ANTIBACTERIAL RESISTANCE PATTERNS AND INCIDENCE OF NOSOCOMIAL PSEUDOMONAS AERUGINOSA BACTEREMIA IN A TERTIARY-CARE EDUCATIONAL HOSPITAL IN TURKEY: A PERSPECTIVE BETWEEN 2001 AND 2019

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ABSTRACT

Background*: Pseudomonas aeruginosa (PSA) is one of the most important pathogens causing nosocomial bacteremia in most parts of the world.*

Objectives*: In this study it was aimed to evaluate the resistance patterns and incidence of microbiologically confirmed nosocomial bacteremia (MCNB) related PSA strains between 2001-2019.*

Methods*: Any patient in whom PSA was isolated in at least one set of blood cultures (sent to the bacteriology laboratory 72h after hospital admission) was considered to have microbiologically confirmed NB. Blood cultures were performed on Back/Alert (bioMerieux, Durham, NC). Bacterial identifications were performed by automated API (bioMerieux, Durham, NC). Antibacterial susceptibility tests were evaluated according to Clinical Laboratory Standards Institute (CLSI) criteria until 2014 and EUCAST between 2015 and 2019. Incidence density of PSA MCNB was calculated by using hospital electronic database.*

Results*: A total of 1705 strains of P.aeruginosa fulfilling study inclusion criteria, were isolated during the 19-year study period in the hospital from intensive care units and clinics and included in the study. When the 2001–2002 and 2018–2019 periods were compared, there was a decrease in resistance to meropenem and amikacin (31.1%-20.4% p: 0.025 and 34.3%-22.8% p:0.029). However, the analysis of the resistance patterns of carbapenem-resistant P. aeruginosa strains as a subgroup (2001-2002) vs (2018 vs 2019), ciprofloxacin and cefepime resistance rates increased significantly (58%-79% p:0.0096 and 46%-72% p: 0.026). P. aeruginosa bacteremia rates incidence density rates ranged between 0.11 and 0.30 episodes per thousand hospital day during the study period.*

Conclusion*: During the 19 years there was a significant decrease in amikacin and meropenem resistance while there was a significant increase in the subgroup of carbapenem-resistant strains. More infection control and antimicrobial stewardship efforts are needed to decrease the antibacterial resistance rates and incidence.*

Keywords: *Bacteremia, nosocomial Infection, Pseudomonas aeruginosa, carbapenem resistance, infection control.*

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Introduction

Pseudomonas aeruginosa is one of the major causes of opportunistic and nosocomial infections in most parts of the world. It is associated with increased morbidity, mortality and longer hospitalization[(1)]. Healthcare-associated *P. aeruginosa* infection or antibiotic resistance rates (such as cephalosporins, beta lactam-beta lactamase inhibitors, carbapenems, aminoglycosides, quinolones, and colistin) differ among to countries, cities, hospitals, and years across the world[(2-5)]. Ten, 50, and 90 percentile carbapenem-resistance rate in P. aeruginosa strains causing healthcare-associated infections in Turkish tertiary-care university hospitals were 12.59%, 35.92% and 60.16% in 2019, respectively while overall cumulative carbapenem-resistance was 34.92% (463 hospitals, 1849/5295 strains)[(6)]. While appropriate empirical therapy may be associated with increased survival, inappropriate therapy is

associated with mortality in the management of severe healthcare-associated infections[1]. Periodic antibiotic susceptibility screening is important to establish the most rational empirical therapy choices and to evaluate the resistance dynamics. Herein, we analysed the antibacterial resistance patterns and the incidence of microbiologically confirmed nosocomial bacteremia (MCNB) related to P. aeruginosa strains between 2001 and 2019 retrospectively.

Material and methods

Our setting is a 1809 bedded tertiary-care educational hospital, 198 of which are in ICUs.

Any patient in whom *P. aeruginosa* was isolated in at least one set of blood cultures (sent to the bacteriology laboratory 72 h after hospital admission) was considered to have MCNB. Data of antibacterial resistance and hospital admission dates were extracted from hospital patient record database[7,8]. Resistance patterns of *P. aeruginosa* strains isolated from hospital wide MCNB patients between 2001 and 2019 were evaluated retrospectively. Double or more isolates during each episode were counted as one episode and the 1st isolate was included in the study.

Blood cultures were performed on BACT/ALERT system (bioMerieux, Durham, NC). Conventional methods, automated system (VITEK 2 bioMérieux, France) and after the year 2012, MALDI-TOF®MS (VITEK MS, bioMérieux, France) were used for bacterial identification. Kirby Bauer disc diffusion method and automated system (VITEK 2 bioMérieux, France) were used for determination of antibiotic susceptibility. Antibiotic susceptibility of strains were performed and evaluated according to CLSI until 2014 and EUCAST between 2015 and 2019[9, 10].

Furthermore, data of the number of overall hospitalized patients and the total patient days for each year between 2001 and 2019 were extracted from the hospital electronic records. By using those parameters, we calculated the nosocomial P.aeruginosa bacteremia annual incidence for every 1000 patient days and 1000 patients (7).

Resistance patterns were compared by χ^2 test with Yate's correction test and χ^2 test by using SPSS 25.0. A p-value <0.05 was considered to be significant[7].

The Institutional Review board approved the study (Decision date: 1/8/2019, decision number: 19-7T/56)

Results

A total of 1705 MCNB causing P.aeruginosa strains fulfilling the study inclusion criteria during the 13-year study period, were included in the study.

Antimicrobial resistance rates of the study strains during the 19-year study period are listed in Table 1. Minimum and maximum resistance rates for amikacin, ciprofloxacin, ceftazidime and meropenem ranged between 13.8%-33.8%, 10.9%-41.7%, 7.44%-38%, and 9.4%-65.7%, respectively (Table 1).

Comparison of the 2001–2002 and 2018–2019 periods resulted in a significant decrease in resistance to meropenem and amikacin (p: 0.025 and p:0.029) (Table 2).

When we analysed the resistance patterns of carbapenem-resistant P. aeruginosa strains as a separate group (2001-2002) vs (2018 vs 2019), cefepime and ciprofloxacin resistance rates increased significantly (Table 3).

Evaluation of the total P. aeruginosa MCNB rates per 1000 days and 1000 patients showed an increase in the 2005-2010 period (Table 4; Figure 1). Incidence density rates ranged between 0.11 and 0.30 episodes per thousand hospital day. Total nosocomial P. aeruginosa MCNB incidence and total carbapenem-resistant P. aeruginosa MCNB per patient in the 2001–2002 period vs. the 2018–2019 period did not change significantly (p:0.723 and p:0.063) (Table 4).

Discussion

In addition to being naturally resistant to many antibiotics, P.aeruginosa may also develop multiple-drug resistant (MDR) strains during antibiotic therapy. Related resistance mechanisms are mainly the release of beta-lactamases, reduction of outer membrane permeability, and active external pumping systems. When active external pumping systems are activated by chromosomal beta-lactamases, or via other mechanisms, resistance to many antibiotics, including carbapenems codevelop. More importantly, this mechanism may get activated during treatment and thus MDR strains may appear[11].

Nosocomial infections are among important health problems in Turkey as well as the whole world. They cause increased economic costs, morbidity, and mortality rates. In a multicenter study conducted in Turkey in 1997, seven university hospitals and one large community hospital from six different

	Resistance rate (%)																		
	2001 (n=71)	2002 (n=65)	2003 (n=55)	2004 (n=74)	2005 (n=66)	2006 (n=80)	2007 (n=93)	2008 (n=95)	2009 (n=85)	2010 (n=105)	2011 (n=101)	2012 (n=67)	2013 (n=100)	2014 (n=94)	2015 (n=110)	2016 (n=104)	2017 (n=130)	2018 (n=106)	2019 (n=104)
Amikacin	33.8	28.1	22.6	15.3	15.4	26.6	23.1	22.7	18.3	26.9	22.7	32.8	32.7	13.8	**16.3**	**14.4**	**21.7**	**17.9**	**23**
Netilmicin	44.3	25.9	11.4	34.9	24.4	80.0	100.0	50.0	100.0	100.0	50.0	100.0	26.8	**15.8**	**25.2**	**33.7**	**37.5**	**36**	**43.2**
Aztreonam	42.3	28.1	27.3	32.4	20.3	32.0	40.0	43.2	50.0	66.7	20.0	NA	NA	**NA**	**36**	**NA**	**NA**	**NA**	**NA**
Ceftazidime	38.0	24.6	20.4	35.1	16.7	23.7	25.3	31.9	27.4	33.3	33.0	23.1	11.2	**7.44**	**20.1**	**14.4**	**16.1**	**27.3**	**25.9**
Cefoperazone	28.6	26.4	17.4	15.9	3.6	100.0	0.0	0.0	100.0	0.0	0.0	0.0	28.1	**14.2**	**36.3**	**NA**	**NA**	**NA**	**NA**
Cefepime	37.3	35.8	22.2	14.3	6.7	42.5	57.4	38.9	56.8	54.4	48.9	72.4	31.6	**11.7**	**21.1**	**20.1**	**29.2**	**34.9**	**32.6**
Pip/Taz	39.1	32.3	21.8	32.4	12.7	25.0	27.8	21.1	36.6	43.8	29.1	41.9	32.7	**19.3**	**31.7**	**23.3**	**35.3**	**40.9**	**34.9**
Ciprofloxacin	40.0	16.7	10.9	26.4	30.3	43.2	33.3	41.7	29.6	34.3	20.9	31.1	28.6	**14.8**	**20.5**	**16.3**	**25.3**	**20.7**	**27.8**
Imipenem	50.0	21.5	13.5	27.9	22.2	73.2	53.1	39.7	17.4	39.4	25.9	73.0	47.7	**39.5**	**24.7**	**26**	**32.2**	**25.7**	**29.8**
Meropenem	49.3	18.5	9.4	24.2	15.6	63.9	58.3	62.5	41.7	60.0	39.6	65.7	42.4	**26.8**	**20**	**14.4**	**25.3**	**20.7**	**25**
Colistin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.1	40.5	35.1	40.9	7.7	1.5	**4.49**	**2.72**	**2.9**	**7.2**	**3.9**	**1.9**

Table 1: Resistance rates of *P. aeruginosa* strains.
(NA:not available)

cities participated Pseudomonas spp. was the most frequently isolated Gram-negative species (33.4%), and 24.6% were *P. aeruginosa* (24.6%)[8]. In another multicenter study conducted in 10 settings in 2008-2009, approximately half of the Gram-negative bacterial isolates were from intensive care units while 40.4% were associated with bacteremia and 49.2% were *P. aeruginosa*[11].

	2001-2002 (n=136)	2018-2019 (n=210)	p
Amikacin	42/135 (31.1%)	43/210 (20.4%)	0.029
Netilmicin	45/124 (36.2%)	81/204 (39.7%)	0.560
Aztreonam	48/135 (35.5%)	NA	
Ceftazidime	43/136 (31.6%)	56/210 (26.6%)	0.332
Cefoperazone	34/123 (27.6%)	NA	
Cefepime	41/112 (36.6%)	71/210 (33.8%)	0.625
Pip/tazobactam	46/129 (35.6%)	79/208 (37.9%)	0.728
Ciprofloxacin	38/130 (29.2%)	51/210 (24.2%)	0.313
Imipenem	48/133 (36%)	58/209 (27.7%)	0.119
Meropenem	46/134 (34.3%)	48/210 (22.8%)	0.025
NA:Not available			

Table 2: Comparison of 2001-2002 and 2018-2019 periods.
(NA: not available)

In another study, the distribution and antibiotic susceptibility profiles of 355 nonfermentative Gram-negative bacteria that are isolated from blood culture samples (nosocomial or community-acquired bacteremia not differentiated) in the XXX University Medical Faculty Hospital between December 2017 and December 2018 were investigated retrospectively. Of the isolates, 191 (53.8 %) were P.aeruginosa and 38% were carbapenem-resistant[12]. In concordance with these studies, we can see that the number of P.aeruginosa isolates have increased gradually over the years and relatively more resistant strains have emerged. *P. aeruginosa* MCNB per 1000 days and 1000 patients increased especially in the 2009-2010 and 2012-2013 periods and decreased especially in the 2017-2018.

	2001-2 r/total (%)	2018-19 r/total (%)	p
Amikacin	28/51 (54%)	36/59 (61%)	0.564
Netilmicin	31/48 (64%)	45/56 (80%)	0.080
Ciprofloxacin	23/49 (46%)	43/59 (72%)	0.0096
Cefoperazone	21/48 (43%)	NA	NA
Ceftazidime	28/51 (54%)	39/59 (66%)	0.248
Cefepime	24/41 (58%)	47/59 (79%)	0.026
Colistin	NA	3/59 (5)	NA

Table 3: Resistance patterns of carbapenem-resistant strains related to 2001-2 and 2018-19 periods.
(NA: not available)

Long periods of exposure to antibiotics in recurrent infections and the use of broad-spectrum antibiotics in polymicrobial infections are considered to be the main cause the selection of MDR bacteria High and/or inappropriate antibiotic use and inadequate infection control measures are associated with increased resistance rates[1]. The changes in resistance rates of *P. aeruginosa* might have been affected by the amount of antibiotics used, too. For example; aztreonam has never been used during the study period in our setting. Besides, netilmicin is not used in recent years due to lack of availability in Turkey. Nevertheless, netilmicin resistance rates were stable in study strains (36.2% vs 39.7%) on the other hand, amikacin and meropenem resistant

rates decreased statistically significantly (0.029 and 0.025). when we compared 2001-2002 and 2018-19 data.

	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2001-2	2018-19
Total-PSA(N)*	71	65	55	74	66	80	93	95	85	105	101	67	100	94	110	104	130	106	104	136	210
Total-PSA-PTP**	1,38	1,22	1	1,33	1,18	1,22	1,4	1,47	1,56	1,96	1,86	1,18	1,62	1,39	1,68	1,56	1,74	1,24	1,15	1,29	1,19
Total-PSA--PT-DOH***	0,156	0,133	0,114	0,155	0,134	0,144	0,167	0,193	0,179	0,229	0,216	0,145	0,214	0,199	0,255	0,242	0,300	0,242	0,234	0,144	0,238
Total Patients per year	51444	53178	54997	55347	55860	64322	65381	63899	53610	53542	53670	55685	60970	67143	65273	66292	74558	85224	90308	104622	175532
Total days of hospitalization	454626	488513	479664	475966	491450	546449	550894	486612	467355	458169	463683	454250	460655	470001	430149	428246	432436	437199	443412	943139	880611

Table 4: Microbiologically confirmed nosocomial *P. aeruginosa* bacteremia incidence per 1000 patients and 1000 patient days from 2001 to 2019.
PSA: Pseudomonas aeruginosa ** -PTP:Per 1000 patients * -PTDOH: Per 1000 days of hospitalization*
***** Total PSA: Total healthcare-associated bacteremia Pseudomonas aeruginosa isolates*

Prior studies from different parts of the world and from Turkey showed that ceftazidime susceptibility decreased whereas carbapenem resistance is increased[13-20]. However, our results revealed a non-significant decrease in both ceftazidime and cefepime resistance in 2001-2002 and 2018-19 comparison. When we analysed the resistance patterns of carbapenem-resistant P. aeruginosa strains as a separate group in terms of 2001-2002 vs 2018-2019, cefepime and ciprofloxacin resistance rates increased significantly. We may speculate that the possible reason of these outcomes may be temporal changes in the empirical treatment options due to enter of new antibiotics in the market such as tigecycline, ertapenem, fosfomycin, cefoperazone/sulbactam (mostly due to multidrug-resistant Acinetobacter spp which is an important nosocomial infection pathogen), and colistin in carbapenem-resistant strains[21]. Carbapenems remained to be active against P.aeruginosa with resistance rates ranging from 0% to 66.3%[22], depending to area. In our study, the rates of meropenem and imipenem resistance decreased in the mid-2000s, after which they were observed to fluctuate year by year at high rates similar to other studies. In our study, meropenem resistance rate was 29.8% and imipenem resistance rate was 25% in 2019. These rates were lower when compared with the 46.61% (50 percentile rate) in university hospitals in Turkey in the national hospital infections annual report 2019[23]. In the presented study, amikacin resistance decreased in non-carbapenem-resistant strains while ciprofloxacin and cefepime resistance increased in carbapenem-resistant strains. We may speculate that this may also be related to the resistance enzyme type and plasmid profile, but molecular epidemiology could not be investigated in our hospital during the study period. Especially colistin, which is a relatively toxic antibiotic, is commonly used due to increasing carbapenem-resistance in recent years. Although the national hospital infections annual report includes carbapenem resistant P.aeruginosa rates, there are no data regarding colistin resistance for P.aeruginosa. Although colistin resistance is low (9.7%) in our study between 2008 and 2019, colistin resistance is an important issue for the future.

Annual nosocomial infection point prevalence of studies conducted in our hospital for a long while. The prevalence of hospital infections was 4.6% in 2002, 4.9% in 2004, while it was 6.11% in 2018 and 7.27% in 2019. When the infectious agents were evaluated in order of frequency, PSA was the most common pathogen in 2002 and 2004, while it was found to be 17.2% in 2018 (the most common pathogen) and 8% in 2019 (third most common pathogen)[24,25,26].

Infection control precautions and resistance rates are expected to be associated with each other. But until 2013, additional infection control precautions were not applied except active surveillance and hand hygiene studies. Since 2017, double environmental cleaning application has been carried out while we have never been able to check the efficiency of these cleaning procedures during the study period. Contact isolation precautions are performed only in colistin-resistant P.aeruginosa strains and rectal screening is not performed for P.aeruginosa. The hand hygiene rates (under observation) increased from 32% to 68%[27].

Under financement of hospitals, relatively low hand hygiene compliance rates[28], lack of adequate staffing[29] and the inability to obtain hand hygiene supplies regularly[30] might have caused temporary problems in infection control thus the observed fluctuations in the P.aeruginosa MCNB incidence density during the study period. In spite of these disadvantages, to the best of our knowledge, this is the biggest dataset regarding MCNB P.aeruginosa and its incidence in Turkey.

The presented study has several limitations. The study is based on retrospective data. Furthermore, it is possible that every case with fever might have not been performed blood culture during the study period. Hence, the presented data represent the overall P.aeruginosa MCNB but may not represent all the P.aeruginosa bacteremia episodes. We also did not make the distribution of P.aeruginosa isolates according to clinics and evaluate the treatment regimens and clinical outcomes. The change in resistance rates can be related to the amounts of antibiotic use in one respect, but no further molecular studies have been performed. Molecular epidemiological analysis might give more precise clues about the association of possible dominant bacterial clones or antibacterial resistance-associated enzymes vs susceptibility rate fluctuations.

In conclusion, during the 19 years, there was a significant decrease in amikacin and meropenem resistance while there was a significant increase in the subgroıup of carbapenem-resistant strains. More infection control and antimicrobial stewardship efforts are needed to decrease the P. aeruginosa resistance rates and incidence.

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