Journal of Microbiology, Immunology and Infection (2017) 50, 677–683

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Risk factors and clinical significance of bacteremia caused by *Pseudomonas aeruginosa* resistant only to carbapenems

Chia-Hsin Lee [a], Ting-Yi Su [a], Jung-Jr Ye [a], Po-Chang Hsu [a], An-Jing Kuo [b,c], Ju-Hsin Chia [b,c], Ming-Hsun Lee [a,*]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[b] *Department of Laboratory Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan*
[c] *Department of Medical Biotechnology and Laboratory Science, Chang Gung University, Taoyuan, Taiwan*

Received 27 November 2014; received in revised form 8 May 2015; accepted 12 June 2015
Available online 27 June 2015

KEYWORDS
bacteremia;
carbapenem resistance;
mortality;
Pseudomonas aeruginosa

Background/purpose: Carbapenem-resistant *Pseudomonas aeruginosa* infections have been a challenge and issue in hospital settings. However, the clinical impact of *P. aeruginosa* blood isolates resistant only to carbapenems has never been discussed previously.
Methods: To assess the risk factors and clinical significance of bacteremia caused by carbapenem resistance only *P. aeruginosa* (CROPA), a 6-year retrospective case–control study was conducted. The CROPA strains were defined as isolates susceptible to ciprofloxacin, antipseudomonal penicillins and cephalosporins, and aminoglycosides but resistant to one antipseudomonal carbapenem (imipenem or meropenem) or both. The controls were selected among patients with bacteremia due to *P. aeruginosa* susceptible to all above classes of antipseudomonal antibiotics, which was defined as all-susceptible *P. aeruginosa*.
Results: Twenty-five patients had at least one blood culture positive for CROPA, and 50 controls had all-susceptible *P. aeruginosa* bacteremia. CROPA bacteremia had a high 30-day mortality rate (72.0%), as compared to 26.0% for the controls ($p < 0.001$). Through multivariate analysis, carbapenem exposure was the only risk factor for developing CROPA bacteremia ($p = 0.002$). A comparison between the surviving and deceased patients with CROPA bacteremia showed that nine (50%) of those who died, but none of the survivors, received carbapenems as the initial empirical therapy ($p = 0.027$).

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, 5 Fu-Shin Street, Gueishan 333, Taoyuan, Taiwan.
E-mail address: drharrylee@gmail.com (M.-H. Lee).

http://dx.doi.org/10.1016/j.jmii.2015.06.003

Conclusion: Carbapenem exposure was associated with emergence of CROPA infections. Repeated carbapenem use in such patients might increase rates of inappropriate initial empirical treatment and mortality. Prudent carbapenem use is important to reduce the emergence of CROPA.

Introduction

Pseudomonas aeruginosa is a leading cause of nosocomial infections in hospital settings.[1] The in-hospital mortality related to *P. aeruginosa* bloodstream infections is from 25.5% to 39%.[2,3] Imipenem is a mainstay in the treatment of severe *P. aeruginosa* infections, but the emergence of increasing imipenem resistance among clinical *P. aeruginosa* isolates has become a major concern of clinicians.[4,5] The average 30-day mortality of imipenem-resistant *P. aeruginosa* bacteremia was up to 41%, and these isolates were more likely to have cross-resistance to other common antipseudomonal agents.[3,6,7] The mechanisms of carbapenem resistance for *P. aeruginosa* are production of metallo-β-lactamase, overexpression of efflux, and loss of the outer membrane protein.[8–11] Either production of metallo-β-lactamase or overexpression of efflux could induce resistance to other antipseudomonal β-lactams.

During a 6-year period from 2004 to 2010, we noted the emergence of an unusual group of *P. aeruginosa* strains, which were resistant only to carbapenems (imipenem, meropenem, or both) via the disk diffusion method in accordance with the Clinical and Laboratory Standards Institute (CLSI) document M100-S22.[12] We defined this phenotype of *P. aeruginosa* strain as carbapenem resistance-only *P. aeruginosa* (CROPA),[13] which were susceptible to all antipseudomonal antibiotics tested (amikacin, gentamicin, piperacillin, piperacillin–tazobactam, aztreonam, ceftazidime, cefepime, and ciprofloxacin) but were resistant to carbapenems (imipenem, meropenem, or both). The percentage of CROPA strains among all the clinical *P. aeruginosa* blood isolates increased from 1.8% to 4.9% during the 6-year period from 2004 to 2010 at our hospital. The clinical impact of bacteremia caused by these CROPA strains has never been discussed in the English literature.

Thus, we conducted a 6-year retrospective case–control study to address the risk factors and clinical significance of CROPA bacteremia.

Materials and methods

Study site and ethical approval

Chang Gung Memorial Hospital Linkou is a 3715-bed university-affiliated medical center providing both primary and tertiary care in northern Taiwan. The ethical approval for this study was given by the hospital Institutional Review Board with a reference number of 100-0795B.

Study design and patients

A retrospective cohort 1:2 matched case–control study was conducted to collect cases with *P. aeruginosa* bacteremia between October 2004 and October 2010. We identified all the hospitalized patients with an age $\geq$18 years and at least one blood culture positive for CROPA by searching the microbiology laboratory database. Patients were considered cases if they had symptoms and signs suggestive of systemic infection with an imipenem or meropenem minimal inhibitory concentration (MIC) of their first isolate ≥ 4 μg/mL.[12] The symptoms and signs of infection included at least two of the following clinical characteristics: (1) temperature $<$ 36°C or $>$ 38°C; (2) heart rate $>$ 90 beats/min; (3) tachypnea: respiratory rate $>$ 20 breaths/min, or arterial partial pressure of carbon dioxide $<$ 32 mmHg; (4) white blood cell count $<$ 4.0×10^9 cells/L or $>$ 12.0×10^9 cells/L; or (5) the presence of $>$10% immature neutrophils. The controls were patients hospitalized during the study period with bacteremia due to *P. aeruginosa* susceptible to all the tested antipseudomonal agents, including amikacin, gentamicin, ciprofloxacin, aztreonam, ceftazidime, cefepime, piperacillin–tazobactam, piperacillin, imipenem, and meropenem. This type of *P. aeruginosa* strains were defined as all-susceptible *P. aeruginosa* (ASPA) and all the first isolates had MICs $<$ 4 μg/mL for both imipenem and meropenem.[12] For each patient with CROPA bacteremia, two matched controls were selected by a stepwise matching technique to identify the appropriate control patient matched to a case for gender, age $\pm$ 5 years, and the year of *P. aeruginosa* being isolated. Only the first episode of bacteremia was included for analysis. Patients with polymicrobial bacteremia were excluded to avoid the influence of multiple pathogens on the analysis of prognosis.

Data collection and definitions

Patients' demographics and clinical characteristics were obtained from their medical records, including age, sex, and length of hospital stay before *P. aeruginosa* bacteremia, laboratory data, and clinical outcomes. Variables as risk factors included comorbid illnesses (such as diabetes mellitus, liver cirrhosis, end-stage renal disease, chronic obstructive lung disease, solid tumors, hematological malignancies, and cerebral vascular accident), sources of bacteremia, Pittsburgh bacteremia scores for disease severity, and antibiotic exposure prior to bacteremia.

A nosocomial infection was considered if the infection was not evident until >48 hours of hospitalization. Severity of illness was evaluated on the 1st day of bacteremia onset by means of Pittsburgh bacteremia score.[14] The sources of

bacteremia were determined according to the medical records, image studies, surgical findings, and microbiologic evidence. The sources were further categorized into lower respiratory tract, intra-abdominal sites, urinary tract, skin, soft tissue, bone, and central venous catheter. If there was no definite source, it was categorized as *primary bacteremia*.

Prior antibiotic exposure was defined as the exposure to antimicrobial agents for at least 3 consecutive days within 3 months of CROPA bacteremia onset. The following classes of antibiotics were recorded: penicillin and its derivatives, aminoglycosides, cephalosporins, antipseudomonal cephalosporins, carbapenems, and glycopeptides. The penicillin class of antibiotics included penicillin, oxacillin, ampicillin, piperacillin, amoxicillin–clavulanate, ampicillin–sulbactam, and piperacillin–tazobactam. Aminoglycosides included gentamicin and amikacin. Cephalosporins included cefazolin, cefuroxime, ceftriaxone, flomoxef, ceftazidime, cefepime, and cefpirome. Antipseudomonal cephalosporins included ceftazidime, cefepime, and cefpirome. Carbapenems included ertapenem, imipenem, and meropenem. Fluoroquinolones included moxifloxacin, levofloxacin, and ciprofloxacin. Glycopeptides included vancomycin and teicoplanin. Initial empirical antibiotic treatment was defined as the first antibiotic prescribed within 72 hours of blood culture collection, and was classified as appropriate if the antibiotic was active *in vitro* against the identified pathogens.

Microbiologic analysis

Blood cultures were processed in the clinical microbiology laboratory, using an automated blood culture system (BACTEC 9240 system; Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). *P. aeruginosa* isolates were identified according to routine bacteriological procedures. Antibiotic susceptibility testing was determined by the CLSI disk diffusion method.[12] The antibiotic disks (BD Microbiology Systems, Cockeysville, MD, USA) for *P. aeruginosa* included amikacin, gentamicin, piperacillin, piperacillin–tazobactam, aztreonam, ceftazidime, cefepime, imipenem, meropenem, and ciprofloxacin. The control strain, *P. aeruginosa* ATCC 27853, was included in each test run. Interpretation of disk diffusion results was made in accordance with the CLSI document M100-S22.[12] The susceptibility of *P. aeruginosa* to imipenem and meropenem was initially screened with disk-diffusion testing, and was confirmed by the Etest method according to the manufacturer's instructions (AB Biodisk, Solna, Sweden). The MIC breakpoint for imipenem and meropenem resistance was 4 μg/mL (intermediate resistance) and ≥8 μg/mL (resistance).[12]

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables were reported as a proportion of the total number of patients. Univariate analysis was conducted using either a χ^2 test or Fisher exact test for categorical variables, and Student *t* test or Mann–Whitney *U* test for continuous variables, as appropriate. To eliminate confounding factors in predicting the risk factors for developing CROPA bacteremia, all variables with $p \leq 0.1$ by univariate analysis were entered into a multivariate logistic regression model for further assessment. All statistical calculations were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Results were expressed as adjusted odds ratios, and corresponding 95% confidence interval. All *p* values were 2-tailed, and $p < 0.05$ were considered statistically significant.

Results

Patients and clinical characteristics

A total of 1431 patients with *P. aeruginosa* bacteremia were identified during the study period, and only 49 adults had CROPA bacteremia. We excluded 22 cases of polymicrobial bacteremia and two cases with a change of *in vitro* susceptibility from CROPA to either ASPA or drug-resistant *P. aeruginosa* (resistant to aztreonam and ciprofloxacin) in the follow-up blood cultures. Thus, 25 patients were enrolled as *case patients*. All of the 25 CROPA blood isolates from the case patients had a high-level resistance to imipenem, including 24 with imipenem MICs >16 μg/mL and one with an imipenem MIC of 8 μg/mL. Furthermore, 24 of the 25 CROPA isolates had meropenem MICs ≥4 μg/mL.

A total of 50 control patients were matched. Matching results, demographics, initial presentations, previously used antibiotics, and 30-day mortality are shown in Table 1. There was no significant difference in comorbidities and the source of bacteremia between the case and control groups (Table 1). Compared with the control group, the case group had a longer hospital stay before bacteremia onset (mean: 42.8 days vs. 18.8 days, $p = 0.002$), and most of the case patients acquired infections from nosocomial route (88.0% vs. 62.0%, $p = 0.02$). Pittsburgh bacteremia score was higher in the case group than the control (3.9 ± 2.5 vs. 2.2 ± 2.3, $p = 0.007$).

Prior antibiotic exposure, mainly carbapenems, antipseudomonal cephalosporins and glycopeptides, were more frequently seen in the case group than the control (68.0% vs. 8.0%, $p < 0.001$; 52.0% vs. 22.0%, $p = 0.009$; and 52.0% vs. 20.0%, $p = 0.005$; respectively). Seventeen case patients had ever received carbapenem treatment before CROPA bacteremia onset and these carbapenems were administrated for extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* ($n = 7$) and *Escherichia coli* ($n = 2$), drug-resistant *Acinetobacter baumannii* ($n = 3$), or empirical therapy without identified offending pathogens ($n = 5$). Multivariate analysis showed that prior carbapenem exposure was the only risk factor for CROPA bacteremia under the model adjusted for the length of hospital stay, Pittsburgh bacteremia scores, platelet count, serum creatinine level, and prior exposure to antipseudomonal cephalosporins and glycopeptides (odds ratio, 360.72; 95% confidence interval, 8.101–16061.832; $p = 0.002$; Table 2). The 30-day mortality rate for the case

Table 1 Demographics, clinical characteristics, and outcome analysis of 25 patients with carbapenem resistance-only *Pseudomonas aeruginosa* (CROPA) bacteremia and 50 patients with all-susceptible *P. aeruginosa* (ASPA) bacteremia.

Variables	CROPA ($n = 25$)	ASPA ($n = 50$)	p
Demographics			
Sex, male	12 (48.0)	24 (48.0)	>0.999
Age (y)	61.6 ± 18.3	62.0 ± 17.9	0.935
Length of hospital stay (d)	42.8 ± 37.3	18.8 ± 28.0	0.002
Comorbidities[a]			
Diabetes mellitus	10 (40.0)	13 (26)	0.165
Hypertension	9 (36.0)	14 (28)	0.326
End stage renal disease	3 (12)	7 (14)	0.559
Liver cirrhosis	2 (8)	2 (4)	0.407
Solid organ cancer	8 (32)	19 (38)	0.402
Hematologic malignancy	3 (12)	10 (20)	0.302
COPD	3 (12)	4 (8)	0.429
CVA	4 (16)	9 (18)	0.552
Initial presentations			
Nosocomial infection	22 (88)	31 (62)	0.020
Pittsburgh score	3.9 ± 2.5	2.2 ± 2.3	0.007
White blood cells ($\times 10^9$/L)	10.236 ± 8.417	11.487 ± 8.325	0.541
Haemoglobin (g/dL)	9.6 ± 2.2	9.6 ± 2.2	0.975
Platelet ($\times 10^9$/L)	110.9 ± 107.3	159.7 ± 117.1	0.090
C-reactive protein (mg/L)	169.3 ± 161.4	110.9 ± 92.6	0.175
Creatinine (mg/dL)	1.5 ± 1.0	2.2 ± 2.6	0.097
Bacteraemia source[b]			
Primary	12 (48)	21 (42)	0.341
Lower respiratory tract infection	10 (40)	9 (18)	0.078
Intra-abdominal infection	0 (0)	2 (4)	0.441
Skin and skin structure infection	0 (0)	2 (4)	0.441
Urinary tract infection	2 (8)	11 (22)	0.115
CRBSI	1 (4)	6 (12)	0.250
Intra-vascular catheters	20 (80)	30 (60)	0.068
Antibiotic exposure within 3 mo[c]			
Penicillin class antibiotics	7 (28)	12 (24)	0.707
Aminoglycosides	4 (16)	7 (14)	>0.999
Cephalosporins	18 (72)	26 (52)	0.097
Antipseudomonal cephalosporins	13(52)	11 (22)	0.009
Carbapenems	17 (68)	4 (8)	<0.001
Fluoroquinolones	6 (24)	5 (10)	0.106
Glycopeptides	13 (52)	10 (20)	0.005
30-day mortality	18 (72)	13 (26)	<0.001

[a] There was no statistic difference in comorbidities and the source of bacteremia between CROPA and ASPA groups.
[b] There were two patients in the ASPA group having both lower respiratory tract infection and urinary tract infection.
[c] Penicillin class antibiotics include penicillin, oxacillin, ampicillin, amoxicillin–clavulanate, ampicillin–sulbactam, piperacillin, and piperacillin–tazobactam. Aminoglycosides include gentamicin and amikacin. Antipseudomonal cephalosporins include ceftazidime, cefepime, and cefpirome. Carbapenems include ertapenem, imipenem, and meropenem. Fluoroquinolones include moxifloxacin, levofloxacin, and ciprofloxacin. Glycopeptides include vancomycin and teicoplanin.
Data are presented as n (%) or mean ± SD.
COPD = chronic obstructive pulmonary disease; CRBSI = catheter-related blood stream infection; CVA = cerebrovascular accident; SD = standard deviation.

patients was 72.0%, as compared to 26.0% for the controls ($p < 0.001$; Table 1).

Influence of appropriate antibiotic therapy and the survival analysis of patients with CROPA bacteremia

A comparison between the surviving and nonsurviving patients with CROPA bacteremia showed that those who died had a more severe anemia (9.0 ± 2.0 g/dL vs. 11.2 ± 2.0 g/dL, $p = 0.042$) and a lower platelet count (72.4 ± 61.8 × 10^9/L vs. 226.2 ± 136.8 × 10^9/L, $p = 0.01$), but there was no statistical difference in Pittsburgh bacteremia score between them (Table 3). All those who survived (7/7, 100%) had an appropriate initial empirical antibiotic treatment, but more than half of the deceased patients (10/18, 55.6%) did not have the appropriate initial empirical antibiotic treatment ($p = 0.02$; Table 3). The

Table 2 Multivariate analysis of risk factors for carbapenem resistance-only *Pseudomonas aeruginosa* bacteremia.

Variables[a]	Odds ratio (95% CI)	*p*
Carbapenem within 3 mo[b]	360.72 (8.101−16061.832)	0.002
Antipseudomonal cephalosporins within 3 mo[c]	0.237 (0.017−3.275)	0.283
Glycopeptides within 3 mo[d]	2.182 (0.339−14.024)	0.411
Hospital stay	0.970 (0.932−1.010)	0.140
Pittsburgh score	1.361 (0.974−1.903)	0.071
Platelet count	1.000 (0.094−1.007)	0.938
Creatinine	0.558 (0.282−1.102)	0.093

[a] The variables with $p < 0.1$ in univariate analysis of Table 1 were included in a multivariate regression model.
[b] Carbapenems include ertapenem, imipenem and meropenem.
[c] Antipseudomonal cephalosporins include ceftazidime, cefepime, and cefpirome.
[d] Glycopeptides include vancomycin and teicoplanin.
CI = confidence interval.

inappropriate initial empirical antibiotic prescribed for these 10 deceased patients included imipenem ($n = 6$), meropenem ($n = 1$), cefazolin ($n = 1$), cefuroxime ($n = 1$), and tigecycline ($n = 1$). Among the 18 deceased patients, nine (50%) received carbapenems as initial empirical antibiotic treatment, but none of the survivors received carbapenems as initial empirical antibiotic treatment ($p = 0.027$; Table 3).

Discussion

Risk factors of developing carbapenem-resistant *P. aeruginosa* are comorbidities, length of hospital stay, mechanical ventilation, arterial catheter insertion, prolonged neutropenia, and broad-spectrum antipseudomonal antibiotic use.[6,9,15–17] Most of the carbapenem-resistant *P. aeruginosa* blood isolates in previous studies had cross-resistance to other antipseudomonal antibiotics.[3,6,7]

This study described the clinical characteristics, risk factors and prognosis of patients with bacteremia caused by CROPA strains, which have rarely been reported in the English literature. Under the multiple regression analysis, prior carbapenem exposure was the only risk factor for CROPA bacteremia. The difference between this study and previous studies is that we chose the patients with ASPA bacteremia as controls in order to remove the impact of carbapenem-susceptible *P. aeruginosa* isolates with varied susceptibility to other antipseudomonal agents.

The implication and mechanism of this unique pattern of antibiotic resistance (carbapenem resistance only) in clinical *P. aeruginosa* isolates are not clear. Shu et al[13] conducted a matched-pair study comparing 10 genetically unrelated CROPA isolates with their counterpart carbapenem-susceptible strains. Briefly, the protein electrophoresis demonstrated OprD production in only one of the 10 carbapenem-susceptible isolates, while various *oprD* mutations with early terminations were demonstrated in nine of the 10 CROPA isolates. Besides, RNA analysis revealed *oprM* hyperexpression with normal *mexA* expression in eight of the carbapenem-susceptible ones, while the *oprM* expression was reduced in seven of their CROPA counterparts. Under antibiotic selective pressure, reduced production of OprM promoted the selective spontaneous changes in *oprD*, leading to the carbapenem resistance in a group of pan-susceptible *P. aeruginosa* isolates carrying an *oprD*-group 1A allele, particularly imipenem.[13] In our study, 17 case patients (68%) had ever received carbapenem

Table 3 A comparison between the survived and the deceased among patients with for carbapenem resistance-only *Pseudomonas aeruginosa* bacteremia.

Variables	Deceased ($n = 18$)	Survived ($n = 7$)	*p*
Initial presentations			
Nosocomial infection	17 (94.4)	5 (71.4)	0.180
Pittsburgh score	4.3 ± 2.6	2.6 ± 2.0	0.112
White blood cells ($\times 10^9$/L)	9.183 ± 9.596	12.942 ± 3.261	0.109
Haemoglobin (g/dL)	9.0 ± 2.0	11.2 ± 2.0	0.042
Platelet ($\times 10^9$/L)	72.4 ± 61.8	226.2 ± 136.8	0.010
Creatinine (mg/dL)	1.4 ± 0.8	1.7 ± 1.7	0.649
Treatment			
Appropriate initial empirical antibiotics	8 (44.4)	7 (100.0)	0.020
Initial empirical treatment with carbapenems[a]	9[b] (50.0)	0 (0.0)	0.027

[a] Carbapenems include imipenem and meropenem.
[b] Seven patients had carbapenem as inappropriate initial empirical therapy, and two patients had the change of carbapenems to the appropriate treatment within 3 days of blood culture collection.
Data are presented as *n* (%) or mean ± SD.

treatment before CROPA bacteremia onset and selective pressure from carbapenems might be the most important factor for *P. aeruginosa* to develop such a type of drug resistance.

In this study, the all-cause mortality of patients with CROPA bacteremia was up to 72.0%, which was not only much higher than that of the control (26.0%), but also higher than that in previous studies for *Pseudomonas* bacteremia, which ranged from 25.2% to 58.8%.[2,3,18,19] Compared to carbapenem-susceptible *P. aeruginosa* bacteremia, carbapenem-resistant *P. aeruginosa* bacteremia had a higher mortality.[16,18,20] Factors for the higher mortality in patients with *P. aeruginosa* bacteremia are nosocomial infection, underlying diseases, severe sepsis, acute respiratory failure, respiratory tract infection, and delay in initiating effective antimicrobial therapy.[2,3,15,19,21]

This study revealed that the appropriateness of empirical antibiotics was associated with a better survival rate by the 30th day. Similarly, at least two retrospective cohort studies for patients with *P. aeruginosa* bloodstream infection reported that inappropriate empirical antimicrobial treatment was associated with greater in-hospital mortality among patients with infections.[22,23] In our study, all of the surviving patients had appropriate initial empirical antibiotic treatment, while all of the 10 patients who had received inappropriate initial empirical antibiotic treatment died, including seven (70%) receiving carbapenems. In addition to the seven patients, two had initial empirical antibiotic treatment with carbapenems, and changed carbapenems to appropriate antibiotics within 3 days of blood culture collection. Both of them also died within 2 weeks, and all nine patients with initial empirical antibiotic treatment using carbapenems had poor outcome. Thus, it is advised to prescribe carbapenems carefully and to not repeat using carbapenems in patients who had carbapenem treatment for serious infections.

In conclusion, this is the first matched case—control study focusing on CROPA. CROPA bacteremia was associated with a high mortality. Prudent use of carbapenem is the best strategy to reduce the emergence of CROPA in the hospital setting. Appropriate choice of empirical antibiotic therapy may have a better survival among patient with CROPA bacteremia. This study alerts physicians that the emergence of CROPA in hospital settings could be an issue of infection control.

Conflicts of interest

All authors declare no conflicts of interest.

References

1. Klevens RM, Edwards JR, Gaynes RP, National Nosocomial Infections Surveillance System. The impact of antimicrobial resistant, health care-associated infections on mortality in the United States. *Clin Infect Dis* 2008;**47**:927—30.
2. Kang CI, Kim SH, Kim HB, Park SW, Choe YJ, Oh MD, et al. *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and influence of delayed receipt of effective antimicrobial therapy on clinical outcome. *Clin Infect Dis* 2003;**37**:745—51.
3. Suárez C, Peña C, Tubau F, Gavaldà L, Manzur A, Dominguez MA, et al. Clinical impact of imipenem-resistant *Pseudomonas aeruginosa* bloodstream infections. *J Infect* 2009;**58**:285—90.
4. Deshpande LM, Fritsche TR, Jones RN. Molecular epidemiology of selected multidrug-resistant bacteria: a global report from the SENTRY Antimicrobial Surveillance Program. *Diagn Microbiol Infect Dis* 2004;**49**:231—6.
5. Furtado GH, Bergamasco MD, Menezes FG, Marques D, Silva A, Perdiz LB, et al. Imipenem-resistant *Pseudomonas aeruginosa* infection at a medical-surgical intensive care unit: risk factors and mortality. *J Crit Care* 2009;**24**:625. e9—14.
6. Onguru P, Erbay A, Bodur H, Baran G, Akinci E, Balaban N, et al. Imipenem-resistant *Pseudomonas aeruginosa*: risk factors for nosocomial infections. *J Korean Med Sci* 2008;**23**:982—7.
7. Dambrauskiene A, Adukauskiene D, Jeroch J, Vitkauskiene A. *Pseudomonas aeruginosa* bacteremia: associations with a source of infection and antibiotic resistance. *Medicina (Kaunas)* 2009;**45**:1—7 [Article in Lithuanian].
8. Zhang JF, Chen BL, Xin XY, Zhao HB, Wang HY, Song H, et al. Carbapenem resistance mechanism and risk factors of *Pseudomonas aeruginosa* clinical isolates from a University Hospital in Xi'an, China. *Microb Drug Resist* 2009;**5**:41—5.
9. Tam VH, Chang KT, LaRocco MT, Schilling AN, McCauley SK, Poole K, et al. Prevalence, mechanisms, and risk factors of carbapenem resistance in bloodstream isolates of. *Pseudomonas aeruginosa*. *Diagn Microbiol Infect Dis* 2007;**58**:309—14.
10. Gutiérrez O, Juan C, Cercenado E, Navarro F, Bouza E, Coll P, et al. Molecular epidemiology and mechanisms of carbapenem resistance in *Pseudomonas aeruginosa* isolates from Spanish hospitals. *Antimicrob Agents Chemother* 2007;**51**:4329—35.
11. Büscher KH, Cullmann W, Dick W, Opferkuch W. Imipenem resistance in *Pseudomonas aeruginosa* resulting from diminished expression of an outer membrane protein. *Antimicrob Agents Chemother* 1987;**31**:703—8.
12. Clinical and Laboratory Standards Institute. *Performance standards for antimicrobial susceptibility testing; twenty-second informational supplement*. Wayne, PA: CLSI; 2012. CLSI document M100—S22.
13. Shu JC, Su LH, Chiu CH, Kuo AJ, Liu TP, Lee MH, et al. Reduced production of OprM may promote oprD mutations and lead to imipenem resistance in *Pseudomonas aeruginosa* carrying an oprD-Group 1A allele. *Microb Drug Resist* 2015;**21**:149—57.
14. Rhee JY, Kwon KT, Ki HK, Shin SY, Jung DS, Chung DR, et al. Scoring systems for prediction of mortality in patients with intensive care unit-acquired sepsis: a comparison of the Pitt bacteremia score and the Acute Physiology and Chronic Health Evaluation II scoring systems. *Shock* 2009;**31**:146—50.
15. Krcméry Jr V, Trupl J, Kunová A, Spánik S, Ilavská I, Hel'pianska L, et al. Imipenem-resistant *Pseudomonas aeruginosa* bacteremia in cancer patients: risk factors, clinical features and outcome. *Bratisl Lek Listy* 1996;**97**:647—51.
16. Zavascki AP, Cruz RP, Goldani LZ. Risk factors for imipenem-resistant *Pseudomonas aeruginosa*: a comparative analysis of two case-control studies in hospitalized patients. *J Hosp Infect* 2005;**59**:96—101.
17. Harris AD, Smith D, Johnson JA, Bradham DD, Roghmann MC. Risk factors for imipenem-resistant *Pseudomonas aeruginosa* among hospitalized patients. *Clin Infect Dis* 2002;**34**:340—5.
18. Joo EJ, Kang CI, Ha YE, Kang SJ, Park SY, Chung DR, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia: clinical impact of antimicrobial resistance on outcome. *Microb Drug Resist* 2011;**17**:305—12.
19. Vitkauskienė A, Skrodenienė E, Dambrauskienė A, Macas A, Sakalauskas R. *Pseudomonas aeruginosa* bacteremia: resistance to antibiotics, risk factors, and patient mortality. *Medicina (Kaunas)* 2010;**46**:490—5.

20. Lautenbach E, Synnestvedt M, Weiner MG, Bilker WB, Vo L, Schein J, et al. Imipenem resistance in *Pseudomonas aeruginosa*: emergence, epidemiology, and impact on clinical and economic outcomes. *Infect Control Hosp Epidemiol* 2010;**31**:47—53.
21. Suárez C, Peña C, Gavaldà L, Tubau F, Manzur A, Dominguez MA, et al. Influence of carbapenem resistance on mortality and the dynamics of mortality in *Pseudomonas aeruginosa* bloodstream infection. *Int J Infect Dis* 2010;**14**:e73—8.
22. Chamot E, El Boffi, Amari E, Rohner P, Van Delden C. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother* 2003;**47**:2756—64.
23. Micek ST, Lloyd AE, Ritchie DJ, Reichley RM, Fraser VJ, Kollef MH. *Pseudomonas aeruginosa* bloodstream infection: importance of appropriate initial antimicrobial treatment. *Antimicrob Agents Chemother* 2005;**49**:1306—11.