Risk Factors for Resistant Gram Negative Infections in Intensive Care Unit

Sercan SAHUTOGLU 1, Yusuf SAVRAN 2*, Bilgin COMERT 3*

ABSTRACT

Objective: The most common resistant gram negative bacteria isolated in hospital-acquired blood stream infections are Pseudomonas aeruginosa, Acinetobacter species and Klebsiella pneumoniae. These infections are associated with increased mortality rates. In this study, we aimed to identify the risk factors for emerging resistant gram negative bacterial infections.

Methods: Data of 280 patients hospitalized in Medical Intensive Care Unit (ICU) between September 1st, 2013 and September 30th, 2014 were reviewed retrospectively.

Results: Resistant gram negative bacterial infections were detected in 80 patients. Acinetobacter baumannii, Klebsiella pneumoniae and Pseudomonas aeruginosa were the most resistant strains, respectively. APACHE II score, duration of mechanical ventilation, length of ICU stay and length of hospital stay were independent risk factors for resistant gram negative bacteria isolation. Mechanical ventilation and central venous catheterization were related with increased mortality rates. Length of ICU stay was an independent risk factor for resistant A. baumannii isolation. Prolonged mechanical ventilation, hospital and ICU stay were common risk factors for resistant K. pneumoniae and P. aeruginosa isolation. Total parenteral nutrition was an additional risk factor for resistant K. pneumoniae isolation and mortality rates for K. pneumoniae were higher than the other bacteria.

Conclusion: In the management of critical patients; prolonged ICU and hospital stays should be avoided as much as possible and central venous catheterization should only be used for appropriate indications and removed as soon as possible to prevent resistant gram negative bacterial infections. In addition, mechanically ventilated patients should be weaned from the ventilator as soon as possible, parenteral nutrition products should not be used instead of enteral nutrition if it’s not necessary and antibiotics must be used appropriately.

Keywords: Bacteria, critical care, resistance, antibiotic, risk factors

Introduction

Despite advances in intensive care treatment modalities and broad-spectrum antibiotics, nosocomial blood-stream infections still cause a considerable amount of mortality and morbidity (1). Gram-negative bacteria constitute approximately 25% of blood-stream infections in intensive care unit (ICU)s (2). Pseudomonas aeruginosa, Acinetobacter spp. and Klebsiella pneumoniae are the leading gram-negative bacteria isolated in nosocomial blood-stream infections and cause extended hospital stay, increased economical burden and mortality (all-cause mortality >%40) (3,4).

Broad-spectrum antibiotics are widely used for various aerobic and anaerobic infections(5). Unfortunately, metallo-beta-lactamase related resistance in gram-negative bacteria and carbapenemase-related resistance in Klebsiella pneumoniae is growing widespread around the world since 1996. The resistance patterns cause inevitable morbidity and mortality especially in ICUs. There are many risk factors associated with increased resistance and mortality of which some can be avoidable.

In this retrospective case-control study we aimed to identify the risk factors that cause resistant Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae isolation in ICU and evaluate the necessary precautions to decrease mortality rates.
Materials and Methods

This study was conducted in a tertiary ICU of a university hospital. 280 adult patients admitted to ICU with any diagnosis who were hospitalised for more than 24 hours, anytime between September 1st, 2013 and September 30th, 2014 were enrolled in the study. Only the first stay period of rehospitalised patients were included in the study. There were no other exclusion criteria. The hospital registration records and ICU medical records of all patients were reviewed. Medical data including date of admission, age and gender, main ICU admission diagnosis, comorbid diseases [diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic renal failure (CRF), cancer, immune suppression etc.] total parenteral nutrition (TPN), major surgery in the last 3 months before ICU admission, central venous catheterization (CVC), mechanical ventilation (MV), length of ICU/hospital stay and duration of MV were recorded. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated.

In patients with clinical and laboratory signs indicating a responsible infection (fever, increased respiratory secretion, respiratory distress, pyuria, sepsis etc or radiological signs of active infection such as active infiltration in chest X-ray) blood, urine and tracheal aspiration were sampled for culture prior empirical antibiotherapy. Patients with a culture-positive (CP) (thought to be responsible of the infection excluding colonization) for Acinetobacter baumannii, Klebsiella pneumoniae and Pseudomonas aeruginosa in blood, urine and tracheal aspiration were identified with resistance patterns for each. The risk factors associated with isolation of resistant strains were evaluated. Resistance patterns of bacteriae are classified as: Pandrug-resistant (PDR); resistant to all antimicrobial agents, Extensively drug-resistant (XDR); resistant to some of the most effective antimicrobial agents and Multidrug-resistant (MDR); resistant to multiple antimicrobial agents.

All categorical variables were expressed as numbers and percentages. Categorical variables between groups were compared with chi-square or Fisher’s exact tests. The independent effect of each variable on resistant gram negative bacteria CP was assessed with multivariate logistic regression analysis backward conditional method. A two-tailed p value of <0.05 was considered statistically significant. Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences Version 22; IBM Corporation, USA) program.

Results

A total number of 280 patients were identified (152 males, 128 females). Identified underlying conditions in enrolled patients were pneumonia, congestive heart failure, chronic obstructive pulmonary disease exacerbation, sepsis/septic shock, complications due to malignancies, trauma, electrolyte disorders, ileus, pulmonary embolism, lipid embolism, gastrointestinal hemorrhage, acute respiratory distress syndrome, hepatic coma, hepatorenal syndrome, intoxications, diabetic ketoacidosis, complications secondary to acute and chronic renal failure, cerebrovascular diseases and acute pancreatitis. The sum of infected patients with gram-negative bacteria (GNB) CP were 80; 44 males and 36 females. The rest of the patients were classified as control group (108 males and 92 females). Median age of infected patients with GNBCP and GNB culture negativity (CN) were 68.2±15.1 and 66.5±17.3, respectively. Age and gender had no significant effect on CP (p=0.05). There was no statistically significant difference between GNBCP and GNBPC regarding comorbid conditions (p >0.05; Table 1). MV support was significantly higher in infected patients with GNBCP (p<0.005). CVC was found to be more frequent in patients with GNBCP (p<0.05). The mean of APACHE II scores was significantly higher in patients with GNBCP (p<0.01). The mean duration of MV, length of ICU and hospital stay were significantly higher in patients with GNBCP (p<0.001). In logistic regression analysis including APACHE II score, MV, length of ICU and hospital stay, CVC and duration of MV; only duration of MV was detected to be an independent risk factor for GNBCP (p<0.001). The impact of factors on resistant GNBCP is shown in Table 1.

Only 103 of 280 patients were survivors. The distribution of mortality according to gender was 107 males and 70 females. Male gender mortality was significantly higher (p<0.01). Among the studied comorbidities only cancer was detected to increase mortality significantly. 97 patients had a diagnosis of cancer of whom only 18 patients were survived. There was a significant relationship between cancer and mortality (p<0.001).

The number of patients with MV support, TPN usage, CVC and GNBCP were significantly higher in nonsurvivors (p<0.001, p<0.05, p<0.001 ve p<0.005; respectively).

Mean age of nonsurvivors and survivors were 68.6±15.4 and 64.3±18.4, respectively. The mean of APACHE II scores were higher, and duration of MV and length of ICU stay were significantly longer in nonsurvivors (p<0.001, p<0.001 and p<0.05; respectively).

Table 1. Impact of factors on GNB isolation

|                      | GNB CP (n=80) | GNB CN (n=200) | p value |
|----------------------|--------------|---------------|---------|
| Gender (m/f)         | 44/36        | 108/92        | >0.05   |
| Age                  | 68.2±15.1    | 66.6±17.3     | >0.05   |
| APACHE II score      | 30.3±6.5     | 27.6±9.1      | <0.01   |
| Duration of Mechanical Ventilation (days) | 28.3±24.1 | 7.4±14.4 | <0.001 |
| Length of ICU stay (days) | 31.2±25.8 | 10.1±11.9 | <0.001 |
| Length of hospital stay (days) | 47.3±31.5 | 25.0±24.2 | <0.001 |
| Complicated DM       | 8 (%10)      | 31 (%15.5)    | >0.05   |
| Noncomplicated DM    | 13 (%16.3)   | 29 (%14.5)    | >0.05   |
| COPD                 | 16 (%20)     | 38 (%19)      | >0.05   |
| CRF                  | 17 (%21.3)   | 41 (%20.5)    | >0.05   |
| Cancer               | 30 (%37.5)   | 67 (%33.5)    | >0.05   |
| Surgery              | 7 (%8.8)     | 16 (%8)       | >0.05   |
| Mechanical ventilation | 71 (%88.8) | 146 (%73)    | <0.005  |
| TPN                  | 31 (%38.8)   | 55 (%27.5)    | >0.05   |
| Immune suppression   | 17 (%21.3)   | 55 (%27.5)    | >0.05   |
| CVC                  | 79 (%98.8)   | 181 (%90.5)   | <0.05   |

APACHE: Acute Physiology and Chronic Health Evaluation, ICU: Intensive Care Unit, COPD: Chronic Obstructive Pulmonary Disease, CRF: Chronic Renal Failure, TPN: Total Parenteral Nutrition, CVC: Central Venous Catheterisation DM: Diabetes Mellitus
Logistic regression model analysis identified gender, APACHE II scores, cancer, length of ICU stay, CVC and duration of MV as independent risk factors for mortality. Factors affecting survival were displayed in Table 2.

PDR strain was not detected in analysis of cultures and antibiograms of 80 infected patients. A. baumannii was detected in 53 patients. 48 of them were XDR and 5 were MDR. Among the A. baumannii strains none were PDR. P. aeruginosa was detected in 19 patients; 6 XDR, 5 MDR and 8 sensitive strains. K. pneumoniae, detected in 39 patients with resistance patterns of 28 XDR, 9 MDR and 2 sensitive strains. The resistance patterns of these three bacteria are displayed in Table 3.

APACHE II scores, duration of MV, length of ICU and hospital stay and CVC were detected to be significantly higher in patients infected with A. baumannii (p < 0.005, p < 0.001, p < 0.001, p < 0.005 ve p < 0.02, respectively) (Table 4). Impact of factors on resistant A. baumannii strains are displayed in Table 4.

In logistic regression model analysis only length of ICU stay (p < 0.001) was detected as an independent risk factor for resistant A. baumannii infection.

Duration of MV, length of ICU stay and hospital stay were significantly longer in patients infected with resistant P. aeruginosa (p < 0.01, p < 0.01 and p < 0.001 respectively. Table 5).
Logistic regression analysis detected only duration of MV as an independent risk factor for *P. aeruginosa* CP (p<0.001).

Duration of MV, length of ICU and hospital stay were longer and TPN usage rates were significantly higher in patients with resistant *K. pneumoniae* infections (p<0.001, p<0.001, p<0.001 and p<0.05 respectively, Table 6). Logistic regression analysis detected only duration of MV as an independent risk factor for resistant *K. pneumoniae* CP (p<0.001).

**Discussion**

Nosocomial infections are risk factors for extended hospital stays, economical burden and mortality. Underlying comorbidities, frequent invasive procedures, ineffective infection control precautions and inappropriately long antibiotic administrations are mainly responsible of resistant strain isolations. Immune suppression and frequent administration of extended-spectrum antibiotics contribute to antimicrobial resistance in ICUs. (6).

A recent multinational study “European Prevalence of Infection in Intensive Care (EPIC II)” reported respiratory system as the main source of infection in 64% of patients enrolled worldwide (4). “Sepsis Occurrence in Acutely Ill Patients (SOAP)” study reported 37.4% prevalence for sepsis in 3.147 patients of whom 68 % of the source was respiratory system (7). In our study we detected sepsis and septic shock secondary to pneumonia in 138 (49.2%) of 280 patients as the leading source of infection. This was compatible with previous studies. Although, many studies report an increase in isolation of gram-positive bacteria such as coagulase-negative staphylococcus, S. aureus and *Enterococcus spp.* in the last years, gram negative bacteria are still the most common bacteria in ICUs and maintain their importance due to multidrug-resistance (8). Respiratory system specimen cultures showed the highest rate of isolation of bacteria in EPIC II study and gram-negative bacteria were the most common bacteria isolated. *P. aeruginosa* was the most common bacteria isolated followed by gram positive bacteria (*S. aureus* being the most common) and fungal infections (4). In a study from Turkey in 2005, the distribution of isolated gram-negative bacteria, was reported as 42% *P. aeruginosa*, 20% *E. coli*, 18% *Acinetobacter spp.* and 9% *Klebsiella spp.* (9). Al Johani et al. in a 5-year survey ICU study reported isolation of 66,6% gram-negative bacteria and 33,4% gram positive bacteria. The most common isolated gram-negative bacteria were *Acinetobacter spp.* (31,7%), *P. aeruginosa* (30,6%), *E. coli* (14,0%) and *K. pneumoniae* (10,2%) (10). In our study we evaluated only resistant strains of gram-negative bacteria including *A. baumannii, K. pneumoniae* and *P. aeruginosa* and reported a prevalence of %28,5. The most commonly isolated bacteria was *A. baumannii* %18,9 followed by *K. pneumoniae* %13,9 and *P. aeruginosa* %6,8. Especially, prevalence of *A. baumannii* varies between districts and countries. Regional precautions for infection may have an impact on infection rates which may explain different isolation prevalences in various studies.

Resistant GNB were identified in 80 patients in our study. 200 patients with none resistant GNB isolation were accepted as control group. Various studies have been conducted on this topic due to the increase in prevalence of resistance in years. ICU studies reported advanced age, comorbid diseases (e.g. DM, renal failure, malignancies, immune suppression), more severe disease states, sustained hospitalization prior ICU admission and long ICU stay as risk factors for resistance (4,11). In our study we detected significantly higher APACHE II scores, prolonged MV, ICU stay, and hospital stay in patients infected with GNB.

In a study by Michalopoulos et al. in 2011 there was no significant difference in APACHE II scores between the compared patient groups (12). In another study SAPS II score was not related with isolation of MDR strains in ICU, but SAPS II scores where higher in patients with infection (13). In our study; APACHE II score, duration of MV and length of ICU stay were detected as independent risk factors for GNBCP in logistic regression analysis. We detected higher APACHE II scores in patients infected with resistant GNB but age and gender were not significant risk factors for resistant GNBCP. This was compatible with most of the studies (4,12,13). Longer ICU and hospital stay were significant risk factors for resistant GNBCP which was compatible with prior studies. Joshi et al., reported a hospital stay of 8-14 days as a risk factor for isolation of nonfermentative GNB (14). Likewise, S. Nseir et al., detected longer hospital stay before ICU admission as significant risk factor (13). Comorbid diseases (myocardial infarction, gastrointestinal hemorrhage, congestive heart failure, liver and kidney failure, respiratory failure, trauma, sepsis), invasive procedures (dialysis, mechanical ventilation, tracheostomy, CVC), blood transfusion, operation, burns and trauma and utilization of antibiotics prior to ICU admission were reported as risk factors for isolation of nonfermentative GNB (15). In a study investigating the risk factors for bacteremia with MDR GNB, only DM was found to be significant risk factor among comorbid diseases (DM, CRF, COPD, cancer) (16). In our study we did not detect any significant relationship between DM,

### Table 6. Factors associated with resistant *K. pneumoniae* isolation

|                  | *K. pneumoniae* CP (n=37) | *K. pneumoniae* CN (n=243) | p value |
|------------------|---------------------------|---------------------------|---------|
| Gender (m/f)     | 20/17                     | 132/111                   | >0.05   |
| Age              | 60.7±15.4                 | 66.6±16.9                 | >0.05   |
| APACHE II        | 30.1±6.4                  | 28.1±8.7                  | >0.05   |
| Mechanical ventilation | 32 (%86.5)           | 185 (%76.1)               | >0.05   |
| Duration of Mechanical Ventilation (days) | 33.7±27.4       | 10.3±14.7                 | <0.001  |
| Length of ICU stay | 38.3±29.9                 | 12.8±14.8                 | <0.001  |
| Length of hospital stay     | 54.1±33.9                 | 27.9±25.7                 | <0.001  |
| Complicated DM   | 5 (%13.5)                 | 34 (%14)                  | >0.05   |
| Noncomplicated DM | 4 (%10.8)                | 38 (%15.6)                | >0.05   |
| COPD             | 9 (%24.3)                 | 45 (%18.5)                | >0.05   |
| CRF              | 10 (%27.0)                | 48 (%19.8)                | >0.05   |
| Cancer           | 15 (%40.5)                | 82 (%33.7)                | >0.05   |
| Surgery          | 5 (%13.5)                 | 18 (%7.4)                 | >0.05   |
| TPN              | 18 (%48.6)                | 68 (%28.0)                | >0.05   |
| Immune suppression | 8 (%21.6)                | 64 (%26.3)                | >0.05   |
| CVC              | 36 (%97.3)                | 224 (%92.2)               | >0.05   |

APACHE: Acute Physiology and Chronic Health Evaluation, ICU: Intensive Care Unit, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, CRF: Chronic Renal Failure, TPN: Total Parenteral Nutrition, CVC: Central Venous Catheterisation, CP: Culture Positivity
COPD, CRF, cancer, immune suppression and surgery; but MV was a significant risk factor for resistant GNB isolation. Joshi et al., reported invasive procedures as risk factor for nonfermentative GNB isolation (14). Baraibar et al., reported invasive interventions in respiratory system to be risk factor for respiratory system infections with nonfermentative bacteria (17). MV and CVC were reported as significant risk factors for sepsis and resistant GNB isolation (4,11,12,18). In the light of all these studies we think that reducing invasive interventions should decrease GNB isolations and resistance.

In our study mortality rates in patients infected with GNB was %77,5. In studies which enrolled only patients with resistant GNB infections, mortality rates were reported as 36-55%; whereas when both MDR GNB and sensitive GNB infections were enrolled, mortality in patients with CP was 14-92% and 4-54% in CN patients.

Previous studies reported that there is no significant difference in mortality between patients infected with non-resistant GNB and patients infected with multi-drug resistant GNB species (19-22). In studies focused on MDR GNB; MV, length of ICU stay and septic shock were identified as independent risk factors for mortality (23,24). Besides, delay in starting appropriate treatment, APACHE II score, presence of fatal comorbid disease, progression of pneumonia and advanced age were also detected as triggering factors for mortality (23,25-28). EPIC II study reported advanced age, presence of fatal comorbid disease, being infected with Acinetobacteri species, Pseudomonas aeruginosa and Enterococcus spp., MV, renal replacement therapy and comorbidities such as cancer, heart failure, cirrhosis and immune suppression as independent risk factors for mortality. In our study we detected male gender, high APACHE II score, prolonged MV, CVC, TPN and cancer as risk factors for increased mortality. Recent surgery was not a significant risk factor for mortality which is compatible with the study conducted by Michalopoulos et al (12).

TPN increases bacterial translocation in gut and especially in advanced aged and septic patients causes an increase in resistant bacterial overgrowth (29). A study in 2015 reported TPN as an independent risk factor for mortality in septic ICU patients due to pneumonia (30). Likewise, in our study the most common source of infection was pneumonia and TPN was detected as an independent risk factor for mortality.

In our study, mortality rates in culture positive resistant A.baumannii, K.pneumoniae and P.aeruginosa patients were higher and this finding was statistically significant especially for resistant A.baumannii and K.pneumoniae strains.

Up to date, various risk factors were identified for blood-stream infections with A.baumannii including length of ICU stay, MV, recent surgery, wide spectrum antibiotic history, immune suppression, trauma, burns, malignancies, CVC, invasive procedures and prolonged hospital stay (31-33). History of colonization with methicillin-resistant Staphylococcus aureus, prior consumption of beta-lactam antibiotics; especially carbapenems and floroquinolones, immobility, ICU stay, CVC, recent surgery , MV, hemodialysis and malignancies were reported as risk factors for evolution of resistant Acinetobacteria strains (34-36).

We detected higher APACHE II score, prolonged MV, prolonged hospital stay and CVC as risk factors for resistant Acinetobacter baumannii proliferation. 79,2% of the patients with CP for Acinetobacter baumannii could not survive. Infections with Acinetobacteria come up especially in mechanically ventilated patients. Although it is not possible to predict an exact mortality rate due to other comorbidities in ICU patients; different studies reported 35-75% mortality rates for Acinetobacteria associated pneumonia (37-40). A study reported higher mortality rates in patients infected with MDR Acinetobacter strains when compared to patients infected with sensitive strains but, when the underlying disease states and disease severities are considered the higher mortality rates in MDR strains were attributed to prolonged length of ICU and hospital stays (41). We also detected higher rates of resistant strains in patients with longer hospital and ICU stays.

The mortality rate of patients infected with K.pneumoniae was 81% in our study. K.pneumoniae infection is mainly observed in immune-compromised patients. DM, alcohol consumption, malignancies, hepatobiliary diseases, COPD, glucocorticoid consumption and renal failure are some of the risk factors for increased infection rates (42-44). Klebsiella spp. are responsible of 3-8% of nosocomial bacterial infections and the most common manifestations are urinary tract infections, pneumonia and primary bacteremia (45,46). Major risk factors are reported as prior antibiotic consumption and invasive instrumentation such as urinary catheters, endotracheal tubes and intravenous catheterization (45,46).

Extended spectrum beta lactamase (ESBL) positivity is identified to increase mortality in K.pneumoniae infections which may be as high as 50% (47). Prior wide spectrum antibiotic consumption is a major risk factor for multidrug resistance in K.pneumoniae strains (47,48). We detected significantly longer duration of MV, ICU and hospital stay and more TPN usage in patients infected with resistant K.pneumoniae strains. Regression analysis detected prolonged ICU stay as an independent risk factor for MDR K.pneumoniae strains. We had limited access to the patients’ prior antibiotic consumption and therefore could not study this factor.

The mortality rate of resistant P.aeruginosa culture positive patients was 72,7% in our study. P.aeruginosa is the most common MDR bacteria responsible of pneumonia in hospitalized patients. HITIT-2 surveillance study; a study investigating isolated P.aeruginosa species in Turkey, reported 55,5% of P.aeruginosa to be resistant to imipenem (49). Pseudomonas spp. are highly colonized in ICU’s, burn units, mechanical ventilators, chemotherapy units and in units with wide spectrum antibiotic consumption and this causes predisposition for invasive infections (49,50). We detected longer ICU and hospital stay and prolonged mechanical ventilation as risk factors for resistant P.aeruginosa isolation. Regression analysis detected prolonged mechanical ventilation as an independent risk factor for MDR P.aeruginosa isolation.

First limitation of our study is being a retrospective cohort study reflecting only a limited population during a limited time interval. Second limitation is not being able to reach most of the enrolled patients’ antibiotic consumption prior ICU admission.
Conclusions

It’s obvious that hospital environment itself and invasive procedures are sources for the spread of resistant strains. Control of disease precautions should be strictly applied in the whole hospital but especially in clinics where critically ill patients are hospitalized. Inappropriate unnecessary invasive procedures, prolonged ICU and hospital stays, prolonged mechanical ventilation, TPN usage and unnecessarily prolonged antibiotic treatment if applicable should be avoided.

References

1. Suljagić V, Cobelić M, Janković S, et al. Nosocomial bloodstream infections in ICU and non-ICU patients. Am J Infect Control 2005;33:333–40. [CrossRef]
2. Weinstein RA, Gaynes R, Edwards JR. Overview of nosocomial infections caused by gram-negative bacilli. Clin Infect Dis 2005;41:848–54. [CrossRef]
3. Sligl W, Taylor G, Brindley PG. Five years of nosocomial Gram-negative bacteremia in a general intensive care unit: epidemiology, antimicrobial susceptibility patterns, and outcomes. Int J Infect Dis 2006;10:320–5. [CrossRef]
4. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323–9. [CrossRef]
5. Hynes-Gay P, Lalla P, Leo M, et al. Understanding sepsis: from SIRS to septic shock. Dynamics 2002;13:17–20, 22–4; quiz 25–6.
6. Zaragoza R, Ramírez P, López-Pueyo MJ. Nosocomial infections in intensive care units. Enferm Infecc Microbiol Clin 2014;32:320–7. [CrossRef]
7. Sprung CL, Sakr Y, Vincent JL, et al. An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence in Acutely Ill Patients (SOAP) study. Intensive Care Med 2006;32:421–7. [CrossRef]
8. Hawkey PM. Multidrug-resistant Gram-negative bacteria: a product of globalization. J Hosp Infect 2015;89:241–7. [CrossRef]
9. Koseoglu Eser O, Kocagoz S, Ergin A, et al. Yoğun bakım unidadırında enfeksiyon etkeni olan gram-negatif basillerin değerlendirme. Infeksiyon Dergisi (Turkish Journal of Infection) 2005;19:75–80.
10. Al Johani SM, Akhter J, Balkhy H, et al. Prevalence of antimicrobial resistance among gram-negative isolates in an adult intensive care unit at a tertiary care center in Saudi Arabia. Ann Saudi Med 2010;30:364–9. [CrossRef]
11. Kaye KS, Cosgrove S, Harris A, et al. Risk factors for emergence of resistance to broad-spectrum cephalosporins among Enterobacter spp. Antimicrob Agents Chemother 2001;45:2628–30. [CrossRef]
12. Michalopoulos A, Falagas ME, Karatzas DC, et al. Epidemiologic, clinical characteristics, and risk factors for adverse outcome in multiresistant gram-negative primary bacteremia of critically ill patients. Am J Infect Control 2011;39:396–400. [CrossRef]
13. Neer S, Graillies G, Soury-Lavergne A, et al. Accuracy of American Thoracic Society/Infectious Diseases Society of America criteria in predicting infection or colonization with multidrug-resistant bacteria at intensive-care unit admission. Clin Microbiol Infect 2010;16:902–8. [CrossRef]
14. Joshi SG, Litake GM, Satpute MG, et al. Clinical and demographic features of infection caused by Acinetobacter species. Indian J Med Sci 2006;60:351–60. [CrossRef]
15. Fadda G, Spanu T, Ardito F, et al. Antimicrobial resistance among non-fermentative Gram-negative bacilli isolated from the respiratory tracts of Italian inpatients: a 3-year surveillance study by the Italian Epidemiological Survey. Int J Antimicrob Agents 2004;23:254–61. [CrossRef]
16. Karageorgopoulos DE, Falagas ME. Current control and treatment of multidrug-resistant Acinetobacter baumannii infections. Lancet Infect Dis 2008;8:751–62. [CrossRef]
17. Baraibar J, Correa H, Mariscal D, et al. Risk factors for infection by Acinetobacter baumannii in intubated patients with nosocomial pneumonia. Chest 1997;112:1050–4. [CrossRef]
18. Vincent JL, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006;34:344–53. [CrossRef]
19. Johnson LE, D’Agata EM, Paterson DL, et al. Pseudomonas aeruginosa bacteremia over a 10-year period: multidrug resistance and outcomes in transplant recipients. Transpl Infect Dis 2009;11:227–34. [CrossRef]
20. Lye DC, Earnest A, Ling ML, et al. The impact of multidrug resistance in healthcare-associated and nosocomial Gram-negative bacteraemia on mortality and length of stay: cohort study. Clin Microbiol Infect 2012;18:502–8. [CrossRef]
21. Ye JJ, Lin HS, Kuo AJ, et al. The clinical implication and prognostic predictors of tigecycline treatment for pneumonia involving multidrug-resistant Acinetobacter baumannii. J Infect 2011;63:351–61. [CrossRef]
22. Tumbarello M, Repetto E, Treccarichi EM, et al. Multidrug-resistant Pseudomonas aeruginosa bloodstream infections: risk factors and mortality. Epidemiol Infect 2011;139:1740–9. [CrossRef]
23. Lee NY, Lee HC, Ko NY, et al. Clinical and economic impact of multidrug resistance in nosocomial Acinetobacter baumannii bacteremia. Infect Control Hosp Epidemiol 2007;28:713–9. [CrossRef]
24. Cao B, Wang H, Sun H, et al. Risk factors and clinical outcomes of nosocomial multi-drug resistant Pseudomonas aeruginosa infections. J Hosp Infect 2004;57:112–8. [CrossRef]
25. Kuo LC, Lai CC, Liao CH, et al. Multidrug-resistant Acinetobacter baumannii bacteremia: clinical features, antimicrobial therapy and outcome. Clin Microbiol Infect 2007;13:196–8. [CrossRef]
26. Anderson DJ, Engemann JJ, Harrell L, et al. Predictors of mortality in patients with bloodstream infection due to ceftazidime-resistant Klebsiella pneumoniae. Antimicrob Agents Chemother 2006;50:1715–20. [CrossRef]

ETHICS COMMITTEE APPROVAL: Dokuz Eylül University Non-Interventional Clinical Research Ethics Committee 30/10/2014 no:2014/33-15

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.
27. Lim SK, Lee SO, Choi SH, et al. The outcomes of using colistin for treating multidrug resistant Acinetobacter species bloodstream infections. J Korean Med Sci 2011;26:325–31. [CrossRef]

28. Liao CH, Sheng WH, Chen YC, et al. Predictive value of the serum bactericidal test for mortality in patients infected with multidrug-resistant Acinetobacter baumannii. J Infect 2007;55:149–57. [CrossRef]

29. Vardakas KZ, Rafaillidou PI, Konstantelias AA, et al. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: the study, the patient, the bug or the drug? J Infect 2013;66:401–14. [CrossRef]

30. Takir HB, Karakurt Z, Salturk C, et al. Does Total Parenteral Nutrition Increase the Mortality of Patients with Severe Sepsis in the ICU? Turk Thorac J 2015;16:53–58. [CrossRef]

31. Wisplinghoff H, Edmond MB, Pfaller MA, et al. Acinetobacter baumannii ventilator-associated pneumonia: epidemiological and clinical findings. Intensive Care Med 2005;31:649–55. [CrossRef]

32. Chen HP, Chen TL, Lai CH, et al. Predictors of mortality in Acinetobacter baumannii bacteremia. J Microbiol Immunol Infect 2005;38:127–36.

33. Garcia-Garmendia JL, Ortiz-Leyba C, Garnacho-Montero J, et al. Risk factors for Acinetobacter baumannii nosocomial bacteremia in critically ill patients: a cohort study. Clin Infect Dis 2001;33:939–46. [CrossRef]

34. Tilley PA, Roberts FJ. Bacteremia with Acinetobacter species: risk factors and prognosis in different clinical settings. Clin Infect Dis 1994;18:896–900. [CrossRef]

35. Tacconelli E, Cataldo MA, De Pascale G, et al. Prediction models to identify hospitalized patients at risk of being colonized or infected with multidrug-resistant Acinetobacter baumannii calcoaceticus complex. J Antimicrob Chemother 2008;62:1130–7. [CrossRef]

36. Dizbay M, Tunccan OG, Sezer BE, et al. Nosocomial imipenem-resistant Acinetobacter baumannii infections: epidemiology and risk factors. J Infect Dis 2010;201;33:939–46.

37. Vitkauskiene A, Dambrauskiene A, Cerniauskiene K, et al. Risk factors and outcomes in patients with carbapenem-resistant Acinetobacter infection. Scand J Infect Dis 2013;45:213–8. [CrossRef]

38. Leung WS, Chu CM, Tsang KY, et al. Fulminant community-acquired Acinetobacter baumannii pneumonia as a distinct clinical syndrome. Chest 2006;129:102–9. [CrossRef]

39. Garnacho-Montero J, Ortiz-Leyba C, Fernández-Hinojosa E, et al. Acinetobacter baumannii ventilator-associated pneumonia: epidemiological and clinical findings. Intensive Care Med 2005;31:649–55. [CrossRef]

40. Fagon JY, Chastre J, Hance AJ, et al. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 1993;94:281–8. [CrossRef]

41. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, et al. Treatment of multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. Clin Infect Dis 2003;36:1111–8. [CrossRef]

42. Tsay RW, Siu LK, Fung CP, et al. Characteristics of bacteremia between community-acquired and nosocomial Klebsiella pneumoniae infection: risk factor for mortality and the impact of capsular serotypes as a herald for community-acquired infection. Arch Intern Med 2002;162:1021–7. [CrossRef]

43. Hasegawa C, Kim SH, Bang JW, et al. Community-acquired versus nosocomial Klebsiella pneumoniae bacteremia: clinical features, treatment outcomes, and clinical implication of antimicrobial resistance. J Korean Med Sci 2006;21:816–22. [CrossRef]

44. Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. Ann Intern Med 2004;140:26–32. [CrossRef]

45. Vardakas KZ, Proussas S, Tselioti P, et al. Predictors of mortality in patients with infections due to multi-drug resistant Gram negative bacteria: the study, the patient, the bug or the drug? J Infect 2013;66:401–14. [CrossRef]

46. Tumbarello M, Spanu T, Sanguinetti M, et al. Bloodstream infections caused by extended-spectrum-beta-lactamase-producing Klebsiella pneumoniae: risk factors, molecular epidemiology, and clinical outcome. Antimicrob Agents Chemotherapy 2006;50:498–504. [CrossRef]

47. Zarkotou O, Pournaras S, Tselioti P, et al. Predictors of mortality in patients with bloodstream infections caused by KPC-producing Klebsiella pneumoniae and impact of appropriate antimicrobial treatment. Clin Microbiol Infect 2011;17:1798–803. [CrossRef]

48. Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial infections. Ann Intern Med 2004;140:26–32. [CrossRef]

49. Gur D, Hascelik G, Aydin N, et al. Antimicrobial resistance in gram-negative hospital isolates: results of the Turkish HITTIT-2 Surveillance Study of 2007. J Chemother 2009;21:383–9. [CrossRef]

50. Bonten MJ, Weinstein RA. Transmission pathways of Pseudomonas aeruginosa in intensive care units: don’t go near the water. Crit Care Med 2002;30:2384–5. [CrossRef]