Letter to the Editor

Risk factors for carbapenem-resistant *Pseudomonas aeruginosa* infection in a tertiary care hospital in Serbia

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Introduction

Pseudomonas aeruginosa is well-known cause of hospital infections with high morbidity and mortality rates [1]. According to the National Nosocomial Infections Surveillance System (NNISS), *P. aeruginosa* is responsible for approximately 8% of all hospital infections. It was the most frequent cause of ventilator-associated pneumonias (VAP), the fourth-rated on the list of causes of hospital urinary infections, and fifth cause of surgical site infections according to frequency of occurence (2). Infections caused by *P. aeruginosa* are difficult to control and treat due to its high rate of resistance to antibiotics and to the limited number of available antibiotics with efficacy against *P. aeruginosa*. During the last decade, an increase in resistance to imipenem and meropenem was observed among many strains of Gram-negative bacteria, and especially among isolates of *P. aeruginosa* [3,4,5]. Numerous studies have also shown that carbapenem-resistant *P. aeruginosa* (CRPA) is frequently simultaneously resistant to other anti-pseudomonal antibiotics, making the treatment very difficult [6].

A number of risk factors for the emergence of CRPA-caused hospital infections was identified, including spending time in an intensive care unit and/or prior use of certain antibiotics [7,8,9,10]; however, for the majority of factors, the strength of the association was either low or equivocal. Sound knowledge of the risk factors and quantification of their influence on hospital infections are important for proper prevention and treatment of the CRPA-caused nosocomial infections.

The aim of this study was to identify risk factors associated with the CRPA-caused hospital infections.

The study

The prospective cohort study was conducted in a large tertiary-care hospital (1,183 beds, 50,000 inpatients per year) in Kragujevac, Serbia, from January 2009 to December 2011. There were two study cohorts: a group of patients with CRPA-caused intrahospital infections and a group of patients with intrahospital infections caused by carbapenem-sensitive *P. aeruginosa* (CSPA).

All patients hospitalized during the study period were enrolled if they fulfilled the following inclusion criteria: CRPA or CSPA-caused hospital infection and age over 18. The hospital infections were diagnosed according to standard criteria established by the Centers for Disease Control and Prevention, Atlanta. United States [11]. Sources of the study data were patient files and interviews with clinicians and patients. Each of the cases was analyzed by the Department for Prevention and Control of Hospital Infections (DPCHI), and more complex cases were evaluated by a special study group, composed of three independent experts for infectious diseases. All patients just colonized with *P. aeruginosa* without any overt sign of infection were excluded from the study.

Isolation and identification of *P. aeruginosa* was performed in the hospital microbiology laboratory by conventional biochemical methods [12], and testing of

Table 1. Basic characteristics of patients with nosocomial infections caused by carbapenem-resistant *P. aeruginosa* (CRPA) and carbipenem-sensitive *P. aeruginosa* (CSPA)

Variable	CRPA (n = 167)	CSPA (n = 94)	p
Age	59.21 ± 16.32	61.43 ± 15.87	t=-1.063 p=0.289
Gender (male)	135 (80.8%)	61 (64.9%)	χ^2=8.176 p=0.004
Prior stay at some other ward	86 (51.5%)	40 (42.6%)	χ^2=1.927 p=0.165
Hospitalizaton >1 month before the hospital infection	33 (19.8%)	16 (17.0%)	χ^2=0.296 p=0.586
Diabetes mellitus	19 (11.4%)	13 (13.8%)	χ^2=0.336 p=0.562
Trauma on admission	51 (30.5%)	24 (25.5%)	χ^2=0.736 p=0.391
Cancer	21 (12.6%)	10 (10.6%)	χ^2=0.216 p=0.642
Other chronic disease*	49 (29.3%)	30 (31.9%)	χ^2=0.189 p=0.664
Antibiotics used in the last month	141 (84.4%)	70 (75.4%)	χ^2=3.855 p=0.050
Surgery	124 (74.3%)	53 (56.4%)	χ^2=8.799 p=0.003
Urinary catheter	143 (85.6%)	80 (85.1%)	χ^2=0.013 p=0.909
Urinary catheter >7 days	132 (79.0%)	53 (56.4%)	χ^2=14.962 p<0.001
Peripheral venous catheter	155 (92.8%)	87 (92.6%)	χ^2=0.006 p=0.938
Central venous catheter	96 (57.5%)	22 (23.7%)	χ^2=27.579 p<0.001
Mechanical ventilation	77 (46.1%)	25 (26.6%)	χ^2=9.618 p=0.002
Length of hospitalization (days)	34.17±16.53	30.69±13.55	t=1.740 p=0.083
Number of hospitalization days before onset of hospital infection	19.95±12.41	16.73± 1.33	t=2.047 p=0.039
Stay in the Intensive care unit	135 (80.8%)	45 (47.9%)	χ^2=30.539 p<0.001
Prior use of piperacillin+tazobactam	21 (12.6%)	9 (9.6%)	χ^2=0.532 p=0.466
Prior use of ampicillin+sulbactam	18 (10.8%)	4 (4.3%)	χ^2=3.316 p=0.069
Prior use of cefazoline	8 (4.8%)	4 (4.3%)	χ^2=0.039 p=0.843
Prior use of cefuroxime	49 (29.3%)	19 (20.2%)	χ^2=2.601 p=0.107
Prior use of cefotaxime	6 (3.6%)	3 (3.2%)	χ^2=0.029 p=0.865
Prior use of ceftriaxone	22 (13.2%)	15 (16.0%)	χ^2=0.383 p=0.536
Prior use of ceftazidime	44 (23.6%)	12 (12.8%)	χ^2=6.538 p=0.010
Prior use of imipenem	29 (17.4%)	3 (3.2%)	χ^2=11.232 p=0.001
Prior use of meropenem	45 (26.9%)	10 (10.6%)	χ^2=9.617 p=0.002
Prior use of gentamicin	8 (4.8%)	4 (4.3%)	χ^2=0.039 p=0.843
Prior use of amikacin	69 (41.3%)	26 (27.7%)	χ^2=4.846 p=0.028

Table 1 (continued). Basic characteristics of patients with nosocomial infections caused by carbapenem-resistant *P. aeruginosa* (CRPA) and carbipenem-sensitive *P. aeruginosa* (CSPA)

Variable	CRPA (n = 167)	CSPA (n = 94)	p
Prior use of ciprofloxacin	51 (30.7%)	18 (19.1%)	χ^2=4.124 p=0.042
Prior use of trimethoprim-sulphametoxazole	9 (5.4%)	5 (5.3%)	χ^2=0.001 p=0.981
Prior use of vancomycin	37 (22.3%)	8 (8.5%)	χ^2=7.961 p=0.005
Prior use of metronidazole	46 (27.5%)	17 (18.1%)	χ^2=2.939 p=0.086

Results are presented as $\overline{x}$ ± SD, or n (%)
*chronic heart disease, chronic obstructive lung disease, hypertension, chronic hepatic and renal disease

Table 2. Multivariate analysis (logistic regression) of risk factors for carbapenem-resistant *P. aeruginosa* infections

Risk factors	B	OR	95% CI	p
Gender (male)	0.839	2.313	1.173-4.562	0.016
Antibiotics used in the last month	-0.165	0.848	0.408-1.760	0.657
Surgery	-0.357	0.700	0.366-1.337	0.280
Urinary catheter >7 days	-0.833	0.435	0.214-0.882	0.021
Central venous catheter	-0.793	0.453	0.193-1.062	0.069
Mechanical ventilation	0.623	1.865	0.767-4.530	0.169
Stay in Intensive care unit	-0.788	0.455	0.209-0.990	0.047
Prior use of piperacillin+tazobactam	0.352	1.422	0.552-3.669	0.466
Prior use of ceftazidime	-0.160	0.852	0.368-1.971	0.708
Prior use of imipenem	-1.751	0.174	0.046-0.659	0.010
Prior use of meropenem	-0.404	0.668	0.269-1.659	0.384
Prior use of amikacin	-0.307	0.736	0.380-1.424	0.362
Prior use of ciprofloxacin	-0.385	0.680	0.329-1.408	0.299
Prior use of vancomycin	-0.037	0.964	0.357-2.606	0.942

*significant difference; B – coefficient of logistic regression analysis; OR – Odds Ratio; CI – confidence interval

resistance to antibiotics was made by disk-diffusion method and interpreted according to the guidelines of the Clinical and Laboratory Standards Institute, formerly the National Committee for Clinical Laboratory [13].

The following study variables were measured: age; gender; prior hospitalization; admission diagnosis; comorbidity (diabetes mellitus, cancer, injury, chronic heart failure, chronic obstructive pulmonary disease [COPD], hypertension and kidney diseases); prior administration of antibiotics (at least 24 hours of treatment during 14 days before hospitalization); admission and release dates; stay in intensive care unit; applied diagnostic and therapeutic procedures (*e.g.*, stay in intensive care unit, existence of central venous catheter, urinary catheter, mechanical ventilation, surgical intervention, transfusion); length of hospitalization; and treatment outcomes.

The study was approved by the local Ethics Committee.

Primary analysis of collected data was made by descriptive statistics, using measures of central tendency (mean and median) and dispersion (standard deviation and range). Significance of differences among the study groups was tested by the Student's t-test for continual variables, and by the Chi-square test for categorical variables. The variables which turned out to be significant predictors of nosocomial

infections after univariant logistic analysis were included in a multivariant binary logistic regression analysis. The level of significance was set at 0.05 probability of null hypothesis. The statistical software SPSS version 18 for Windows (IBM SPSS, Inc, Chicago, Ill, USA), was used for all calculations.

During the study period there were 267 hospital infections caused by the *P. aeruginosa*. Six cases were excluded because the data on resistance of the isolates to antibiotics were not available to the investigators. There were 167 patients classified as cases who had nosocomial infections caused by CRPA, while the 94 control patients were matched to the cases, and selected from the remaining patients with CSPA infections.

Among the total number of patients with *P. aeruginosa* hospital infections, more men (n = 196; 75.1%) were identified than women (n = 65; 24.9%). The average age of the patients was 60.01 ± 16.16 years. According to anatomical location, the infections caused by *P. aeruginosa* were divided to pneumonias (42.1%), surgical site infections (28.7%), urinary tract infections (22.6%), infections of skin and soft tissues (5.4%), and infections of blood (1.1%). Hospital-acquired pneumonia was significantly more frequent in the group of CRPA (47.3%) compared to the CSPA group of nosocomial patients (33.0%) ($\chi^2 = 5.063$; p = 0.024), while urinary tract infections were more often present in the CSPA group (33.0%) compared to the CRPA group (16.8%) ($\chi^2 = 9.036$; p = 0.003). Infections of skin and soft tissues were also more frequent in CSPA (11.7%) then CRPA group (1.8%) ($\chi^2 = 11.626$; p = 0.001).

The majority of the studied patients were from the intensive care unit (51.7%), followed by the patients from the surgery (17.6%) and neurology (11.9%) wards, while the rest of the patients were from various other hospital wards.

Characteristics of the study cohorts with nosocomial infections are shown in Table 1. Significant risk factors for CRPA infections were male gender ($\chi^2 = 8.176$; p = 0.004); antibiotic use during seven or more days within the last month ($\chi^2 = 3.855$; p = 0.050); surgical intervention ($\chi^2 = 8.799$; p = 0.003); duration of urinary bladder catheterization more than seven days ($\chi^2 = 14.962$; p < 0.001); central line ($\chi^2 = 27.579$ catheterization; p < 0.001); artificial ventilation ($\chi^2 = 9.618$; p = 0.002); stay in intensive care unit ($\chi^2 = 30.539$; p < 0.001); and prior use of ceftazidime ($\chi^2 = 6.538$; p=0.010), imipenem ($\chi^2 = 11.232$; p = 0.001), meropenem ($\chi^2 = 9.617$; p=0.002), amikacin ($\chi^2 = 4.846$; p = 0.028), ciprofloxacin ($\chi^2 = 4.124$; p = 0.042) or vancomycin ($\chi^2 = 7.961$; p = 0.005).

The results of multivariate binary logistic regression are shown in Table 2. There are four significant predictors of nosocomial infections caused by CRPA: male gender (OR = 2.313; 95% CI = 1.173-4.562; p = 0.016); duration of urinary bladder catheterization more than seven days (OR = 0.435; 95% CI = 0.214-0.882; p = 0.021); stay in intensive care unit (OR = 0.455; 95% CI = 0.209-0.990; p = 0.047); and prior use of imipenem (OR = 0.174; 95% CI = 0.046-0.659; p = 0.010). The Hosmer-Lemeshow Goodness-of-Fit Test for this logistic regression was $\chi^2 = 3.400$; df = 8; p = 0.907.

Total length of hospitalization of patients with CRPA infection was 34.17 ± 16.52 days, and 30.69 ± 13.55 days for patients infected with CSPA (t = 1.740; p = 0.063). Lethal outcome of treatment occurred in 63 (37.7%) patients with CRPA infection and in 20 (21.3%) with CSPA infection ($\chi^2 = 7.503$; p = 0.006).

Conclusion

The results of our study pointed to male gender, stay in intensive care unit (ICU), urinary bladder catheterization more than seven days long, and prior use of imipenem as important risk factors associated with CRPA infections, which bear higher mortality than those caused by CSPA strains. Early removal of urinary catheter from male patients (after no more than five days) and avoidance of unjustified utilization of imipenem in patients from ICU could contribute to a decrease in the rate of potentially deadly CRPA infections.

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References

1. Rossolini GM, Mantengoli E (2005) Treatment and control of severe infections caused by multiresistant *Pseudomonas aeruginosa*. Clin Microbiol Infect 11 (Suppl 4): 17-32.
2. 2. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, Fridkin SK, National Healthcare Safety Network Team and Participating National Healthcare Safety Network Facilities (2008) NHSN annual update: Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect Control Hosp Epidemiol 29: 996-1011.
3. Klevens RM, Edwards JR, Gaynes RP (2008) National Nosocomial Infections Surveillance System .The impact of

antimicrobial-resistant, health care-associated infections on mortality in the United States. Clin Infect Dis 47: 927-930.
4. Deshpande LM, Fritsce TR, Jones RN (2004) Molecular epidemiology of selected multidrug-resistant bacteria: a global report of the SENTRY Antimicrobial Surveillance Program. Diagn Microbiol Infect Dis 49: 231-236.
5. Fortaleza CM, Freire MP, Filho Dde C, de Carvalho Ramos M (2006) Risk factors for recovery of imipenem- or ceftazidime-resistant *Pseudomonas aeruginosa* among patients admitted to a teaching hospital in Brazil. Infect Control Hosp Epidemiol 27: 901-906.
6. Onguru P, Erbay A, Bodur H, Baran G, Akinci E, Balaban N, Cevik MA (2008) Imipenem-Resistant *Pseudomonas aeruginosa*: Risk Factors for Nosocomial Infections J Korean Med Sci 23: 982-987.
7. Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y (2006) Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. Antimicrob Agents Chemother; 50: 43-48.
8. Harris AD, Smith D, Johnson JA, Bradham DD, Roghmann MC (2002) Risk factors for imipenem-resistant *Pseudomonas aeruginosa* in hospitalized patients. Clin Infect Dis 34: 340-345.
9. Zavascki AP, Cruz RP, Goldani LZ (2005) Risk factors for imipenem-resistant *Pseudomonas aeruginosa*: a comparative analysis of two case-control studies in hospitalized patients. J Hosp Infect 59: 96-101.
10. Lautenbach E, Weiner MG, Nachamkin I, Bilker WB, Sheridan A, Fishman NO (2006) Imipenem resistance among *Pseudomonas aeruginosa* isolates: risk factors for infection and impact of resistance on clinical and economic outcomes. Infect Control Hosp Epidemiol 27: 893-900.
11. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections. Am J Infect Control 16: 128-140.
12. Kiska DL, Gilligan PH (1995) *Pseudomonas* and *Burkholderia*. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, editors. Manual of clinical microbiology. Washington, DC: American Society for Microbiology. 517-525.
13. National Committee for Clinical Laboratory Standards (2000) Performance standards for antimicrobial disk susceptibility tests. Approved standard. NCCLS document M2-A5. 6th ed. Wayne, PA: NCCCLS.

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