7%, P<0.001); ciprofloxacin (80.0% vs. 52.7%, P<0.002). MDR strains were more sensitive to amikacin than non-MDR *P. aeruginosa* strains (18.3% vs. 39.0%, P<0.001) (Tables 1 and 2).

Of the 549 *P. aeruginosa* strains, 544 were serogrouped. Of the 14 serogroups established by the International Antigen Typing Scheme (IATS), 11 serogroups were identified: O:A (10.1%), O:B (29.0%), O:C (1.7%), O:D (1.8%), O:E (34.7%), O:F (1.7%). O:G (8.3%), O:H (0.7%), O:N (0.2%), O:I (11.4%), O:K (0.2%). Serogroups O:E and O:B were the most common among all *P. aeruginosa* serogroups investigated (P<0.05).

The resistance of the most prevalent serogroups to commonly used antipseudomonal antibiotics was

Antibiotic	S	Ι	R	MIC <sub>50</sub> ,	MIC <sub>90</sub> ,
	%	%	%	mg/Ľ	mg/Ĺ
Carbenicillin	18.8	12.6	46.1	512.0	4096.0
Piperacillin	52.4	_	47.6	64.0	512.0
Cefoperazone	50.3	15.7	34.1	8.0	512.0
Ceftazidime	78.9	8.4	12.8	2.0	32.0
Cefotaxime	44.6	32.1	23.3	32.0	1024.0
Cefepime	60.8	18.8	20.2	8.0	64.0
Imipenem	73.6	2.6	23.9	2.0	32.0
Meropenem	70.9	17.9	11.3	2.0	16.0
Gentamicin	30.2	15.7	54.1	16.0	512.0
Amikacin	45.9	15.1	39.0	32.0	256.0
Tobramycin	61.7	6.6	31.7	2.0	64.0
Ciprofloxacin	41.2	6.0	52.5	4.0	64.0

Table 1. Resistance rates of Pseudomonas aeruginosa strains to antibiotics

S – susceptible; I – intermediately resistant; R – resistant;  $MIC_{50}$  – minimal concentration, inhibits 50% of analyzed strains;  $MIC_{90}$  – minimal concentration, inhibits 90% of analyzed strains.

Table 2. Resistance rates of multidrug-resistant *Pseudomonas aeruginosa* strains to antibiotics

S – susceptible; I – intermediately resistant; R – resistant;  $MIC_{50}$  – minimal concentration, inhibits 50% of analyzed strains;  $MIC_{90}$  – minimal concentration, inhibits 90% of analyzed strains.

compared. Most piperacillin-resistant bacteria belonged to serogroups O:E and O:A compared to other serogroups (P<0.001). Bacteria of serogroups investigated were quite sensitive to ceftazidime except serogroup O:E, which was more resistant (25.7%) than other serogroups (P<0.02). More imipenem-resistant strains were observed only in serogroup O:B as compared to other serogroups (P<0.002). A few *P. aeruginosa* serogroups were resistant to meropenem. The strains of serogroups O:B and O:E were the most resistant to ciprofloxacin compared to the strains of other serogroups (P<0.001) (Table 3).

MDR *P. aeruginosa* strains belonged to seven serogroups: O:E (48.3%), O:B (25.0%), O:I (10.0%), O:A (8.3%), O:G (5.0%), O:N (1.7%), O:D (1.7%). Serogroup O:E was the most common among MDR *P. aeruginosa* strains (48.3%).

The resistance of serogroups of MDR *P. aeruginosa* strains to antibiotics was analyzed. Bacteria of serogroup O:E were statistically significantly more resistant to piperacillin as compared to serogroup O:B (P<0.001). *P. aeruginosa* serogroup O:E was more resistant to gentamicin than serogroup O:B (P<0.02). Bacteria of serogroup O:B were more resistant to imipenem in comparison with serogroup O:E (P<0.003). Serogroup O:E was more resistant to meropenem than serogroup O:B (P<0.02). The resistance of serogroups

O:B and O:E to ciprofloxacin was very similar, but these two serogroups were more resistant compared to serogroups O:I (P<0.004 and P<0.001, respectively) and O:G (P<0.001). The resistance rate of MDR strains of serogroup O:A to ceftazidime and meropenem was 20%. Bacteria of serogroup O:G were quite sensitive to all antibiotics except imipenem (66.7%). About half of serogroup O:I bacteria were resistant to piperacillin, gentamicin, amikacin, and imipenem, but only one-third of them were resistant to ceftazidime and ciprofloxacin; the most sensitive they were to meropenem. The resistance of *P. aeruginosa* serogroups O:D, O:N, and O:G was not analyzed due to small number of isolates, but it is presented in Table 4.

# Discussion

*P. aeruginosa* is inherently resistant to most penicillins, cephalosporins, tetracyclines, sulfonamides, chloramphenicol, and nalidixic acid. *P. aeruginosa* is naturally susceptible to aminoglycosides, antipseudomonal penicillins, cephalosporins, quinolones, and carbapenems. However, acquired antibiotic resistance of *P. aeruginosa* during treatment is a common phenomenon (1, 6, 9). This determines increased morbidity, mortality, and treatment costs (10–12).

As our research showed, *P. aeruginosa* strains were resistant to many antibiotics, and this just confirms

Table 3. Resistance rates of	Pseudomonas aerug	<i>inosa</i> serogroups to ant	tibiotics
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Sero-	N	Resistance, %						
group	Ν	Piperacillin	Ceftazidime	Gentamicin	Amikacin	Imipenem	Meropenem	Ciprofloxacin
O:A	55	60.0	8.9	35.7	33.9	14.3	7.1	38.2
O:B	159	10.8	3.1	47.8	38.4	38.4	10.1	58.2
O:E	189	91.8	25.7	85.3	44.5	22.0	20.4	80.1
O:G	45	5.0	2.2	26.7	37.8	17.8	2.2	15.6
O:I	62	25.0	11.4	15.9	34.9	14.3	1.6	11.1

Sero- group N	Ът	Resistance, %						
	Ν	Piperacillin	Ceftazidime	Gentamicin	Amikacin	Imipenem	Meropenem	Ciprofloxacin
O:A	5	60.0	20.0	80.0	-	100.0	20.0	60.0
O:B	15	13.3	_	53.3	_	100.0	6.7	93.3
O:D	1	100.0	_	100.0	100.0	100.0	_	100.0
O:E	29	88.5	75.9	93.1	24.1	58.6	37.9	89.7
O:G	3	33.3	33.3	35.3	_	66.7	_	33.3
O:N	1	100.0	100.0	100.0	_	100.0	100.0	100.0
O:I	6	50.0	33.3	66.7	50.0	50.0	16.7	33.3

the importance of this problem. According to the SENTRY antimicrobial surveillance program (1997–1999), in USA, 12.1–17.3% of *P. aeruginosa* strains were resistant to piperacillin, and in Europe, this percentage was 4.4–26.2% (13). During our study, significantly more strains resistant to piperacillin were obtained (47.6%). According to the data of the MYSTIC study (1998–2001), the resistance rates of *P. aeruginosa* to ceftazidime in Europe and USA were 29.6% and 13.1–18.2%, respectively (14, 15). In comparison with the above-mentioned studies, we found fewer strains resistant to ceftazidime (12.8%).

The results of our research show that 54.1% of *P. aeruginosa* strains were resistant to gentamicin. In Europe, according to the SENTRY data, this percentage was just 18.3% (13), in USA (according to MYSTIC data) – 15.0% (15). In our study, the percentage of *P. aeruginosa* strains resistant to gentamicin was lower (54.1%) in comparison with the data of studies performed in Russia (73.5%) (10) and Turkey (78.5%) (16). Amikacin is one of the most commonly prescribed aminoglycoside in the treatment of *P. aeruginosa* infection. According to the SENTRY data, the resistance of *P. aeruginosa* to amikacin was 3.1-6.5% (13). However, during our research, we obtained more *P. aeruginosa* strains resistant to amikacin (39.0%).

The resistance of *P. aeruginosa* to carbapenems differed: 23.9% of strains were resistant to imipenem, 11.3% – to meropenem. During European MYSTIC study, 31.8% of *P. aeruginosa* strains resistant to carbapenems were obtained, 7.0% in USA, 54.3% in Turkey, 6.7% in UK (15, 16). Russian study showed that 22.9% of *P. aeruginosa* strains were resistant to imipenem (10). Strains resistant to imipenem can be sensitive to meropenem (10). According to the data of the SENTRY program, 5.1–8.4% of *P. aeruginosa* strains obtained in Canada were resistant to meropenem, 10.2–26.2% in Europe, and 7.6–9.0% in USA (13, 15). The prevalence of *P. aeruginosa* strains resistant to meropenem in our study was similar as in Europe and USA.

The data of MYSTIC program show that in Europe, 36.7% of *P. aeruginosa* strains were resistant to ciprofloxacin, 37.2% in USA (15, 16). The results of our research show that more strains resistant to ciprofloxacin were obtained (52.7%).

It is quite hard to compare the data on the prevalence of MDR *P. aeruginosa* strains with the data of other investigators because the consensus definition of MDR strains is still missing.

The comparison of the activity of antibiotics ( $MIC_{50}$  and  $MIC_{90}$  values) against *P. aeruginosa* strains

and MDR strains showed that all antibiotics investigated were less effective in inhibiting the growth of MDR *P. aeruginosa* strains. Fewer MDR *P. aeruginosa* strains resistant just to amikacin were identified in comparison with non-MDR strains. Therefore, if isolates are resistant to other antibiotics, they may be susceptible to amikacin, and this antimicrobial could be used as one of the therapeutic options for treatment of MDR *P. aeruginosa* infections.

Serogrouping of *P. aeruginosa* is based on antigenic determinants of cell wall lipopolysaccharides. This is an appropriate method for the detection of sources of infection and evaluating the importance of various serogroups in infectious pathology of the patient (1, 17, 18). Researching *P. aeruginosa* in Japanese hospitals, it was shown that serogroups O:E and O:G (21.8%) were dominant (19), in France serogroups O:G (15.3%) and O:E (14.5%) (14), in Slovenia serogroups O:G (36.0%) and O:E (25.0%) (20), in Croatia – serogroup O:E (34.0%) (21). In our study, serogroups O:E and O:B were dominant. Of the 14 serogroups identified by IATS, 11 serogroups were found. There were no serogroups O:L, O:J, and O:M among *P. aeruginosa* strains investigated.

MDR *P. aeruginosa* strains belonged to seven serogroups. Serogroups O:C, O:F, O:H, and O:K identified among non-MDR strains were not observed. In our study, the most common serogroup among MDR *P. aeruginosa* strains was O: E serogroup. In the study done in Greece, MDR strains belonged to serogroups O:E and O:L (22), in Brazil – serogroup O:E (19). MDR *P. aeruginosa* belonged to serogroup O:L in France (14) and in intensive care units of Germany (12).

According to the literature, in the hospitals of many countries *P. aeruginosa* serogroups O:E, O:G, and O:I were dominant (4, 14, 17, 20). Serogroup O:E was the most common during the outbreaks; *P. aeruginosa* strains of the serogroup O:L were associated with high resistance to antibiotics (22). In our study, as mentioned before, the most common serogroups of MDR *P. aeruginosa* strains were O:E, O:B, O:I, O:A, and O:G; serogroup O:E was dominant among MDR and non-MDR *P. aeruginosa* strains. Thus, serogroups obtained during our research did not differ from the *P. aeruginosa* serogroups identified by researchers in medical institutions of other countries.

#### Conclusions

The present study and studies mentioned above affirm the importance of *P. aeruginosa*, as an etiological factor of infections. Identifying the serogroups of these bacteria is informative as an initial screening procedure in epidemiological studies. The analysis of the resistance of *P. aeruginosa* to antibiotics in our research showed the same trends in antibiotic resistance as in other European countries. However, in order to prevent the emergence of multidrug-resistant *P. aeruginosa* strains, it is necessary to improve the administration of antibiotics in the treatment of infections and, employing the methods of the determination of phenotype and genotype markers, to evaluate and control the sources and prevalence of multidrug-resistant strains in hospitals.

# Pseudomonas aeruginosa atsparumo antibiotikams ir serogrupių paplitimo ypatybės

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Raktažodžiai: Pseudomonas aeruginosa, atsparumas, antibiotikai, serogrupės.

Santrauka. Pseudomonas aeruginosa yra vienas dažniausių gramneigiamų aerobinių mikroorganizmų, nustatomų tiriamojoje medžiagoje. Pseudomonas aeruginosa padermių tipavimas leidžia nustatyti infekcijos šaltinį, kontroliuoti kryžmines infekcijas ir antimikrobinio gydymo veiksmingumą.

*Šio tyrimo tikslas* – įvertinti *Pseudomonas aeruginosa* atsparumą antibiotikams ir serogrupių paplitimą Kauno medicinos universiteto klinikose.

*Metodai*. Nustatyta minimali inhibicijos koncentracija šiems antibiotikams: karbenicilinui, piperacilinui, cefoperazonui, ceftazidimui, cefotaksimui, cefepimui, imipenemui, meropenemui, gentamicinui, amikacinui, tobramicinui, ciprofloksacinui – 609 *Pseudomonas aeruginosa* padermių, išskirtų iš įvairios tiriamosios medžiagos 2001/11–2002/11, serijinio skiedimo Mueller-Hinton agare metodu, vadovaujantis NCCLS (angl. *National Committee for Clinical Laboratory Standards*) rekomendacijomis bei kriterijais. *Pseudomonas aeruginosa* serogrupė pagal O antigeną nustatyta naudojant Seiken Co. Ltd (Tokyo, Japan) serumus su specifiniais antikūnais prieš *Pseudomonas aeruginosa* O antigenus.

*Rezultatai. Pseudomonas aeruginosa* padermės jautriausios ceftazidimui (78,9 proc.), imipenemui (73,6 proc.), meropenemui (70,9 proc.), atspariausios gentamicinui (54,1 proc.) ir ciprofloksacinui (52,5 proc.). Dauginio atsparumo antibiotikams padermės sudarė 9,85 proc. tirtų *Pseudomonas aeruginosa* padermių. Dauginio atsparumo antibiotikams *Pseudomonas aeruginosa* padermės 1,5–3,5 karto atsparesnės antibiotikams, lyginant su padermėmis, nepasižyminčiomis dauginiu atsparumu antibiotikams padermės yra jautresnės (81,7 proc.) lyginant su padermėmis, nepasižyminčiomis dauginiu atsparumu antibiotikams (61,0 proc.). Dažniausiai nustatytos 4 *Pseudomonas aeruginosa* serogrupės: O:E (34,7 proc.), O:B (29,0 proc.), O:I (11,4 proc.), O:A (10,1 proc.). Tarp dauginio atsparumo antibiotikams padermių vyrauja O:E (48,3 proc.) *Pseudomonas aeruginosa* serogrupė.

*Išvados*. Nustatyta, kad daugiausia paplitusios ir atsparios antibiotikams yra O:E serogrupės *Pseudomonas aeruginosa* padermės.

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