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Risk Factors for Resistant Gram Negative Infections in Intensive Care Unit

Sercan SAHUTOGLU[1], Yusuf SAVRAN[2], Bilgin COMERT[3]

[1]Aegean University Faculty of Medicine, Department of Internal Medicine, Izmir, Turkey

[2]Dokuz Eylul University Faculty of Medicine, Department of Internal Medicine , Izmir, Turkey

[3]Dokuz Eylul University Faculty of Medicine, Department of Medical Intensive Care, Izmir, Turkey

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Corresponding Author: Yusuf Savran
E mail: yusuf.savran@deu.edu.tr

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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 bacteriae.

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 an 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-positivity (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-resistanct (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 GNBCN 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±11.4	<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

Table 2. Impact of factors on survival

	Nonsurvivors (n=177)	Survivors (n=103)	p value
Gender (m/f)	107/70	45/58	<0.01
Age	68.6±15.4	64.3±18.4	>0.05
APACHE II	31.1±7.3	23.7±8.4	<0.001
Mechanical ventilation	161 (%91.0)	56 (%54.4)	<0.001
Duration of Mechanical Ventilation (days)	17.2±20.9	6.8±11.2	<0.001
Length of ICU stay	18.1±21.7	12.8±14.4	<0.05
Length of hospital stay	29.1±26.1	35.3±31.5	>0.05
Complicated DM	26 (%14.7)	13 (%12.6)	>0.05
Noncomplicated DM	26 (%14.7)	16 (%15.5)	>0.05
COPD	34 (%19.2)	20 (%19.4)	>0.05
CRF	40 (%22.6)	18 (%17.5)	>0.05
Cancer	79 (%44.6)	18 (% 17.5)	>0.001
Surgery	14 (%7.9)	9 (%8.7)	>0.05
TPN	64 (%36.2)	22 (%21.4)	>0.05
Immune suppression	52 (%29.4))	20 (%19.4)	>0.05
CVC	176 (%99.4)	84 (%81.6)	<0.001
GNB CP	62 (%35)	18 (%17.5)	<0.005
Resistant *A.baumannii*	42 (%23.7)	11 (%10.7)	<0.01
Resistant *P.aeruginosa*	8 (%4.5)	3 (%2.9)	>0.05
Resistant *K.pneumoniae*	30 (%16.9)	7 (%6.8)	>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 , GNB CP: Gram-negative bacteria culture positivity

Table 3. The distribution of isolated GNB according to resistance patterns

	Sensitive	MDR	XDR	PDR	Total
A.baumannii	0	5 (%1.8)	48 (%17.1)	0	53 (%18.9)
P.aeruginosa	8 (%2.9)	5 (%1.8)	6 (%2.1)	0	19 (%6.8)
K.pneumoniae	2 (%0.7)	9 (%3.2)	28 (%10)	0	39 (%13.9)

MDR: Multi drug resistant, XDR: Extensively-drug resistant, PDR: pandrug resistant

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.

Table 4. Factors associated with resistant *A.baumanii* isolation

	A.baumanii CP (n=53)	*A.baumanii* CN (n=227)	p value
Gender (m/f)	32/21	120/107	>0.05
Age	66.5±16.0	67.2±16.9	>0.05
APACHE II	30.8±5.4	27.8±8.9	<0.005
Mechanical ventilation	46 (%86.8)	171 (%75.3)	>0.05
Duration of Mechanical Ventilation (days)	26.1±22.3	10.4±16.3	<0.001
Length of ICU stay	29.2±23.6	13.1±17.1	<0.001
Length of hospital stay	42.4±29.1	28.8±27.5	<0.005
Complicated DM	6 (%11.3)	33 (%14.5)	>0.05
Noncomplicated DM	9 (%17)	33 (%14.5)	>0.05
COPD	10 (%18.9)	44 (%19.4)	>0.05
CRF	12 (%22.6)	46 (%20.3)	>0.05
Cancer	19 (%35.8)	78 (%34.4)	>0.05
Surgery	5 (%9.4)	18 (%7.9)	>0.05
TPN	16 (%30.2)	70 (%30.8)	>0.05
Immune suppression	8 (%15.1)	64 (%28.2)	>0.05
CVC	53 (%100)	207 (%91.2)	>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 , GNB CP: Gram-negative bacteria culture positivity

Table 5. Factors associated with resistant *P.aeruginosa* isolation

	P.aeruginosa CP (n=11)	*P.aeruginosa* CN (n=269)	p value
Gender (m/f)	4/7	148/121	>0.05
Age	70.7±11.9	66.9±16.8	>0.05
APACHE II	32.6±5.8	28.2±8.5	>0.05
Mechanical ventilation	10 (%90.9)	207 (%77.0)	>0.05
Duration of Mechanical Ventilation (days)	38.9±27.3	12.3±17.5	<0.01
Length of ICU stay	42.8±26.9	15.1±18.4	<0.01
Length of hospital stay	64.4±36.1	30.0±27.1	<0.001
Complicated DM	2 (%18.2)	37 (%13.8)	>0.05
Noncomplicated DM	2 (%18.2)	40 (%14.9)	>0.05
COPD	2 (%18.2)	52 (%19.3)	>0.05
CRF	5 (%45.5)	53 (%19.7)	>0.05
Cancer	3 (%27.3)	94 (%34.9)	>0.05
Surgery	1 (%9.1)	22 (%8.2)	>0.05
TPN	4 (%36.4)	82 (%30.5)	>0.05
Immune suppression	2 (%18.2)	70 (%26.0)	>0.05
CVC	11 (%100)	249 (%92.6)	>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, GNB CP: Gram-negative bacteria culture positivity

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.).

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	69.5±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	38.1±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

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% prevalance 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.aeuroginosa* and reported a prevalance of %28,5. The most commonly isolated bacteria was *A.baumannii* %18,9 followed by *K.pneumoniae* %13,9 and *P.aeuroginosa* %6,8. Especially, prevalance of *A.baumannii* varies between districts and countries. Regional precautions for infection may have an impact on infection rates which may explain different isolation prevalances 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 prevalance 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, tracheosthomy, 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,

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.aeuroginosa* 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.

AUTHOR CONTRIBUTIONS:

Concept: SS, BC; **Design:** BC, YS; **Supervision:** BC, YS; **Fundings:** BC, SS, YS; **Materials:** SS, BC, YS; **Data Collection and/or Processing:** SS, YC, BC; **Analysis and/or Interpretation**: SS, BC, YS; **Literature Search:** SS, YC, BC; **Writing Manuscript**: SS, YC, BC; **Critical Review:** BC, YS, SS.

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