ANTIMICROBIAL RESISTANCE PROFILE AND SEROTYPING OF PSEUDOMONAS AERUGINOSA IN UNIVERSITY CLINICAL CENTRE OF KOSOVO

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ABSTRACT

***Introduction**: Pseudomonas aeruginosa is one of the most common opportunistic pathogens in nosocomial infections. It is also one of the primary organisms responsible for drug resistant infections. The aim of this study was to investigate the antimicrobial resistance profile of P. aeruginosa, the presence of multidrug-resistant P. aeruginosa (MDR), extensively drug-resistant (XDR) and pan-drug-resistant (PDR) strains and distribution of the most common serotypes among hospitalized patients in University Clinical Center of Kosovo (UCCK).*

***Materials and methods**: During a one-year period, 229 P. aeruginosa were isolated from infected patients in clinics of UCCK from a variety of clinical sites. 80 isolates were studied as the primary isolates from the group of infected patients. P. aeruginosa isolates were identified using standard laboratory procedures. Susceptibility of isolates to antimicrobial agents was investigated using the Kirby-Bauer disk diffusion assay (EUCAST 2013). All isolates were serotyped by slide agglutination with commercial sera from Biorad.*

***Results**: The most prevalent serotype was O11; this serotype showed higher resistance to antibiotics compared with other serotypes. Serotype 011 isolates were generally susceptible to imipenem and meropenem, and most often resistant to amikacin, gentamicin, tobramycin and piperacillin-tazobactam. Thirteen of 80 (28.3%) P. aeruginosa were MDR and 7 of 80 (8.8%) P. aeruginosa were XDR of the isolates tested. No PDR P. aeruginosa were detected. Multiply resistant strains were most frequently isolated from Intensive Care Unit patients.*

***Conclusion**: The present study provides data gathering from a region where there is not a wealth of data available. It is of utmost importance in an increasing "antibiotic crisis". Prudent use of carbapenems is of deep importance. Imipenem and meropenem should be reserved for treatment of MDR P. aeruginosa. Existence and escalation of multiresistant strains, especially of MDR, XDR P. aeruginosa necessitates continuous surveillance, development strategies and increased control of prescription practices.*

***Key words**: Pseudomonas aeruginosa, antimicrobial resistance, serotyping, ICU.*

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Introduction

Pseudomonas aeruginosa is a gram-negative opportunistic nosocomial pathogen responsible for a wide range of infections especially among debilitated patients, like burn patients, cystic fibrosis patients and hospitalized patients, particularly those intubated and in intensive care units (ICU). Infections are very difficult to treat due to the high rate of intrinsic, as well as acquired, resistance[1-5].

Previous prevalence studies in Kosovo reported high rates of healthcare associated infections with 17.4 percent of patients acquiring nosocomial infections in the University Clinical Center of Kosovo (UCCK). Sixty eight point seven (68.7) percent of these patients were in the ICU[6].

Based on the antigenic specification of the oligosaccharide side of LPS (O-Antigen), many serological classification systems for *P. aeruginosa* were proposed, but the most reliable typing system

was the one suggested by the International Committee of Microbiology (ICM) in 1970[7]. The results shown in earlier studies, recommend serotyping as an initial screening procedure in epidemiological studies of *P. aeruginosa*. Typing of strains is important for eradication of environmental sources as well as prevention of cross- infections and monitoring of antimicrobial therapeutic efficacy[8].

Antibiotic resistance is a worldwide problem of major importance[9]. Each year in Europe, approximately 400,000 patients, with hospital-acquired infections, present with resistant strains. Resistance is a particular problem with *P. aeruginosa*, because of the low permeability of its cell wall, together with mutations leading to antibiotic-resistance via over-expression of efflux pumps, decreased expression of porins, or mutations in quinolone targets, that make *P. aeruginosa* a pathogen with high propensity to becoming multi-resistant to antibiotic therapy[10, 11].

Antimicrobial resistance is among the major challenges in the health care of Kosovo. There is no functional system for supervision of antibiotic usage or national antibiotic surveillance. For many years, in Kosovo, cephalosporins were the drugs of choice in empiric treatment in the ICU and they have been used without restrictions both in ICUs, throughout hospital wards and ambulatory care[6]. Studies on antimicrobial resistance from some health care settings in Kosovo have shown alarming results. Previously reported resistance rates of *P. aeruginosa* against ciprofloxacin/ofloxacin were 78.7%, imipenem 18.7% and piperacillin 31.2%[12].

The current increase in incidence of multidrug-resistant (MDR) isolates of *P. aeruginosa* raises serious concerns. Infections caused by multidrug resistant gram-negative bacteria, especially MDR *P. aeruginosa* have been associated with increased morbidity, mortality and costs[13].

Our study followed the definition of MDR, extensively drug-resistant (XDR) and pandrug-resistant (PDR) *P. aeruginosa* as stated by European Centre for Disease Prevention and Control (ECDC)[14]. There have been no studies regarding the distribution of serotypes and antimicrobial resistance of *P. aeruginosa* and its multiresistant strains in Kosovo.

The aim of our investigation was to assess the distribution of different serotypes, antimicrobial resistance, presence of MDR, XDR and PDR *P. aeruginosa* isolates collected from different clinics in University Clinical Center of Kosovo as the only tertiary care center in Kosovo with 2100 beds.

Materials and methods

Study design

This cross-sectional study was conducted in the Department of Microbiology of the National Institute of Public Health of Kosovo. During one-year period, December 2013 - December 2014, a total of 229 isolates of *P. aeruginosa* were analyzed in the Department of Microbiology, as the only laboratory for microbiology analysis for UCCK. From those samples we obtained 80 non-repetitive isolates - only the first isolates from a patient. The Ethics Committee of Faculty of Medicine in Pristina approved the study (approval reference number 1853). Informed consent was not needed for this study, because the samples were collected from patients as part of routine diagnostic care.

Identification

Identification of *P. aeruginosa* was done by the standard laboratory techniques, observing the colony characteristics on the blood agar and MacConkey agar plates, biochemical tests (oxidase, urease, motility and sugar fermentation tests), and Vitek automatic system 2 (bioMerieux-France).

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed by the disk-diffusion tests on Mueller-Hinton agar, using antibiotic discs. Results were interpreted as susceptible, intermediate or resistant according to the criteria recommended by EUCAST Breakpoint table v 3.1. (2013) The following antimicrobials were tested: ceftazidime 10μg, cefepime 30μg, ciprofloxacin 5μg, norfloxacin 10μg, amikacin 30μg, tobramycin 10μg, gentamicin 10μg, piperacillin-tazobactam 30μg, imipenem 10μg and meropenem 10μg.

Serotyping

Serotyping was done using a slide agglutination test, with commercial antisera (Bio-Rad) and live antigens taken directly from 24h antimicrobial susceptibility plates.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22; SPSS Inc., Chicago, IL, USA. Frequency of P. aeruginosa, MDR, XDR *P. aeruginosa* and

percentage of resistant antibiotics was calculated.

Results

A total of 229 samples were analyzed during the study period, from which we obtained 80 non-repetitive samples. Isolates were most frequently recovered from tracheostomy tubes 30 (37.5%), endotracheal aspirate 18 (22.5%) and wounds 17 (21.3%). Other isolates were recovered from punctate 7 (8.8%), blood culture 2 (2.5%), drainage swabs 2 (2.5%) and other miscellaneous sites less than 2 % as shown in Table 1.

Site	Frequency	Percent (%)
Abdominal liquid	1	1.3
Aspirate	1	1.3
Blood culture	2	2.5
Central venous catheter	1	1.3
Drain swab	2	2.5
Endotracheal aspirate	18	22.5
Punctate	7	8.8
Throat swab	1	1.3
Tracheostomy tubes	30	37.5
Wound	17	21.3
Total	80	100

Table 1: Clinical site from which *Pseudomonas aeruginosa* was isolated. Isolates were most frequently recovered from tracheostomy tubes, endotracheal aspirate and wounds.

Clinics	Frequency	Percent (%)
Obstetrics and gynecology	1	1.3
Hematology Clinic	1	1.3
Infectious Disease	3	3.8
Intensive Care Unit	39	48.8
Neonatology Clinic	12	15
Orthopedics	3	3.8
Pediatric Clinic	2	2.5
Post Intensive Care	3	3.8
Pulmonology Clinic	6	7.5
Surgery Clinic	10	12.5
Total	80	100

Table 2: Distribution of *Pseudomonas aeruginosa* isolates by clinical setting in UCCK. Most *P. aeruginosa* were isolated from the ICU.

Most *P. aeruginosa* were isolated from the ICU 39 (48.8%), followed by the Neonatology Clinic 12 (15%), Surgery 10 (12.5%), Pulmonology 6 (7.5%), Infectious Disease Clinic, Post - Intensive Care and Orthopedics 3 (3.7%), Pediatric 2 (2.5%), Obstetrics and Gynecology and Hematology Clinic 1 (1.2%) as shown in Table 2.

Serotyping

Serotyping resulted in detection of 8 serogroups. The most prevalent were O11 - 52 (65%) and O1 - 14 (17.5%). Other serotypes all with a prevalence of less than 5 were found in 17.5% of isolates: O4, O6, O9 were found in 3 (3.8%) samples each, O12 and O3 in 2 (2.57%) samples each, and O7 in 1(1.2%). No other serotypes were detected. The distribution of serotypes of *P. aeruginosa* is presented in Table 3. O11 serotype was distributed in almost all clinics, but it was more common in the ICU. A greater diversity of serotypes was observed in the Pulmonology clinic where from six samples received during the study we encountered 2 (O1), 1(O11), 1(O3), 1(O7) and 1(O9).

Antimicrobial resistance

An analysis of antimicrobial resistance rates showed that *P. aeruginosa* isolates were resistant to: ceftazidime 31 (38.8%), cefepime 21 (26.3%), amikacin 51 (63.7%), gentamicin 62 (77.5%), tobramycin 44 (55%), ciprofloxacin 23 (28.7%), norfloxacin 24 (30%) and piperacillin-tazobactam 29 (36.3%). Resistance to imipenem 14 (17.5%) and meropenem 10 (12.5%) was low compared with other antimicrobials as shown in Table 4.

Nineteen of 80 (23.8%) *P. aeruginosa* isolates were multidrug-resistant. An isolate was defined as MDR if it was resistant to ≥1 drug in ≥3 categories. The drugs on which our categorization was based included anti-pseudomonal cephalosporins (ceftazidime [CAZ], cefepime [FEP]), carbapenems (imipenem [IMP], meropenem [MER]), piperacillin/tazobactam (PIP-TZ), fluoroquinolone (ciprofloxacin [CIP]), and aminoglycosides (gentamicin [GEN], tobramycin [TOB], amikacin [AMK]).

Serotypes for MDR *P. aeruginosa* were 15 (O11), 2(O1), 1(O9) and 1(O4). The majority were from ICU 14 (73.6%) and the highest number of MDR P.aeruginosa was isolated from tracheostomy tubes 9 (47.3%). Seven (8.8%) of *P. aeruginosa* were XDR; XDR serotypes are O11 with 5 samples,

Clinic	Serotype															
	O1		O3		O4		O6		O7		O9		O11		O12	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Ob/Gyn	0	0	0	0	1	33.3	0	0	0	0	0	0	0	0	0	0
Hematology	0	0	0	0	0	0	0	0	0	0	0	0	1	1.9	0	0
Infec. Disease	0	0	0	0	0	0	1	33.3	0	0	0	0	2	3.8	0	0
Intensive Care Unit	6	42.9	0	0	1	33.3	1	33.3	0	0	0	0	30	57.7	1	50
Neonatology	2	14.3	1	50	0	0	1	33.3	0	0	2	66.6	5	9.6	1	50
Orthopedics	0	0	0	0	0	0	0	0	0	0	0	0	3	5.8	0	0
Pediatric	0	0	0	0	0	0	0	0	0	0	0	0	2	3.8	0	0
Post Intensive Care	1	7.1	0	0	0	0	0	0	0	0	0	0	2	3.8	0	0
Pulmonology	2	14.3	1	50	0	0	0	0	1	100	1	33.3	1	1.9	0	0
Surgery	3	21.4	0	0	1	33.3	0	0	0	0	0	0	6	11.5	0	0
Total	14	100	2	100	3	100	3	100	1	100	3	100	52	100	2	100

Table 3: Serotype distribution in different clinics. O11 serotype was distributed in almost all clinics, but it was more common in the ICU.

Antibiotic	No. of isolates	Percent (%)
ceftazidime	31	38.8
cefepime	21	26.3
amikacin	51	63.8
gentamicin	62	77.5
tobramycin	44	55
ciprofloxacin	23	28.8
norfloxacin	24	30
imipenem	14	17.5
meropenem	10	12.5
piperacillin-tazobactam	29	36.3

Table 4: Antimicrobial resistance profile of 80 *P. aeruginosa* isolates. *P. aeruginosa* showed high resistance against amikacin and gentamicin, while imipenem and meropenem were the most potent antibiotics.

O9 and O4 one sample each. There were 4 (57.1%) samples from ICU, 2 (28.5%) from Surgery and 1 (14.2%) from the Neonatology Clinic.

The current study has shown that most multidrug resistant strains were serotype O11 and were most frequently isolated from ICU patients.

The antimicrobial resistance among MDR and XDR *P. aeruginosa* is presented in Table 5.

Antibiotic				
	MDR		XDR	
	No.	Percent %	No.	Percent %
ceftazidime	13	68.4	7	100
cefepime	8	42.1	5	71.4
amikacin	18	94.7	7	100
gentamicin	19	100	7	100
tobramycin	16	84.2	7	100
ciprofloxacin	11	57.9	6	85.7
norfloxacin	10	52.6	7	100
imipenem	3	15.8	6	85.7
meropenem	0	0	6	85.7
piperacillin-tazobactam	13	68.4	7	100

Table 5: Antimicrobial resistance profile of 19 MDR and 7 XDR strains of *P. aeruginosa*. MDR strains demonstrated 100% resistance against gentamicin while XDR strains demonstrated 100% resistance against most of antibiotics tested.

Discussion

P. aeruginosa has emerged as a major opportunistic pathogen in recent years, ICUs have been clearly noted as endemic settings. Their unique nature makes ICUs a focus for eradicating the emergence and spread of many antimicrobial resistant pathogens[15]. In our study, the majority of isolates were from patients hospitalized in ICU and the highest number of isolates were from tracheostomy tubes, endotracheal aspirates and wounds. Endotracheal tubes and pus were important sources of *P. aeruginosa*[16]. Since 1980, several studies have reported the emergence, spread and persis-

tence of MDR clones in hospitals, mainly in ICU with high antibiotic pressure. Two serotypes O11 and O12 are highly associated with these epidemic strains[17]. In our study O11 was the most prevalent followed by O1. Serotype O11 was the most frequently isolated in other studies also[18-20].

This study also provides important data on current antimicrobial resistance.

A previous study conducted in Kosovo found that the resistance rate of *Pseudomonas spp*. against ampicillin, ceftriaxone, cefotaxime and piperacillin was 88.9, 88.1, 83.9 and 77.9 percent respectively[12].

Another study found the highest number of *P. aeruginosa* had been isolated in ICU (46%)[21]. Our study is consistent with these studies, as the majority of isolates were also from the ICU (48.75%).

The antimicrobial resistance of *P. aeruginosa*-has been reported to be increasing in several studies, and nosocomial outbreaks of MDR *P. aeruginosa* have been described in various European hospitals[22]. Antimicrobial resistance surveillance in Europe (2013) reported that antimicrobial resistance in *P. aeruginosa* is common in Europe, with a majority of countries reporting resistance percentages above 10% for all antimicrobial groups under surveillance. Carbapenem resistance is common, with a EU/EEA population-weighted mean of 17.6% and national estimates ranging between 2.9% and 60.5%. Combined resistance is common in *P. aeruginosa*: 14.3% of the isolates were resistant to at least three antimicrobial groups and 4.6% were resistant to all five groups[23].

Ceftazidime and cefepime are the most frequently prescribed third and fourth generation cephalosporins respectively. High rates of resistance against ceftazidime (98.6%), ciprofloxacin (100%), tobramycin (100%), amikacin (97.3%), gentamicin (98.6%) and imipenem (64.4%) has been reported[24]. Yet another study reported following rate of resistance: ceftazidime (30%), cefepime (33%), amikacin (11%), ciprofloxacin (18%), imipenem (24%), and meropenem (25%)[10]. The resistance to ceftazidime reported was 30%, which is lower than our findings of 38.8%. Meanwhile resistance against amikacin in our study was very high, 63.7% compared with 11% from the previously mentioned study. A study conducted in Romania showed following resistance rates: 21.6% for ceftazidime, 21.1% for amikacin, 28.6% for tobramycin, 28% for ciprofloxacin, 27.1% for imipenem, 26.2% for meropenem and 19.5% for piperacillin-tazobactam[25].

The resistance for piperacillin-tazobactam in our study is 36.3%. A study carried out in Turkey detected resistance towards ceftazidime (48.9%), cefepime (39%), amikacin (42.2%), gentamicin (70.7%), tobramycin (65.5%), ciprofloxacin (27.4%), norfloxacin (25.5%), imipenem (15%) and meropenem (20.4%)[26]. Our study showed similar results for gentamicin (77.5%), ciprofloxacin (28.7 %) and imipenem (17.5%). Gentamicin amikacin, imipenem and ciprofloxacin are considered potent agents in the treatment of infection caused by *P. aeruginosa*[27]. In our study *P. aeruginosa* showed high resistance towards amikacin and gentamicin, while imipenem followed by meropenem were the most potent antibiotics.

In terms of antibiotic susceptibility, the highest resistance of MDR strains were found to be against two antibiotics in different categories: cephalosporins, aminoglycosides, fluoroquinolones and antipseudomonal penicillins+β lactamase inhibitors (piperailin-tazobactam), but most were sensitive to imipenem and meropenem. The ICU Surveillance Study reported a significant increase in MDR *P. aeruginosa* isolates from 4 in 1993 to[14] in 2002[28]. A study conducted in 2013 found MDR *P. aeruginosa* was 52%[29]. Prevalence of multi-drug resistant *P. aeruginosa* of 14 has been reported[30]. Frequency of MDR *P. aeruginosa* in different clinical specimens was found to be 30%, and amikacin was found to be the most effective antibiotic[31]. In our study 23.8% of *P. aeruginosa* were MDR strains and the most effective antibiotics were imipenem and meropenem.

In a study of 198 isolates, 12 (6.06%) were identified as PDR, 23 (11.6%) were XDR and 49 (24.7%) were MDR[32]. In our study XDR isolates of *P. aeruginosa* were 7(8.8%) of the total and we did not detect PDR *P. aeruginosa*. XDR is frequently isolated from ICU patients. Unfortunately, currently colistin is the only available treatment for XDR P. aeruginosa infections[33, 34]. In our study the majority of XDR strains came from ICU.

Conclusion

The present study is important, because data gathering from a region where there is not a wealth of data available is of utmost importance in the context of the "antibiotic crisis". Our study has shown that carbapenems are promising drugs with antipseudomonal activity. Their prudent use is of highest importance and they should be reserved for

treating MDR strains since their broad use could lead to evolutionary pressure that will cause emergence of highly resistant clones. Presence of MDR and XDR strains of *P. aeruginosa* suggest continuous surveillance and development of strategies for antimicrobial resistance control in UCCK.

As in other studies the most prevalent serotype was O11, which demostrates higher resistance compared with other serotypes and is more frequent in ICU.

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