**Pseudomonas aeruginosa bacteremia:** resistance to antibiotics, risk factors, and patient mortality

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**Key words:** Pseudomonas aeruginosa; bacteremia; risk factors.

**Summary.** The aim of our study was to determine the prevalence of Pseudomonas aeruginosa bacteremia, risk factors, and outcome of patients treated at the Hospital of Kaunas University of Medicine.

Material and methods. All hospitalized patients with blood culture positive for Pseudomonas aeruginosa during the 5-year period were included. A retrospective data analysis was performed to evaluate patients’ risk factors and mortality caused by P. aeruginosa bacteremia.

Results. A total of 47 (58.8%) bacteremia episodes occurred in an intensive care unit (ICU). A primary source of bacteremia was identified in 50 (62.5%) episodes. Overall mortality rate was 58.8%. Univariate risk factors analysis showed the factors, which significantly increased the risk of death: mechanical ventilation (13.67 times, P<0.001), patient hospitalization in the ICU (8.51 times, P<0.001), acute respiratory failure (8.44 times, P<0.001), infection site in the respiratory tract (4.93 times, P=0.003), and central vein catheter (4.44 times, P=0.002). Timely and appropriate treatment and surgery were significant protective factors for 30-day mortality (11.1 and 5.26 times, respectively; P=0.001). Meropenem-resistant Pseudomonas aeruginosa strains caused bacteremia more frequently in patients older than 65 years than meropenem-sensitive strains (57.9%, n=11). All 19 patients with meropenem-resistant Pseudomonas aeruginosa bacteremia received inappropriate empirical antibiotic therapy.

Conclusions. Treatment at the intensive care unit, mechanical ventilation, acute respiratory failure, source of infection in respiratory tract, and central vein catheter are the major risk factors associated with an increased mortality rate in patients with Pseudomonas aeruginosa bacteremia.

The patients older than 65 years are at increased risk for bacteremia caused by carbapenem-resistant Pseudomonas aeruginosa strains.

Carbapenems are not antibiotics of the choice of treatment for Pseudomonas aeruginosa bacteremia at the Hospital of Kaunas University of Medicine.

**Introduction**

Bacterial bloodstream infections are serious infections associated with significant mortality and health care costs (1). Despite the advances in hospital care and the introduction of a wide variety of antimicrobial agents, *Pseudomonas aeruginosa* (*P. aeruginosa*) continues to be a common cause of nosocomial infections (2) and is one of the most important microorganisms, which causes problems clinically as a result of its high resistance to antimicrobial agents (3). Mortality from *P. aeruginosa* bacteremia has remained high over the past few decades (4, 5). Most studies have found that mortality rates range from 33 to 61% among all patients with *P. aeruginosa* bacteremia (4, 5).

Risk factors traditionally associated with mortality include underlying diseases and site of infection as well (6). Inappropriate initial antimicrobial treatment of *P. aeruginosa* bloodstream infection is significantly associated with higher mortality as compared to initial treatment with an antimicrobial regimen when bacteria are sensitive to antibiotics administered (7–9). Inappropriate therapy is usually related to antibiotic-resistant strains, which cause infection. *P. aeruginosa* strains are generally resistant to many antibiotics, and treatment of nosocomial infections caused by *P. aeruginosa* strains is one of the major problems in many hospitals. Resistance rates are increasing and they might be different in different settings, so the surveillance of *P. aeruginosa* susceptibility is essential for the definition of empirical regimens. Multidrug resistance is common, and clinical isolates resistant to virtually all antipseudomonal agents are increasingly being reported (10). The emergence of resistance in *P. aeruginosa* limits future therapeutic choices and is associated

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with increased rates of mortality and morbidity and higher costs (11).

The aim of our study was to determine the prevalence of *P. aeruginosa* bacteremia, resistance to antibiotics, risk factors, and outcome of patients treated in a tertiary hospital, the Hospital of Kaunas University of Medicine (KMUH).

**Materials and methods**

**Study population.** The present study was carried out at the KMUH in Lithuania (1987 beds). All hospitalized patients with blood culture positive for *P. aeruginosa* between January 1, 2003, and December 31, 2007, were included into the study. Only patients older than 18 years were enrolled into the study.

**Study design.** A retrospective data analysis was performed to evaluate patients’ risk factors and mortality caused by *P. aeruginosa* bacteremia. For all study patients, the following characteristics were recorded: demographic data, primary source of infection leading to secondary bloodstream infection. The source of bacteremia was confirmed if a localized infection was present before or coincident with the detection of bacteremia; otherwise, the portal of entry was categorized as unknown. The place of patients’ treatment at the time of infection, underlying diseases, antimicrobial agents administered during hospitalization, and causes of death were analyzed. The following predisposing conditions (when present for at least 72 hours before the onset of bloodstream infection) were also investigated: mechanical ventilation, intravascular bladder or urine catheters, and renal dialysis. In addition, previous surgery and previous use of immunosuppressive drugs (e.g. corticosteroids, antineoplastic agents) were taken into account when administered for at least two weeks before the onset of bloodstream infection. Patient mortality within 30 days from the first day of bacteremia was evaluated (30-day mortality).

Antibiotic treatment was defined as empirical when given before species identification and antimicrobial susceptibility test. Treatment was considered adequate when *P. aeruginosa* strain responsible for infection was subsequently found to be susceptible to the administered drug.

**Blood culture technique and microbiological investigation.** Blood culture testing was performed at the request of the attending physician who made the decision concerning patient’s diagnosis. Blood cultures were obtained from patient’s two peripheral sites. Before collecting the blood cultures, skin was disinfected with 70% isopropyl alcohol followed by 2% iodine tincture. All blood samples (10 mL) were inoculated into aerobic medium and processed using the BACTEC 9240 instrument (Becton Dickinson Diagnostics Systems, Sparks, MD). Blood cultures were routinely incubated for 5 days.

*Pseudomonas* strains were selected on *Pseudomonas* agar with cetrimide (Liofilchem, Italy), according to the manufacturer’s instructions for *P. aeruginosa* diagnosis. Cetrimide inhibits a wide variety of bacterial species including *Pseudomonas* species other than *P. aeruginosa*. The latter develops a blue-green pigment due to pyocyanin and fluorescein production. Isolates suspected to be *P. aeruginosa* or not clearly showing blue-green pigment and all strains resistant to carbapenems (imipenem or meropenem) by the disk diffusion method were further identified with the Phoenix ID system (Becton Dickinson, USA) to confirm the strains as *P. aeruginosa*.

For all cultures positive for *P. aeruginosa*, susceptibility testing was done by the Kirby-Bauer method and interpreted according to the guidelines of the Clinical and Laboratory Standards Institute (12). Minimal inhibitory concentration (MIC) values of carbapenem-resistant strains were determined by the E test method (AB Biodisk, Solna, Sweden). Strains with intermediate susceptibility were considered as sensitive.

**Statistical analysis.** Comparison of means between groups of cases and controls were performed by the Student *t* test or Mann-Whitney *U* test (non-parametric values). Proportions were compared using chi-square or Fisher’s exact test. Differences were considered significant at *P*<0.05. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Statistical package SPSS 13.0 for Windows release was used for the data analysis.

**Results**

**The prevalence of P. aeruginosa bacteremia, patients’ characteristics, and demographic data.** *P. aeruginosa* bacteremia accounted for 2.7% of all bacteremias and caused bloodstream infection in 96 patients treated at the KMUH during the 5-year period. Sixteen (16.7%) patients were excluded from analysis due to the presence of polymicrobial bloodstream infection or due to incomplete information. The data of 80 patients (56 males and 24 females) were evaluated. The mean age of patients was 56.7±16.71 years (range, 19–89 years). Patients developed *P. aeruginosa* bacteremia at 17.5±14.0 day on average after admission to the KMUH.

A total of 47 (58.8%) bacteremia episodes occurred in the intensive care unit (ICU) and 33 (41.3%) in other departments. Antibacterial treatment was administered for 49 (61.3%) patients before bloodstream infection occurred. Most of the patients (97.5%) had underlying diseases and conditions at the time of the bacteremia that are summarized in Table 1.

A primary source of bacteremia was identified in 50 (62.5%) episodes. The respiratory tract was the
most common infection site documented in 26 patients (52%); other sources were wounds (26%, n=13), urinary tract (18%, n=9), and bile cysts (4%, n=2).

Risk factors for mortality. Overall mortality from \textit{P. aeruginosa} bacteremia was 58.8%. Table 2 shows the risk factors that were evaluated and their influence on mortality in patients with \textit{P. aeruginosa} bacteremia.

Univariate risk factors analysis showed the factors, which significantly increased the risk of death: mechanical ventilation (13.67 times, \(P<0.001\)), patient hospitalization in the ICU (8.51 times, \(P<0.001\)), acute respiratory failure (8.44 times, \(P<0.001\)), infection site in the respiratory tract (4.93 times, \(P=0.003\)), and central vein catheter (4.44 times, \(P=0.002\)).

Timely and appropriate treatment and surgery were significant protective factors for 30-day mortality (11.1 and 5.26 times, respectively; \(P=0.001\)).

There were no significant differences in mortality regarding patients' age and underlying diseases.

\textit{P. aeruginosa} strains to antibiotics. The resistance of \textit{P. aeruginosa} isolates obtained from bloodstream to antibiotics during the study period is presented in Table 3.

\textit{P. aeruginosa} strains that caused bacteremia in ICU patients were more frequently resistant to

| Table 1. Patients' underlying diseases and conditions in \textit{Pseudomonas aeruginosa} bacteremia episodes |
|---------------------------------------------------------------|
| Underlying disease and condition* | Number (%) of episodes |
| Surgery |
| Abdominal | 7 (8.8) |
| Other | 2 (2.5) |
| Pneumonia | 35 (43.8) |
| Polytrauma | 12 (15) |
| Burn | 21 (26.3) |
| Oncology | 6 (7.5) |
| Pyelonephritis | 7 (8.8) |
| Posttransplantation | 2 (2.5) |
| Chronic airway disease | 3 (3.8) |
| Cardiovascular disease | 10 (12.5) |
| Cerebrovascular disease | 4 (5.0) |
| Diabetes | 1 (1.3) |
| Other | 5 (6.3) |

*Some patients had more than one underlying condition.

| Table 2. Univariate analysis of risk factors influencing mortality among patients with \textit{Pseudomonas aeruginosa} bacteremia |
|---------------------------------------------------------------|
| Risk factor | Nonsurvivors (n=47) | Survivors (n=33) | Odds ratio (95% CI) | \(P\) value |
| Age, mean±SD, years | 57.1±17.1 | 56.2±16.4 | 1.00 (0.98–1.03) | 0.82 |
| Sex (male) | 32 (68.1) | 24 (72.7) | 0.08 (0.03–2.13) | 0.66 |
| Age ≥65 years | 18 (38.3) | 12 (36.4) | 1.09 (0.43–2.73) | 0.86 |
| Treatment in an intensive care unit | 37 (78.7) | 10 (30.3) | 8.51 (3.07–23.59) | <0.001 |
| Surgery | 16 (34.0) | 24 (72.7) | 0.19 (0.07–0.51) | 0.001 |
| Source known | 30 (63.8) | 19 (57.6) | 1.30 (0.52–3.24) | 0.57 |
| Source respiratory tract | 22 (46.8) | 5 (15.2) | 4.93 (1.62–14.96) | 0.003 |
| Source in wound | 11 (23.4) | 6 (18.2) | 1.38 (0.45–4.18) | 0.57 |
| Source in urinary tract | 4 (8.5) | 8 (24.2) | 0.29 (0.08–1.06) | 0.06 |
| Source other | 3 (6.4) | 1 (3.0) | 2.18 (0.22–21.95) | 0.64 |
| Mechanical ventilation | 41 (87.2) | 11 (33.3) | 13.67 (4.45–41.95) | <0.001 |
| Central vein catheter | 36 (76.6) | 14 (42.4) | 4.44 (1.69–11.67) | 0.002 |
| Urinary catheter | 34 (72.3) | 21 (63.6) | 1.50 (0.58–3.88) | 0.41 |
| Respiratory failure | 38 (80.9) | 11 (33.3) | 8.44 (3.03–23.55) | <0.001 |
| Acute renal failure | 16 (34.0) | 7 (21.2) | 1.92 (0.69–5.37) | 0.21 |
| Acute hepatic failure | 3 (6.4) | 0 (0) | – | 0.26 |
| Adequate treatment | 29 (61.7) | 20 (60.6) | 1.05 (0.42–2.61) | 0.92 |
| Timely corrected treatment | 19 (40.4) | 29 (87.9) | 0.09 (0.03–0.31) | <0.001 |
| Temperature, mean±SD, °C | 37.9±1.3 | 38.1±0.8 | 0.82 (0.55–1.22) | 0.29 |
| CRP reactive protein, mean±SD, g/L | 209.0±74.3 | 164.5±98.7 | 1.01 (1.00–1.01) | 0.03 |
| Leukocytes, mean±SD, 10³/L | 11.5±7.9 | 14.8±7.9 | 0.95 (0.90–1.01) | 0.07 |

Values are numbers (percentage) unless otherwise indicated.

| Table 3. Antibiotic resistance of \textit{Pseudomonas aeruginosa} isolates from bloodstream of ICU and non-ICU patients |
|---------------------------------------------------------------|
| Antibiotic | Resistance, n (%) |
| \textit{P. aeruginosa} isolate from ICU patient (n=47) | \textit{P. aeruginosa} isolate from non-ICU patient (n=33) | \(P\) value |
| Ceftazidime | 10 (21.3) | 2 (6.1) | 0.049 |
| Piperaclin | 17 (37.0) | 9 (27.3) | 0.55 |
| Gentamicin | 13 (39.1) | 13 (39.4) | 0.55 |
| Amikacin | 4 (8.5) | 3 (9.1) | 0.61 |
| Ceftaroline | 11 (24.4) | 6 (18.8) | 0.48 |
| Imipenem | 9 (19.1) | 8 (24.2) | 0.39 |
| Meropenem | 12 (25.5) | 7 (21.2) | 0.43 |

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Table 4. Risk factors for Pseudomonas aeruginosa resistance to meropenem

| Risk factor                        | Meropenem-resistant P. aeruginosa strains (n=19) | Meropenem-sensitive P. aeruginosa strains (n=61) | P value |
|------------------------------------|-------------------------------------------------|-------------------------------------------------|---------|
| Treatment at ICU, n (%)            | 12 (63.2)                                        | 35 (57.4)                                        | 0.43    |
| Age >65 years, n (%)               | 11 (57.9)                                        | 20 (32.8)                                        | 0.046   |
| Central vein catheter, n (%)       | 12 (63.2)                                        | 38 (62.3)                                        | 0.58    |
| Urinary catheter, n (%)            | 13 (68.4)                                        | 42 (68.8)                                        | 0.59    |
| Respiratory failure, n (%)         | 12 (63.2)                                        | 37 (60.7)                                        | 0.85    |
| Acute renal failure, n (%)         | 14 (73.7)                                        | 15 (24.6)                                        | 0.02    |
| Mechanical ventilation, n (%)      | 13 (68.4)                                        | 38 (62.3)                                        | 0.42    |
| Infection source respiratory tract, n (%) | 5 (26.3)                                             | 22 (36.1)                                        | 0.31    |
| Infection source wound, n (%)      | 5 (26.3)                                         | 12 (19.7)                                        | 0.37    |
| Infection source urinary tract, n (%) | 4 (21.1)                                              | 8 (13.1)                                         | 0.30    |
| Inadequate treatment, n (%)        | 19 (100)                                         | 0                                               | 0.049   |

ceftazidime as compared with P. aeruginosa strains responsible for bacteremia in the non-ICU patients (21.3%, n=10 and 6.1%, n=2, respectively; P<0.05). There were no differences in resistance of P. aeruginosa strains to other antibiotics comparing the ICU and non-ICU patients.

In patients older than 65 years, meropenem-resistant P. aeruginosa strains were the cause of bacteremia more frequently than meropenem-sensitive P. aeruginosa strains (57.9%, n=11 versus 32.8%, n=20, P=0.046). All 19 patients with meropenem-resistant P. aeruginosa bacteremia received inappropriate empirical antibiotic therapy (Table 4).

Discussion

In our study, a primary source of bacteremia was identified in 50 (62.5%) episodes. The majority of patients had underlying diseases or conditions that predisposed them to the development of infection, being similar to the findings of other publications (13, 14). The respiratory tract was the most common site of infection. Infections of the lower respiratory tract were the predominant sources of P. aeruginosa bacteremia in other studies as well (6, 15, 16). Our study showed a high mortality in patients with P. aeruginosa bacteremia (58.8%). Von Dossow et al. and Kang et al. reported that high mortality rates were observed among patients with respiratory failure and mechanical ventilation, supporting the importance of these factors in overall mortality (17, 18). Mechanical ventilation, acute respiratory failure, and infection source in the respiratory tract were the risk factors associated with increased patients’ mortality in our study as well.

Surgical treatment plays the major role in the treatment of infections, while antimicrobial therapy is only supplementary. We found that surgery and appropriate antimicrobial therapy were significant protective factors for 30-day mortality. There was no significant difference in mortality regarding patients’ age and underlying diseases.

Amikacin showed the best antimicrobial activity (91.5% of susceptible strains were isolated from patients treated in the ICU and 90.9% from non-ICU patients). P. aeruginosa strains that caused bacteremia in the ICU patients were more frequently resistant to ceftazidime as compared with P. aeruginosa strains responsible for bacteremia in the non-ICU patients.

Recently, carbapenems are recommended for treatment of serious infections in the ICU (19). However, increasing antibiotic resistance is making many previously effective antibiotic regimens inappropriate. Our study demonstrated that patients’ age of >65 years was associated with a significantly greater risk of bacteremia caused by meropenem-resistant P. aeruginosa strains. It was showed that 25.5% and 19.1% of P. aeruginosa strains, which caused bacteremia in the ICU, were resistant to meropenem and imipenem, respectively, and our study demonstrated that P. aeruginosa bacteremia caused by meropenem-resistant strains was associated with an inappropriate empiric antibiotic treatment. High mortality in patients with P. aeruginosa bacteremia was most probably mediated by more frequent inappropriateness of antimicrobial therapy for P. aeruginosa bacteremia caused by carbapenem-resistant strains. We failed in proving that inappropriate treatment influenced the outcome of patients, but this may be related to relatively small number of cases investigated by us. Zelenitsky et al. demonstrated the clinical role of antibiotic pharmacodynamics in the treatment and outcome of P. aeruginosa bacteremia, and peak/MIC was the only variable independently associated with treatment outcome. An aggressive dosing with targeted peak/MICs for aminoglycosides and ciprofloxacin were strongly associated with clinical outcome and essential to the appropriate management of P. aeruginosa bacteremia (20). Other study showed that nosocomial infections caused by metallo-beta-lactamases (MBL)-producing P. aeruginosa were associated with increased mortality when compared with those infections caused by non-MBL P. aeruginosa isolates (21). However, the investigators noted high mortality rates for infections caused by P. aeruginosa despite adequate treatment based on
MICs (22). *P. aeruginosa* has different virulence factors, and these factors and inflammatory response can influence the outcome of patients (22–25).

**Conclusions**

Treatment in the intensive care unit, mechanical ventilation, acute respiratory failure, source of infection in the respiratory tract, and central vein catheter were the major risk factors associated with an increased mortality rate in patients with *Pseudomonas aeruginosa* bacteremia.

In patients older than 65 years, meropenem-resistant *P. aeruginosa* strains were the cause of bacteremia more frequently than meropenem-sensitive *P. aeruginosa* strains.

Carbapenems are not antibiotics of the choice of treatment for *Pseudomonas aeruginosa* bacteremia at the Hospital of Kaunas University of Medicine.

**Pseudomonas aeruginosa** bakteriemija: atsparumas antibiotikams, rizikos veiksniams ir pacientų mirštamumams

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**Raktažodžiai:** *Pseudomonas aeruginosa*, bakteriemija, rizikos veiksnių.

**Santrauka.** Tyrimo tikslas. Nustatyti pacientų, gydytų Kauno medicinos universiteto klinikose, *Pseudomonas aeruginosa* sukeltos bakteriemijos dažnį, šių pacientų rizikos veiksnius ir mirštamumą.

**Tyrimo metodai.** Į tyrimą įtraukti visi pacientai, kuriems penkerių metų laikotarpiu iš kraujo buvo išautinta *Pseudomonas aeruginosa* padermė. Atlikta retrospektyvioji šių pacientų duomenų analizė, siekiant nustatyti rizikos veiksnius ir su bakteriemija susijusį mirštamumą.

**Rezultatai.** 47 (58,8 proc.) bakteriemijos epizodai buvo nustatyti intensyviosios terapijos skyriuje gydymais pacientams. Pirminios bakteriemijos židinys buvo nustatytas 50 (62,5 proc.) pacientų. Pacientų mirštamumus – 58,8 proc. Mirštamumo riziką statistiškai patikimai didino: dirbtinė plaučių ventiliacija – 13,67 karto (p<0,001), pacientų būklė, kai būtinas gydymas intensyviosios terapijos skyriuje – 8,51 karto (p<0,001), būtinos gydymas intensyviosios terapijos skyriuje – 8,44 karto (p<0,001), infekcijos židinys kvėpavimo taktuose – 4,93 kartu (p=0,003) ir centrinės venos kateteris – 4,44 kartu (p=0,002). Tinkamas empirinis antibakterinis gydymas ir chirurginė intervencija patikimai mažino mirštamumą, atitinkamai – 11,1 ir 5,26 kartu (p=0,001). Vyresniems nei 65 metų pacientams bakteriemiją dažniau sukėlė atsparios meropenemui *Pseudomonas aeruginosa* padermės, nors tai mirštamumui įtakos neturėjo.

**Išvados.** Dirbtinė plaučių ventiliacija, pacientų būklė, kai būtinas gydymas intensyviosios terapijos skyriuje, būtinos gydymas intensyviosios terapijos skyriuje – 8,44 karto (p<0,001), infekcijos židinys kvėpavimo taktuose ir centrinės venos kateteris – 4,44 kartu (p=0,002). Tinkamas empirinis antibakterinis gydymas ir chirurginė intervencija patikimai mažino mirštamumą, atitinkamai – 11,1 ir 5,26 kartu (p=0,001). Vyresniems nei 65 metų pacientams bakteriemiją dažniau sukėlė karbapenems atsparaus *Pseudomonas aeruginosa*. Karbapenems nėra pirmojo pasirinkimo vaistas gydant *Pseudomonas aeruginosa* sukeltą bakteriemiją Kauno medicinos universiteto klinikose.

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