Changes in Antibiotic Resistance Level of Nosocomial *Pseudomonas Aeruginosa* Isolates in the Largest University Hospital of Lithuania

Dalia Adukauskienė[1], Agnė Vitkauskaitė[2], Erika Skrodenienė[3], Asta Dambrauskienė[3], Astra Vitkauskienė[3]

[1]Department of Intensive Care, Medical Academy, Lithuanian University of Health Sciences, [2]Faculty of Medicine, Medical Academy, Lithuanian University of Health Sciences, [3]Department of Laboratory Medicine, Medical Academy, Medicine of Lithuanian University of Health Sciences, Lithuania

Key words: *resistance level of Pseudomonas aeruginosa to antibiotics; multidrug resistance; minimum inhibitory concentration.*

Summary. *The aim was to estimate changes in the resistance rates of Pseudomonas aeruginosa (P. aeruginosa) strains isolated from patients treated in intensive care units of the largest university hospital.*

Materials and Methods. Isolates were identified with the Phoenix ID system (Becton Dickinson, USA). The minimum inhibitory concentration (MIC) of ceftazidime, ciprofloxacin, and amikacin were determined by the E-test and evaluated following the recommendations of the Clinical Laboratory Standards Institute.

Results. In 2003, the proportion of P. aeruginosa strains resistant to piperacillin was greatest followed by strains resistant gentamicin and ciprofloxacin. In 2008, the resistance rates markedly changed being the highest to ciprofloxacin. An increase in the resistance rates to ciprofloxacin (+24%, P<0.001) and ceftazidime (+8.3%, P<0.05) was documented. In 2003, there were 66.7% of P. aeruginosa strains sensitive to all antibiotics tested, and this percentage decreased to 47.5% in 2008 (P<0.05). During the study, a significant increase in the median MICs for ciprofloxacin and amikacin was observed (P<0.001); however, no significant change was documented for ceftazidime.

Conclusions. P. aeruginosa remains an important nosocomial pathogen with relatively high overall resistance to antimicrobial agents, and the resistance level is increasing.

Introduction

Pseudomonas aeruginosa (*P. aeruginosa*) is identified as a microorganism of normal microflora in healthy individuals, but it may cause severe infections in a critically ill and immunocompromised host. Resistance rates of *P. aeruginosa* to antibiotics are increasing annually and vary in different settings: outpatients, inpatients, intensive care unit (ICU) patients, patients with cystic fibrosis, etc., moreover, it differs from country to country (1, 2). Despite of advances in hospital care and introduction of a wide variety of antimicrobial drugs in clinical practice, it remains a dominative nosocomial pathogen in an ICU, particularly in mechanically ventilated patients (3–5). Nosocomial pneumonia takes part in more than half of all infections acquired in an ICU, and often *P. aeruginosa* is isolated as a causative microorganism (6, 7). Treatment of *P. aeruginosa* infections is usually difficult; mortality rates are high (3, 8). Worse prognosis related to higher virulence of a pathogen was reported (4), and pathogens such as *P. aeruginosa* were found to be associated to excess mortality, especially in case of ventilator-acquired pneumonia (9). Inappropriate antimicrobial treatment is proven to increase mortality of ICU patients as well, and it is associated with the resistance of clinically important pathogens such as *P. aeruginosa* (4, 10, 11). They are resistant to many antibiotics such as antipseudomonal penicillins, third-generation cephalosporins, fluoroquinolones, and aminoglycosides. Acquired *P. aeruginosa* drug resistance is frequently observed among nosocomial isolates, and it often involves more than one antibiotic class (12, 13). Emergence of the evolution of antibiotic-resistant mutants in bacterial population under antibiotic selective pressure and development of multidrug resistance (MDR) of *P. aeruginosa* has become a major social issue because of increased costs of treatment and poor outcome (1, 6, 14–16). MDR is identified more frequently, and isolates of *P. aeruginosa* resistant to all antipseudomonal agents (extreme drug resistance, XDR) are being increasingly reported (17). The easy and changing acquisition of resistance in *P. aeruginosa* requires setting-specific surveillance, which is crucial for guiding physicians on the probable susceptibility in their patients especially when treating nosocomial infections, predicting future local trends,

Correspondence to A. Vitkauskienė, Department of Laboratory Medicine, Medical Academy, Lithuanian University of Health Sciences, Eivenių 2, 50028 Kaunas, Lithuania
E-mail: astravitka@hotmail.com

Adresas susirašinėti: A. Vitkauskienė, LSMU MA Laboratorinės medicinos klinika, Eivenių 2, 50028 Vilnius
El. paštas: astravitka@hotmail.com

and comparing with situation in other countries.

The aim of our study was to estimate the dynamics in the resistance rates of *P. aeruginosa* strains isolated from patients in the ICUs of the Hospital of Lithuanian University of Health Sciences (HLUHS) (former Kaunas University of Medicine), the largest university hospital of Lithuania, by analyzing the resistance rates in 2008 and comparing them with those in 2003, which provides a reference for the estimation of increasing resistance. As the hospital had more than 2200 beds (counting 3 million population of the country) during the study, we assumed our data to be representative of the general status for Lithuania.

Materials and Methods

The present study investigated the sensitivity of all *P. aeruginosa* strains isolated from the respiratory tract of all patients (n=191) treated in ICUs (one isolate per patient) of the HLUHS during years 2003 (n=90) and 2008 (n=101). Isolates were defined as nosocomial if a patient spent more than 48 hours in the hospital. *Pseudomonas* strains were selected on *Pseudomonas* agar with cetrimide (Liofilchem, Italy) according to the manufacturer's instructions for the identification of *P. aeruginosa*. Cetrimide inhibits a wide variety of bacterial species including *Pseudomonas* species other than *P. aeruginosa*. It develops a blue-green pigment due to pyocyanin and fluorescein production. Isolates suspected to be *P. aeruginosa* or not clearly showing blue-green pigment were further identified with the Phoenix ID system (Becton Dickinson, USA) to confirm the strains of *P. aeruginosa*. Antimicrobial susceptibility of all the isolates was tested against piperacillin (100 μg), piperacillin/tazobactam (100 μg/10 μg), ceftazidime (30 μg), cefepime (30 μg), ciprofloxacin (5 μg), gentamicin (10 μg), and amikacin (30 μg) (Becton Dickinson, USA) by the Kirby-Bauer disc diffusion method on Mueller-Hinton agar following the recommendations of the Clinical Laboratory Standards Institute (17). A number of paper discs, each impregnated with a calibrated concentration of an antibiotic, were placed onto an agar plate inoculated with bacteria. A visible zone of growth inhibition of susceptible bacteria formed around some discs according to their antibiotic concentration. The prevalence of MDR was investigated among isolates of *P. aeruginosa* tested with piperacillin, ceftazidime, ciprofloxacin, and gentamicin. Isolates resistant to three or all four of mentioned antimicrobials like representatives of different classes of antibiotics with antipseudomonal activity were considered MDR.

The minimum inhibitory concentrations (MICs) of ceftazidime, ciprofloxacin, and amikacin were determined by the E-test (AB Biodisk, Solna, Sweden) according to manufacturer's instructions and evaluated following the recommendations of the Clinical Laboratory Standards Institute (18). An E-test strip, which contains a gradient of an antibiotic, was placed on an inoculated agar plate, and the pattern of bacterial growth was examined after 24 hours. In using a gradient of an antibiotic, the E-test has a greater precision than the disc diffusion method, allowing better ascertainment of the actual MIC (18). The E-test was used to estimate so-called MIC creep, i.e., an increase in MICs of *P. aeruginosa* strains for tested antibiotics in 2003 and 2008 over time, as it reflects a decreased sensitivity to antibiotics and is associated with decreased clinical efficacy of antibiotics and higher mortality rates.

Statistical Analysis. Comparison of means between groups was performed by using the Student *t* test or Mann-Whitney *U* test (nonparametric values). Proportions were compared using the chi-square or Fisher exact test. Differences were considered significant at $P<0.05$. The statistical package SPSS 13.0 for Windows release was used for data analysis.

Results

The numbers of *P. aeruginosa* isolates resistant to tested antibiotics by the disc diffusion method in years 2003 and 2008 are shown in Table 1. In 2003, the proportion of *P. aeruginosa* strains resistant to piperacillin was greatest (23.3%, n=21), followed by strains resistant gentamicin (20.0%, n=18) and ciprofloxacin (15.6%, n=14). In 2008, the resistance rates markedly changed being the highest to ciprofloxacin (39.6%, n=40) followed by gentamicin (19.8%, n=20) and piperacillin (17.8%, n=18). There was a significant increase in resistance to ciprofloxacin (+24%, $P<0.001$) and ceftazidime (+8.3%, $P<0.05$) during the study period. The resistance of *P. aeruginosa* strains to piperacillin (–4.4%) and piperacillin/tazobactam (–5.5%) showed an insignificant trend to decline and to cefepime (+4.5%) and amikacin (+1.5%) to increase.

In 2003, the percentage of *P. aeruginosa* strains sensitive to all tested antibiotics was 66.7% (60/90) and it decreased to 47.5% (48/101) in 2008 ($P<0.05$).

Table 2 summarizes the contribution of piperacillin-, ceftazidime-, ciprofloxacin-, and gentamicin-resistant (as representatives of different antibiotic classes with antipseudomonal activity) *P. aeruginosa* strains to the development of MDR phenotypes. In 2003, the percentage of *P. aeruginosa* strains sensitive to all tested antibiotics was higher than resistant to one, two, or three-four antibiotics (68.9% vs. 8.9%, 14.4%, and 7.8%; $P<0.05$), and the ratio of sensitive to resistant strains was found to be decreased in 2008 (52.5% vs. 19.8%, 14.9%, and 12.9%; $P<0.05$). The percentage of MDR *P. aeruginosa* strains increased insignificantly from 7.8% (7/90) in 2003 to 12.9% (13/101) in 2008 ($P=0.25$).

Table 3 presents changes in the prevalence of nosocomial *P. aeruginosa* isolates, sensitive to different antibiotics, with MIC of $\leqslant$ median MIC of year 2003 comparing years 2003 and 2008. In 2008,

Table 1. Changes in the Percentages of *Pseudomonas aeruginosa* Nosocomial Isolates Resistant to Tested Antibiotics in the Intensive Care Units of HLUHS in 2003 and 2008

Antimicrobial Agent	Resistant Isolates, n (%)		*P*
	2003 n=90	2008 n=101	
Piperacillin	21 (23.3)	18 (17.8)	0.35
Piperacillin/tazobactam	12 (13.3)	9 (8.9)	0.33
Ceftazidime	5 (5.6)	14 (13.9)	0.05
Cefepime	4 (4.4)	9 (8.9)	0.22
Ciprofloxacin	14 (15.6)	40 (39.6)	<0.001
Gentamicin	18 (20.0)	20 (19.8)	0.97
Amikacin	4 (4.4)	6 (5.9)	0.64

Table 2. Changes in the Contribution of Piperacillin-, Ceftazidime-, Ciprofloxacin- and Gentamicin-Resistant *P. aeruginosa* Strains to the Development of Multidrug Resistant Phenotypes

Year and Number of Isolates	Antibiotics to Which Isolates Were Resistant, n	Isolates, n (%)	Isolates Resistant to Antibiotics, n (%)			
			Piperacillin	Ceftazidime	Ciprofloxacin	Gentamicin
2003, N=90	0	62 (68.9)[a]	0	0	0	0
	1	8 (8.9)[b]	6 (75.0)	0	2 (25.0)	0
	2	13 (14.4)[b]	8 (61.5)	1 (7.7)	6 (46.2)	11 (84.6)
	3–4	7 (7.8)[b]	7 (100)	4 (57.1)	6 (85.7)	7 (100)
2008, N=101	0	53 (52.5)[c]	0	0	0	0
	1	20 (19.8)[d]	1 (5.0)	1 (5.0)	14 (70.0)	4 (20.0)
	2	15 (14.9)[d]	9 (60.0)	2 (13.3)	14 (93.3)	5 (33.3)
	3–4	13 (12.9)[d]	8 (61.5)	11 (84.6)	12 (92.3)	11 (84.6)

P<0.05, a compared with b and c compared with d.

Table 3. Changes in the Percentages of *Pseudomonas aeruginosa* Nosocomial Isolates Sensitive to Different Antipseudomonal Antibiotics With the MIC Values of ⩽ Median MIC in 2003

Antimicrobial Agent	Median MIC in 2003, μg/mL	Isolates With MIC of ⩽ Median MIC in 2003, n (%)		*P*
		2003 N=90	2008 N=101	
Ceftazidime	2.0	62 (68.9)	68 (67.3)	0.82
Ciprofloxacin	0.125	65 (72.2)	38 (37.6)	<0.001
Amikacin	4.0	69 (76.7)	44 (43.6)	<0.001

MIC, minimum inhibitory concentration.

there was a significant increase in the percentages of isolates with MIC of ⩽ median 2003 MIC for ciprofloxacin and amikacin, but the change in the percentage of strains with MIC of ⩽ median 2003 MIC for ceftazidime was insignificant.

Variation in the MIC of ceftazidime, ciprofloxacin, and amikacin for *P. aeruginosa* strains during the 5-year study (MIC creep) is shown in Figs. 1–3.

Discussion

Increasing resistance rates of *P. aeruginosa* strains, particularly hospital strains, to different antipseudomonal agents have been reported worldwide, and it presents a serious therapeutic problem in the management of diseases due to these organisms (19, 20). Susceptibility of *P. aeruginosa* isolates from the HLUHS to various antibiotics was examined in our study. There is a clear trend toward an increase in resistance in all classes of antibiotics as the resistance level in general, which is significantly expressed in some classes of antipseudomonal drugs.

In our study, the resistance to piperacillin decreased insignificantly from 23.3% in 2003 to 17.8% (–5.5%) in 2008. The same decline of 4.4% in resistance to piperacillin/tazobactam was documented. In our opinion, decreased resistance to piperacillin and piperacillin/tazobactam can be associated with the restricted usage of this β-lactam antibiotic in our hospital recently. The similar resistance to piperacillin and piperacillin/tazobactam was found in Belgium (24.0% and 17.5%) and Greece (20.2% and 18.6%) (1, 19). Much higher resistance to piperacillin was observed in Russia (79.0%) (21). The lower resistance to piperacillin was in Italy (12.0%) and Spain (10.0%) (22, 23). The lower resistance to piperacillin/tazobactam was found in the United Kingdom and Ireland and in the United States (5.2% and 8.4%, respectively) (10, 24). The United States reports low resistance rates to piperacillin/tazobactam, and the study by Mutnick et al. has revealed further decreasing resistance to piperacillin/tazobactam (–2.5%) (24).

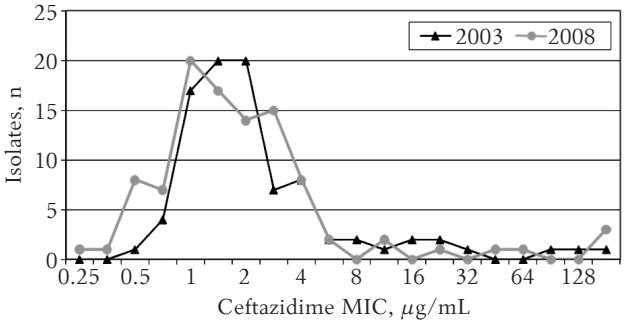

Fig. 1. Ceftazidime minimum inhibitory concentration (MIC) creep during 5 years of study

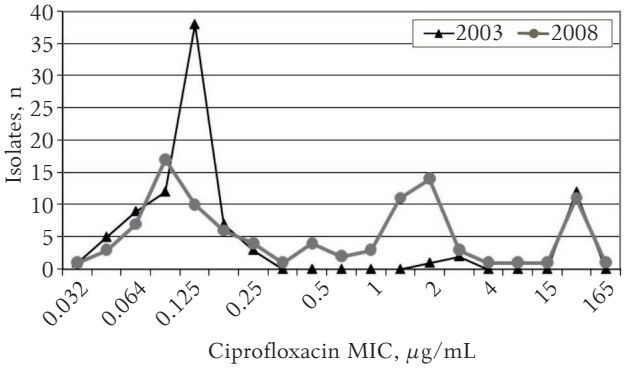

Fig. 2. Ciprofloxacin minimum inhibitory concentration (MIC) creep during 5 years of study

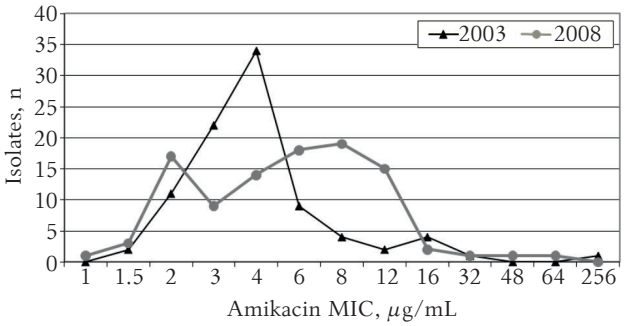

Fig. 3. Amikacin minimum inhibitory concentration (MIC) creep during 5 years of study

In our study, the resistance to ceftazidime increased significantly from 5.6% in 2003 to 13.9% in 2008 (+8.3%) (P=0.05). The documented resistance rate to ceftazidime (13.9%) is close to that observed in the study by Bonfiglio et al. from Italy (13.4%) and Bouza et al. from Spain (15.0%) (22, 23). Data of the studies from Belgium and Greece showed the resistance to ceftazidime to be twofold higher than in our study: 28.5% and 25.5%, respectively (1, 19). In some other countries such as the United Kingdom and Ireland, France, and the United States, the resistance to ceftazidime was lower than in Lithuania (3.8%, 6.2%, and 9.7%, respectively), and a 1.2% decrease was documented in the United States from 1999 to 2002 (10, 24, 25). An increase in the ceftazidime MIC for *P. aeruginosa* strains over time is a phenomenon, known as ceftazidime creep. The prevalence of *P. aeruginosa* strains with MIC values of 1–2 μg/mL changed during 6 years, and the level of resistance to ceftazidime increased as strains with raised MIC became dominant (2–6 μg/mL). Higher MIC is associated with higher mortality rates, and it was reported that even small increases in MIC below the susceptibility breakpoint could affect the clinical efficacy of antibiotics (26).

In our study, the resistance rate to ciprofloxacin increased significantly from 15.6% in 2003 to 39.6% in 2008 (+24%, P<0.001). An MIC creep during the 6-year study was observed as the predominance of *P. aeruginosa* strains with the MIC values of 0.125–0.25 μg/mL in 2003 changed to the predominance of *P. aeruginosa* strains with the MIC values of 1–3 μg/mL and 15–165 μg/mL in 2008. High resistance to ciprofloxacin has been reported worldwide: in Greece, 18.6%; in United States, 22.7% (increase, +10.8%); in Spain, 23.0%; in Belgium, 24.0%; and in Italy, 31.9% (1, 19, 22–24). Only in the United Kingdom and Ireland, the resistance to ciprofloxacin was estimated to be constant (7.4%) (10). Fluoroquinolones, such as ciprofloxacin, are broad-spectrum antimicrobials widely used to treat different infections (27). The broad use of them has led to increased resistance rates of *P. aeruginosa* strains to fluoroquinolones as well as increased multidrug resistance. This causes a serious problem in clinical practice (28).

The resistance to gentamicin in our study did not change: 20.0% in 2003 and 19.8% in 2008. In Spain and the Russian Federation, the resistance rates to gentamicin were higher (31.0% and 75.0%, respectively) (21, 23), but in the United States and the United Kingdom and Ireland – lower (8.4% and 6.3%, respectively) (10, 24).

The resistance rate of *P. aeruginosa* strains to amikacin was 5.9% in our study. In 2003, the MIC values of *P. aeruginosa* strains for amikacin were 2–6 μg/mL, and during the study period, it increased as strains with raised MIC (4–12 μg/mL) became dominant. This MIC creep confirms the level of resistance to amikacin to be increased. In Belgium, Italy, and Spain, the resistance rates to amikacin were higher reaching 9% to 10% (1, 22, 23), while the highest resistance rate to amikacin was reported in Greece (27.5%) (19).

Belgium scientists reported that despite the resistance of *P. aeruginosa* to penicillins, cephalosporins, fluoroquinolones, and aminoglycosides varies among Belgian hospitals, the level of resistance is increasing in general (1). The surveys carried out in Italy and Spain documented the resistance rates of *P. aeruginosa* similar to our study, and an increase in resistance to vast majority of antibiotic classes is being observed as well (22, 23).

The percentage of *P. aeruginosa* strains sensitive to all tested antibiotics significantly decreased from 66.7% (60 of the 90) in 2003 to 47.5% (48 of the 101) in 2008 ($P<0.05$).

In our study, MDR rate increased from 7.1% in 2003 to 12.8% in 2008 (+5.7%). The same trend was found in the US study (29). Several studies have showed that previous antibiotic use increases the risk of a *P. aeruginosa* infection resistant to many commonly used antimicrobials especially fluoroquinolones (15, 30).

A significant increase in MICs for ciprofloxacin and amikacin was documented as the percentage of isolates with MIC lower than median MIC markedly decreased in 2008 as compared with 2003, and it was not a case for ceftazidime.

Antimicrobial drug use is one of the well-established risk factors for the development of antimicrobial resistance (24). Substantial regional variations in the resistance patterns worldwide have been observed, and it is probably related to the different antibiotic treatment regimens used traditionally in different countries (31, 32).

Surveillance of the resistance level of *P. aeruginosa* strains, so called "difficult to treat pathogen," gives clinicians a better understanding of epidemiologic status in a particular setting and allows making an adequate empirical choice of antibiotics in the treatment of life-threatening pseudomonal infections especially in the ICU.

Conclusions

P. aeruginosa remains an important nosocomial pathogen with relatively high overall resistance to the antimicrobial agents in patients who were treated in an intensive care unit. The resistance level of *P. aeruginosa* to ciprofloxacin and amikacin increased during the 5-year period. The resistance to ceftazidime increased more than twofold.

Statement of Conflict of Interest

The authors state no conflict of interest.

Pseudomonas aeruginosa nozokominių padermių atsparumo antibiotikams lygmens pokyčiai didžiausioje Lietuvos universitetinėje ligoninėje

Dalia Adukauskienė[1], Agnė Vitkauskaitė[2], Erika Skrodenienė[3], Asta Dambrauskienė[3], Astra Vitkauskienė[3]

[1]Lietuvos sveikatos mokslų universiteto Medicinos akademijos Intensyviosios terapijos klinika,
[2]Lietuvos sveikatos mokslų universiteto Medicinos akademijos Medicinos fakultetas,
[3]Lietuvos sveikatos mokslų universiteto Medicinos akademijos Laboratorinės medicinos klinika

Raktažodžiai: *Pseudomonas aeruginosa* atsparumo antibiotikams lygmuo, dauginis atsparumas, minimali slopinamoji koncentracija.

Santrauka. *Tyrimo tikslas* – įvertinti *Pseudomonas aeruginosa* padermių, išskirtų pacientams, gydytiems didžiausios universitetinės ligoninės intensyviosios terapijos skyriuose, atsparumo antibiotikams lygmens pokyčius.

Tyrimo metodika. Išskirtos padermės identifikuotos naudojant automatinę „Phoenix ID" sistemą (Becton Dickinson, JAV). Atsparumo lygmens pokytis buvo vertintas E testo metodu nustačius minimalią slopinamąją koncentraciją ceftazidimui, ciprofloksacinui ir amikacinui. Gauti duomenys interpretuoti remiantis Klinikinės laboratorijos standartų instituto rekomendacijomis.

Rezultatai. 2003 metais *P. aeruginosa* padermės dažniausiai buvo atsparios piperacilinui, rečiau gentamicinui ir ciprofloksacinui. 2008 metais atsparumas antibiotikams gerokai pakito. Per penkerius studijos metus atsparumas reikšmingai padidėjo ciprofloksacinui (+24 proc., p<0,001) ir ceftazidimui (+8,3 proc., p<0,05). 2003 m. buvo rasta 66,7 proc. *P. aeruginosa* padermių, jautrių visiems tirtiems antibiotikams, tuo tarpu 2008 m. nustatyta tik 47,5 proc. (p<0,05). Per penkerius metus reikšmingai padidėjo *P. aeruginosa* padermių minimalios slopinamosios koncentracijos mediana ciprofloksacinui ir amikacinui, tačiau reikšmingo minimalios slopinamosios koncentracijos pokyčio ceftazidimui nenustatėme.

Išvados. P. aeruginosa išlieka svarbiu nozokominių pneumonijų sukėlėju intensyviosios terapijos skyriuje gydomiems pacientams. Jo atsparumas antibiotikams yra santykinai didelis ir atsparumo antibiotikams lygmuo didėja.

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