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Urinary Tract Infections Caused by *Pseudomonas aeruginosa*: An 11-Year Retrospective Analysis on Antimicrobial Resistance

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Abstract

Objective: Urinary tract infections (UTIs) are among the most common infections worldwide. *Pseudomonas aeruginosa* is thought to cause 7% to 10% of UTIs. *P. aeruginosa* isolates from UTIs frequently show higher levels of antibiotic resistance than *E. coli* isolates. The aim of this study was to retrospectively determine the antimicrobial susceptibility profile of *Pseudomonas aeruginosa* strains detected as causative agents of UTIs during the 11 years (2009-2019) before the coronavirus disease-19 pandemic and to reveal epidemiologic data.

Methods: Between January 2009 and October 2019, retrospective data of 540 non-repetitive *Pseudomonas aeruginosa* strains were included in our study. For the diagnosis of UTI, results of $\geq 10^4$ CFU/mL in pure culture or $\geq 10^4$ CFU/mL growths of ≤2 bacterial species were accepted as positive urine culture criteria from midstream urine samples. Identification and antimicrobial resistance were determined using the Vitek 2 Compact System. The 11-year antimicrobial resistance and the three-year Minimal Inhibitory Concentration (MIC) data were extracted from the hospital automation system retrospectively.

Results: Of 540 non-repetitive *Pseudomonas aeruginosa* strains, 226 (41.8%) were isolated from male patients and 314 (58.2%) from female patients. The mean age of the patients was 66.54±32.62 years. Co-trimoxazole and colistin were found to be the most effective antimicrobials against *P. aeruginosa*. Piperacillin-tazobactam combination resistance was found to be 52.59%, third-generation ceftazidime, cefoxitin, and ceftriaxone resistance rates were 48.89%, 89.13%, and 60.37%, respectively, and the fourth-generation cefepime resistance rate was 53.7%. The mic50 values of ciprofloxacin and meropenem increased in 2019 compared with 2017.

Conclusion: In conclusion, although antimicrobial resistance fluctuated over the years, there was an increase pattern in MIC values over the years. An increase in MIC values in the quinolone groups should be monitored for UTI infections. Each hospital's monitoring of antimicrobial resistance status is critical for infection control and shedding light on reasonable antibiotic use.

Keywords: *Psedomonas aeruginosa*, urinary tract infections, retrospective analysis, antimicrobial resistance

INTRODUCTION

Urinary tract infections (UTIs) are among the most common infections worldwide, with an estimated annual burden of $1.6 billion in the United States alone (1). Uropathogenic *Escherichia coli* (UPEC) is the dominant causative agent, causing approximately 80% of UTIs. The incidence of UTIs is 10% in women and 3% in men in the United States (2). UTIs are also one of the most common illnesses in hospitalized patients, accounting for 20 to 50% of all noncomial infections. In the hospital setting, *Pseudomonas aeruginosa* is thought to cause 7% to 10% of UTIs (3). *P. aeruginosa* is a non-fermentative, bacillary Gram-negative opportunistic bacterium (1,3). It can cause infections with poorer prognosis because of its ability to adapt to unfavorable environmental conditions, such as pH and

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osmolarity of urine, and its ability to develop multidrug resistance (4). *P. aeruginosa* UTIs are associated with high morbidity and mortality in elderly patients. *P. aeruginosa* isolates from UTIs frequently show higher levels of antibiotic resistance than *E. coli* isolates (1,3,5). *P. aeruginosa* is one of the most important bacteria causing complicated clinical problems (6). Antimicrobial resistance is a significant global health problem. The increasing use of antimicrobials in recent years has made the treatment of infections difficult because of the development of antimicrobial resistance. In addition to the ability of *P. aeruginosa* to develop antimicrobial resistance, increased antimicrobial use during the COVID-19 pandemic has complicated the treatment of infections (7). The aim of this study was to retrospectively determine the antimicrobial susceptibility profile of *Pseudomonas aeruginosa* strains detected as causative agents of UTIs during the 11 years (2009-2019) before the COVID-19 pandemic and to reveal epidemiologic data.

METHODS

Between January 2009 and October 2019, retrospective data of 540 non-repetitive *Pseudomonas aeruginosa* strains were included in our study. These *Pseudomonas aeruginosa* strains were isolated from urine cultures of patients admitted to the internal medicine clinic of a private hospital in İstanbul after suspected UTI. The first positive result among consecutive samples of the same patient was included in the study, and the results of other strains were excluded from the study. Because this study was a retrospective study, there was no need for informed consent. Ethics committee approval was obtained for using retrospective data of *Pseudomonas aeruginosa* strains (Private MedicalPark Fatih Hospital Ethics Committee, application number: 2021-1-1).

For the diagnosis of UTI, results of $\geq 10^4$ CFU/mL in pure culture or $\geq 10^4$ CFU/mL growth of ≤2 bacterial species were accepted as positive urine culture criteria (8). Midstream urine samples from individuals with suspected UTIs were collected in a sterile container and delivered to the laboratory within 1 h. The urine sample was incubated on Cystine Lactose Electrolyte Deficient agar (CLED agar, Oxoid Ltd., Thermo Fisher, Heysham, UK) at 37 °C for 18 h using the colony counting method. Lactose-negative and oxidase-positive colonies on CLED agar were isolated on cetrimide agar (Oxoid Ltd., Thermo Fisher, Heysham, UK). Oxidase-positive and cetrimide-positive colonies were considered to be *P. aeruginosa*. Suspected strains that tested negative for cetrimide were identified using the Vitek 2 Compact System (Biomerieux, Marcy-l'Étoile, France) for confirmation. In addition to colistin, the susceptibilities of antimicrobials were determined using the Vitek 2 Compact System (Biomerieux, Marcy-l'Étoile, France). The broth microdilution method was used to assess colist susceptibility. Antimicrobial susceptibility results were evaluated according to the Clinical Laboratory Standards Institute criteria before 2016 and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria after 2016. *P. aeruginosa* ATCC 27853 was used for quality control in all procedures (9-11). The 11-year data of urine samples evaluated and cultured in the laboratory were retrospectively retrieved from the hospital automation system. In our hospital, MIC ranges were also presented in the results reports of 2017, 2018, and 2019. Therefore, MIC data of antimicrobials were also determined in the data of these years by removing them from the reports. Only descriptive statistical methods were used in this study.

RESULTS

A total of 540 non-repetitive *Pseudomonas aeruginosa* strains with positive urine cultures for suspected UTIs were included in this study. Of all strains, 226 (41.8%) were isolated from male patients and 314 (58.2%) from female patients. The mean age of the patients was 66.54±32.62 years. The distribution of *Pseudomonas aeruginosa* strains according to years is presented in Table 1.

When the antibiotic susceptibility of *Pseudomonas aeruginosa* strains that cause UTIs was analyzed, it was found that co-trimoxazole was the most effective antibiotic, and 94.07% of the strains were susceptible to it. With 90.37%, colistin was the next drug after co-trimoxazole. Cefazolin susceptibility was the lowest at 0.37% (Table 2).

The distribution of antibiotic resistance status of *Pseudomonas aeruginosa* strains found to be causative agents of UTIs according to years is shown in Table 3. Although an increase in the resistance profiles was observed over the years, there was no clear pattern of increase or decrease. As a result, it was determined whether antibiotic resistance increased or decreased over time.

According to the findings of our study, when the antimicrobial resistance of the strains from all years was analyzed, piperacillin resistance among antipseudomonal penicillins was found to be 60.74%, and piperacillin-tazobactam combination resistance was found to be 52.59%. This revealed that piperacillin should be used cautiously in treating infections caused by *Pseudomonas aeruginosa*. The 99.63% resistance to cefazolin, a first-generation cephalosporin, and 89.63% resistance to cefoxitin, a second-generation cephalosporin, were also suggestive. Ceftazidime, a third-generation cephalosporin, and cefepime, a fourth-generation cephalosporin, are antimicrobials with antipseudomonal

activity. The third-generation ceftazidime, cefoxitin, and ceftaxone resistance rates were 48.89%, 89.13%, and 60.37%, respectively, and the fourth-generation cefepime resistance rate was 53.7%. Meropenem susceptibility was studied to reveal resistance to carbapenems, which are recommended as last-line drugs and was found to be 43.7%. Considering all these data, resistance to beta lactam group antibiotics has reached dreadful levels in *P. aeruginosa* strains in our center. When the resistance to aminoglycosides, which are recommended to be used in combination with beta lactams, was analyzed, netilmicin and tobramycin resistance was found to be 43.33% and 27.78%, respectively. Resistance to quinolones was relatively low, with ciprofloxacin and levofloxacin resistance rates of 30% and 21.11%, respectively. However, only 5.93% of the strains to which co-trimoxazole was the most effective antibiotic were resistant. Co-trimoxazole was followed by colistin with a resistance rate of 9.63% (Table 3). In addition, while the resistance rate to colistin was zero in the first

Table 1. Distribution of *Pseudomonas aeruginosa* strains by year

Years	Positive participants n (%)	Male patients n (%)	Female patients n (%)
2009	10 (1.85)	4 (0.74)	6 (1.11)
2010	30 (5.56)	8 (1.48)	22 (4.07)
2011	40 (7.41)	14 (2.59)	26 (4.81)
2012	48 (8.89)	20 (3.70)	28 (5.19)
2013	56 (10.37)	16 (2.96)	40 (7.41)
2014	26 (4.81)	12 (2.22)	14 (2.59)
2015	24 (4.44)	12 (2.22)	12 (2.22)
2016	38 (7.04)	16 (2.96)	22 (4.07)
2017	76 (14.07)	24 (4.44)	52 (9.63)
2018	140 (25.93)	82 (15.19)	58 (10.74)
2019	52 (9.63)	18 (3.33)	34 (6.30)
Total	540 (100.00)	226 (41.85)	314 (58.15)

Table 2. The distribution of antibiotic susceptibility status of *Pseudomonas aeruginosa* strains as causative agents of UTIs

	Susceptible n (%)		Resistant n (%)	
Cefaperazone-sulbactam	80	14.81%	460	85.19%
Cefazolin	2	0.37%	538	99.63%
Cefepime	250	46.30%	290	53.70%
Cefixim	64	11.85%	476	88.15%
Cefoxitin	56	10.37%	484	89.63%
Ceftazidime	276	51.11%	264	48.89%
Ceftriaxon	214	39.63%	326	60.37%
Ciprofloxacin	378	70.00%	162	30.00%
Colistin	488	90.37%	52	9.63%
Co-trimoxazole	508	94.07%	32	5.93%
Levofloxacin	426	78.89%	114	21.11%
Meropenem	304	56.30%	236	43.70%
Netilmicin	306	56.67%	234	43.33%
Nitrofurantoin	6	1.11%	534	98.89%
Piperacillin	212	39.26%	328	60.74%
Piperacillin-tazobactam	256	47.41%	284	52.59%
Tobramycin	390	72.22%	150	27.78%

UTI: Urinary tract infection

three years of the period examined, this rate increased to 23% in 2019. When the first three and last three years were compared, it was discovered that resistance increased significantly ($p<0.05$).

According to the findings of our study, when the antimicrobial resistance rates detected in 3-year periods were compared, it was determined that the antimicrobial resistance rates detected for ceftazidime, ceftriaxone, and cefepime among cephalosporins in 2018-2019 did not increase compared with the antimicrobial resistance rates detected between 2008 and 2011. In contrast, the resistance rates of all other cephalosporin antibiotics increased. Furthermore, in the quinolone group of antibiotics, which are frequently used in treating UTIs, the antimicrobial resistance rates of ciprofloxacin and levofloxacin in 2018-2019 showed a slight increase compared with the antimicrobial resistance rates detected between 2008 and 2011.

MIC_{50} and MIC_{90} values of 268 *P. aeruginosa* strain between 2017 and 2019 are presented in Table 4. It was determined that the mic50 value of ciprofloxacin, which is frequently used for treating UTIs, increased in 2019 compared with 2017. For meropenem, it was found that the data of 2019 showed an increase in terms of both MIC_{50} and MIC_{90} values compared with the 2017 data. Although there was no clear pattern of increase in resistance rates over the years, there was a pattern of increase in MIC values against *P. aeruginosa* in most antimicrobials commonly used in UTIs over the years.

DISCUSSION

P. aeruginosa is an important nosocomial infection agent. In addition to its widespread presence in the hospital environment and its potential to grow on various antiseptics, antimicrobial resistance in these strains is an important public health problem. It is believed to be responsible for 10% of nosocomial UTIs, and the disease has a poor prognosis in elderly and hospitalized patients. Furthermore, the problem of antimicrobial resistance developing at the origin results in treatment failure and increase morbidity and mortality (3-5). In addition, it is thought that the increased use of antimicrobials during the coronavirus disease-19 (COVID-19) pandemic contributed to antimicrobial resistance and complicated the treatment of infections. Therefore, our study aimed to perform a retrospective analysis of the antimicrobial susceptibility profile of *P. aeruginosa* strains detected as causative agents of UTIs during the 11 years before the COVID-19 pandemic.

Erdoğan et al. (12) investigated the antimicrobial resistance status of *Pseudomonas aeruginosa* strains isolated from Malatya Training and Research Hospital intensive care unit patients between 2016 and 2019. The most effective antibiotics for *P.*

Table 3. The distribution of antibiotic resistance status of *Pseudomonas aeruginosa* strains found to be causative agents of UTIs according to years (%)

	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009
Cefaperazone-sulbactam	65.38	70.00	47.37	26.32	25.00	23.08	28.57	33.33	20.00	33.33	20.00
Cefazolin	100.00	100.00	100.00	100.00	100.00	92.31	100.00	100.00	100.00	100.00	100.00
Cefepime	38.46	44.29	36.84	84.21	50.00	30.77	64.29	83.33	80.00	66.67	0.00
Cefixim	80.77	84.29	89.47	94.74	91.67	69.23	100.00	100.00	100.00	73.33	60.00
Cefoxitin	76.92	95.71	92.11	84.21	100.00	61.54	100.00	100.00	95.00	73.33	40.00
Ceftazidime	7.69	34.29	52.63	73.68	58.33	61.54	57.14	66.67	70.00	73.33	0.00
Ceftriaxon	57.69	70.00	55.26	52.63	25.00	46.15	67.86	54.17	40.00	93.33	100.00
Ciprofloxacin	34.62	24.29	13.16	42.11	25.00	38.46	32.14	41.67	50.00	33.33	0.00
Colistin	23.08	11.43	2.63	15.79	8.33	38.46	0.00	8.33	0.00	0.00	0.00
Co-trimoxazole	0.00	0.00	21.05	0.00	8.33	0.00	7.14	4.17	5.00	13.33	20.00
Levofloxacin	11.54	28.57	7.89	31.58	16.67	30.77	17.86	20.83	35.00	13.33	0.00
Meropenem	30.77	27.14	28.95	63.16	41.67	38.46	67.86	50.00	65.00	73.33	60.00
Netilmicin	76.92	72.86	26.32	26.32	16.67	15.38	28.57	29.17	40.00	20.00	20.00
Nitrofurantoin	100.00	100.00	94.74	100.00	100.00	100.00	100.00	100.00	100.00	93.33	100.00
Piperacillin	34.62	60.00	47.37	73.68	58.33	92.31	71.43	54.17	65.00	86.67	60.00
Piperacillin-tazobactam	46.15	35.71	47.37	73.68	58.33	46.15	60.71	66.67	80.00	73.33	0.00
Tobramycin	11.54	40.00	26.32	15.79	33.33	76.92	10.71	8.33	35.00	26.67	20.00

UTIs: Urinary tract infections

aeruginosa strains were colistin and norfloxacin, whereas the lowest susceptibility among the antibiotics studied was found for aztreonam. Susceptibility rates were 76.5% for amikacin, 8.1% for aztreonam, 74.4% for gentamicin, 62.2% for imipenem, 97.1% for colistin, 57.5% for levofloxacin, 61.4% for meropenem, 57.4% for netilmicin, 89.9% for norfloxacin, and 48% for piperacillin/tazobactam,7%, piperacillin 35.7%, cefepime 57.7%, ceftazidime 62.7%, ciprofloxacin 66%, and tobramycin 80.9%, which were similar to the findings of our study (12). Behçet et al. (13) investigated the antimicrobial resistance status of *Pseudomonas aeruginosa* strains isolated from Bolu Abant İzzet Baysal University Medical Faculty Hospital between 2015 and2017. The rates of resistance to colistin 6.7%, amikacin 11.6%, gentamicin 19.7%, ceftazidime 21.6%, piperacillin/tazobactam 22.4%, cefepime 24.2%, levofloxacin 25.5%, ciprofloxacin 27.4%, imipenem 31.6%, and meropenem 32.1%. When the resistance increased during the analyzed years, a significant increase was found only in cefepime resistance (13). Between 2017 and 2021, Öner et al. (14) aimed to determine the antimicrobial resistance status of 2876 *P. aeruginosa* strains isolated from the Pamukkale University Faculty of Medicine between 2017 and 2021. Accordingly, the lowest resistance was found against amikacin (n=88, 3%) and gentamicin (n=174, 6%), whereas the highest resistance was found against ceftazidime (n=602, 21%) and imipenem (n=553, 19%) (14). Notably, the resistance rates found by Behçet et al. (13) and Öner et al. (14) in Bolu and Denizli provinces, respectively, were lower than the findings of our study. This difference may be due to changes in regional treatment regimens. To examine the worldwide *P. aeruginosa* resistance data, the 1997-2016 data of the SENTRY antimicrobial surveillance program, which includes the Asia-Pacific region, Europe, Latin America, and North America, can be considered. Accordingly, in the 20-year analysis of *P. aeruginosa* strains, the cefepime resistance rate was reported as 20.7% and the ceftazidime resistance rate as 22.5%. In addition, the piperacillin/tazobactam resistance rate, which is frequently used in empirical treatment in intensive care units, was found to be 26.8% (15). Considering these findings, it is noteworthy that the resistance to the relevant antibiotics was twice as high in our strains, suggesting that we are inadequate in rational antibiotic use.

The Infectious Diseases Society of America guidelines recognize nitrofurantoin and co-trimoxazole as the current standard of care for uncomplicated UTIs in women. However, all guidelines state that local or regional antimicrobial susceptibility patterns should be considered (16). Kalal and Nagaraj (16) reported in their study in India that aminopenicillins, ciprofloxacin, and co-trimoxazole may not be appropriate options for the empirical treatment of UTI. They reported that *P. aeruginosa*

Table 4. The distribution of MIC_{50} and MIC_{90} values of 268 *P. aeruginosa* strains detected as causative agents of UTI infections between 2017 and 2019

	2019 (52)		2018 (n=140)		2017 (n=76)	
	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
Cefaperazone-sulbactam	16	32	8	16	8	16
Cefazolin	64	64	64	64	64	64
Cefepime	4	16	8	16	4	16
Cefixim	32	64	32	64	32	64
Cefoxitin	32	64	32	64	32	64
Ceftazidime	8	32	16	32	16	32
Ceftriaxon	8	32	4	32	8	32
Ciprofloxacin	0.25	4	0.25	4	0.12	4
Colistin	0.5	2	0.5	2	0.5	2
Co-trimoxazole	4.75/0.25	9.5/0.5	4.75/0.25	9.5/0.5	4.75/0.25	9.5/0.5
Levofloxacin	0.12	4	0.25	4	0.25	4
Meropenem	16	32	16	32	32	64
Netilmicin	2	4	2	4	4	8
Nitrofurantoin	256	256	256	256	256	256
Piperacillin	4	32	8	64	4	64
Piperacillin-tazobactam	8	64	8	64	8	64
Tobramycin	2	16	2	16	2	16

UTI: Urinary tract infection

was resistant to most antibiotics and had a higher level of antibiotic resistance. They emphasized that antibiotic resistance may cause increased morbidity, mortality, cost, and hospital stay because carbapenems are the last line of defense against resistant gram-negative infections (16). Similarly, our data suggest that aminopenicillins, ciprofloxacin, and co-trimoxazole can be used for the empirical treatment of UTI. Jombo et al. (17) found that 92% of the *P. aeruginosa* strains in UTIs in Nigeria were sensitive to ciprofloxacin and 86% were sensitive to cecuroxime. However, all strains were resistant to nitrofurantoin (17). While high resistance to nitrofurantoin was similarly found in our study, our quinolone resistance rates were lower than those in this study. Perween et al. (18) reported a resistance rate of 42.3% for ciprofloxacin, 57.7% for cefepime, 64.3% for ceftazidime, 42.3% for piperacillin-tazobactam, 29.6% for meropenem, 7.4% for colistin, and 50% for nitrofurantoin because of their study analyzing UTI agents in children in India. It was observed that our data were similar to the data of this study, except for nitrofurantoin. Al Mamari et al. (19) observed a decreasing trend of resistance to most antibiotics except imipenem in 47 *P. aeruginosa* strains in 2018 compared with that in 2013. According to the data of our study, a similar decrease or increase in resistance patterns was not detected. Following COVID-19, quinolone and cephalosporin resistance increased significantly, particularly in nosocomial infection agents with high resistance development capabilities, such as *P. aeruginosa*, with lengthening of hospitalization and an increase in empirical treatments (20). In 2020 and 2022, a study conducted in Iran similarly reported an increase in antimicrobial resistance in P. aeruginosa strains, and researchers emphasized the importance of monitoring these data for global public health (21). Er et al. (22) reported in Turkey that the highest resistance rates were found against ceftazidime (85.4%) and piperecillin/tazobactam (86.6%) between 2008 and 2012, *P. aeruginosa* strains isolated from hospitalized patients with UTI. In this study, it is interesting to report that strains isolated from UTI had a similar resistance pattern to blood cultures (22). It was observed that the data of our study were similar. Sader et al. (23) reported that antimicrobial resistance rates of *P. aeruginosa* strains followed up in the USA between 2012 and 2015 were stable, and it was recommended that antimicrobial combination therapies should be selected for empirical treatment. Yayan et al. (24) reported that the antimicrobial resistance pattern of *P. aeruginosa* strains fluctuated over a 10-year period, similar to our study.

Study Limitations

The limitations of our study were that it was a single-center study and did not differentiate UTIs as complicated or uncomplicated. However, it is valuable in containing 11 years of epidemiological data from the pre-COVID-19 period and revealing the epidemiologic antimicrobial resistance pattern.

CONCLUSION

Antimicrobial resistance in *P. aeruginosa* strains is an important public health problem. Our study included patients admitted to a private hospital in İstanbul and revealed the resistance status of all strains isolated over an 11-year period. Accordingly, we believe that resistance is critically high in İstanbul, and empirical treatment should be planned according to the relevant results. Although antimicrobial resistance fluctuated over the years, there was an increase pattern in MIC values over the years. Each hospital's monitoring of antimicrobial resistance status is critical for infection control and shedding light on reasonable antibiotic use. In addition, we believe that these data will contribute to taking effective measures against the problem of antimicrobial resistance by showing the antimicrobial resistance rates that may be detected after COVID-19. We believe that antimicrobial resistance may have increased because of the widespread use of quinolones and cephalosporins in the COVID-19 pandemic. Studies similar to this study should be conducted during the pandemic period.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for using retrospective data of *Pseudomonas aeruginosa* strains (Private MedicalPark Fatih Hospital Ethics Committee, application number: 2021-1-1).

Informed Consent: Retrospective study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: M.G.E., Concept: Ö.Ü., M.D., Design: A.B., M.D., Data Collection or Processing: A.B., M.G.E., Ö.Ü., Analysis or Interpretation: Ö.Ü., Literature Search: A.B., M.G.E., Writing: A.B., M.D.

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