The Effect of Infection Agents Obtained From Intensive Care Patients on the Resistance Pattern and Patient Outcomes

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ABSTRACT

Objective: Infection is a significant problem associated with increased morbidity and mortality in intensive care units (ICU). This study aimed to examine the effect of infectious agents obtained from Medical ICU on the resistance pattern and the patient outcomes in a 3 year period retrospectively.

Material and Method: The patients with positive culture results while hospitalized in a tertiary level medical ICU between January 2016 and April 2019 were included in the study. The patients were grouped as survivors and non-survivors. These groups were compared for infection foci, infectious agents, mortality, and the sensitivity of the infectious pathogens to the antibiotics.

Results: From a total of 426 patients admitted to ICU with the diagnosis of infection, culture positivity was determined in 212 samples. The highest rates of positivity were determined from the urinary tract specimens (n:90, 42.4%), followed by bloodstream specimens (n:62, 29.2%) and then lower respiratory tract specimens (n:47, 22.1%). The most frequently isolated micro-organisms were gram-negative bacteria (n.152, 70.6%) and within these, the most common micro-organism was *Escherichia coli* (n:59, 27.8%). When the micro-organisms evaluated according their antibiotic susceptibility it was found that, *A. baumanii* strains were sensitive to colistin, and *K. pneumonia*, *E.coli*, and *Pseudomonas aeruginosa* (*P. aeruginosa*) strains were sensitive to aminoglycosides and colistin. The mortality rate of the hospitalized patients because of infection was found to be 51.8% (n:112).

Conclusion: When selecting empirical antibiotics in the treatment of infection in critically ill patients, the intensive care unit flora and the antibiotic resistance patterns must be known. Therefore, it is important to periodically determine the infectious agents and antibiotic sensitivity.

Key words: Infection, intensive care unit, antibiotic resistance, mortality

Introduction

One of the most common diagnoses for Intensive Care Unit (ICU) admission is an infection, and the multiple drug-resistant (MDR) micro-organisms are most frequently seen in the ICUs (1, 2). Infections caused by MDR micro-organisms are associated with high morbidity and mortality due to prolonged hospitalization because of the failure of antibiotic treatment, and these continue to be a significant problem worldwide (3). Infection agents and resistance characteristics can show differences between regions, hospitals, and even between different ICUs within a hospital. In the light of these data, it is important for the selection of antibiotics that there is the determination of bacteria isolated from ICUs and their antibiotic resistance profiles.

This study aimed to determine the positive cultures and antibiotic sensitivity of microorganisms in the soft tissue, urine, blood, catheter and endotracheal aspirate (ETA) samples in a medical ICU.

Material and Method

Patients with positive cultures who were admitted to ICU with the initial diagnosis of infection between January 2016 and April 2019 were evaluated retrospectively. The culture samples were obtained from patients with the findings of sepsis/septic shock or at least two of leukocytosis, leukopenia, hypo/hyperthermia, tachycardia, and tachypnea at the ICU admission. The culture samples were taken before starting antibiotics.

The blood, urine, sputum/ETA, or soft tissue culture samples were taken following the

asepsis and antisepsis rules. If the culture resulted as positive and consistent with the patient's clinical status, it was accepted as the infectious agent. In study period culture positivity were reported in 212 samples from 426 patients' samples. Recurrent positive cultures from the same foci of infection from the same patient were excluded from the study.

Patients were grouped as survivors and non-survivors. Age, gender, ICU admission diagnosis, the Simplified Acute Physiology Score (SAPS II) disease score, the requirement for mechanical ventilation and vasopressors, micro-organisms identified in the cultures, and the antibiotics resistance patterns of infectious agents were recorded.

Approval for the study was granted by the Ethics Committee of the university and the Internal Diseases Department academic board. All procedures were applied in compliance with the Helsinki Declaration.

Statistical Analysis

Data obtained in the study were analyzed using SPSS for Windows vn. 22.0 software (IBM Corpn., Armonk, NY, USA). Conformity of the variables to normal distribution was assessed with the Kolmogorov-Smirnov test and antibiotic sensitivity was evaluated with the Chi-square test and Fisher's Exact test. Descriptive statistics were stated as mean ± standard deviation (SD), median and interquartile range (IQR) values, number (n), and percentage. Categorical variables were compared using the Chi square test, and continuous variables with the Student's t-test. A value of $p \leq 0.05$ was considered statistically significant.

Results

Micro-organism production was determined in the cultures taken from various regions because of infection status in 212 of 426 (49.7%) patients in ICU. The 212 patients comprised 110 (51.8%) females and 102 (48.2%) males, all admitted from the Emergency Department. Comorbidities were determined as diabetes mellitus in 68 (32%) patients and hypertension in 77 (36.3%). The patients with culture production were separated into two groups according to the ICU outcome, as survivors and non-survivors. The comparisons of these groups are shown in Table 1. In the non-survivor patient group, age was determined to be older, the SAPS II disease score was higher, length of stay in hospital was longer, and there was a greater need for mechanical ventilation and vasopressors.

Table 1. Demographic and clinical characteristics, and comorbidities of the patients

		Univariate analysis		
		Non-survivor n=110(%51.8)	Survivor n=102(%48.2)	Chi- square test
		n (%)	n (%)	p*
Sex	Male	55(50)	47(46)	0.433
	Female	55(50)	55(54)	
Service admitted to intensive care unit	Emergency	68(61.8)	52(50.9)	
	Internal medicine	23(20.9)	27(26.4)	
	Palliative service	9(8.1)	7(6.8)	
	Orthopedics service	5(4.5)	5(4.9)	
	Other intensive care unit	4(3.6)	8(7.8)	
	Other services	1(0.9)	3(2.9)	
Co-morbidities	Diabetes mellitus	39(35.4)	29(28.4)	
	Hypertension	36(32.7)	37 (36.2)	
	Chronic obstructive pulmonary disease	26(23.6)	18(17.6)	
	Coronary artery disease	21(28.2)	18(17.6)	
	Congestive heart failure	13(11.8)	9(8.8)	
	Chronic renal failure	9(8.1)	5(4.9)	
	Malignancy	5(4.5)	8(7.8)	
Admission diagnosis	Metabolic disorder	61(55.4)	57(55.8)	
	Sepsis/Septic shock	54 (49)	73 (71.5)	
	Pneumonia	21(19)	26(25.4)	
	Respiratory Failure	19 (17.2)	30 (29.4)	
	Acute kidney injury	17(15.4)	21(20.5)	
	Cardiac disease	11(10)	19(18.6)	
	Gastrointestinal disease	9(8.1)	16(15.6)	
	Post CPR	18(16.3)	4 (3.9)	
	Neurological disease	16(14.5)	7(6.8)	
Invasive mechanical ventilation[&]	No	33 (30)	78 (76.4)	<0.001
	Yes	77 (70)	24 (23.5)	
Vasopressor [&]	No	14 (12.7)	81 (79.5)	<0.001
	Yes	96 (87.3)	21 (20.5)	
		Mean±SD	Mean±SD	Student's-t test
Age	year	72.80±13.63	66.43±17.66	<0.001
SAPSII [&]		17.65±12.8	13.51±10.4	0.002
Length of ICU stay [&]	day	19.4±17.5	13.9±15.6	0.016

*Chi-square test, "n=number (percentage)", SD: Standard Deviation, SAPSII: Simplified Acute Physiology Score [&] The data that were significant in univariate analysis were taken into multivariate analysis, Disease history and diagnosis of intensive care admission may include more than one disease.

In both groups, the highest positivity was obtained in the cultures from urinary catheters (n:90, 42.4%), and in the non-survivors from the lower respiratory tract (n:10, 37.3%). The foci of infection in both groups are shown in Table 2. The most frequently isolated micro-organisms were gram-negative bacteria (n.152, 70.6%) and within these, the most common bacteria were *Escherichia coli (E. coli)* (27.8%), *Klebsiella pneumonia(K. pneumonia)* (19.3%), and *Acinetobacter baumanii(A. baumanii)* (17.4%). The most common agent of infection was *A. baumanii* (28.2%) in the non-survivors and *E. coli* (34.3%) in the survivors'.

The infectious agents in both groups are shown in Table 3 infectious. The resistance rates of the gram-negative bacteria are shown in Table 4. The most frequently isolated gram-positive bacteria were coagulase-negative *Staphylococci(Staph.)* (14.1%) and *Enterococcus spp(Enter.)* (11.3%). In coagulase-negative *Staph*, methicillin resistance was determined at the rate of 67.4%. All the coagulase-negative *Staph* strains were determined to be sensitive to vancomycin. The antibiotics initiated on admission are shown in Table 5. No difference was determined between the two groups in respect of the antibiotics administered.

In the multivariate analysis, predictors of mortality in ICU were determined to be a high SAPS II score (odds ratio [OR], 1.49; 95% confidence interval [CI], 1.23–1.61), the requirement for invasive mechanical ventilation (OR, 2.97; 95% CI, 1.37–7.22), the requirement for vasopressors (OR, 3.08; 95% CI, 1.54–6.33), *A. baumanii* infection (OR, 6.27; 95% CI, 1.98– 19.6), and source of infection in the lower respiratory tract (OR, 8.19; 95% CI, 1.53–32.4). The urinary system as the source of infection was determined to be a protective factor (OR, 0.35; 95% CI, 0.19–0.82).

Table 2. Source of infection of the two groups

	Non-survivor n(%)	Survivor n(%)	p*
Lower respiratory tract	41(37.3)	6(5.9)	<0.001
Urinary tract	33(30)	57(55.9)	<0.001
Bloodstream	30(27.3)	32(31.4)	0.512
Soft tissue	6(5.5)	7(6.9)	0.669

*Pearson Chi-Square test, n=number

Table 3. Comparison of the two groups according to the infectious agent

	Non-survivor n(%)	Survivor n(%)	P*
Acinetobacter Baumanii	**31(28.2)**	6(5.9)	<0.001
Escherichia-Coli	24(21.8)	35(34.3)	0.060
Klebsiella Pneumonia	18(16.4)	23(22.5)	0.333
Staphylococus Aerus	15(13.6)	15(14.7)	0.739
Pseudomonas Aeruginosa	10(10)	3(3.9)	0.085
Enterococcus Faecalis	10(9.1)	14(13.7)	0.287
Streptococcus Pneumonia	2(1.8)	4(3.9)	0.356

*Pearson Chi-Square test, n=number

Table 4. Antibiotic resistance rate of gram negative bacteria (%)

Antibiotics	Escherichia Coli	Klebsiella pneumonia	Pseudomonas Aeruginosa	Acinetobacter Baumanii
Ampicillin / sulbactam	76.3	100	-	-
Amoxicillin / clavulanate	76.3	100	-	-
Amikacin	5.3	17.1	30.8	78.4
Gentamycin	5.3	17.1	39.1	70.3
Piperacillin / tazobactam	9.1	72.5	53.8	97.2
Levofloxacin	60	84.2	61.5	100
Ciprofloxacin	52.4	86.7	61.5	100
Imipenem	0	55.6	49.4	78.2
Meropenem	0	51.3	41.7	73.6
Ceftriaxone	41.4	78	61.5	100
Ceftazidime	40.7	78	53.8	100
Colistin	7.1	30.3	12.5	21.4
Tigecycline	-	73.9	-	83.3
Trimethoprim / sulfomethoxazole	73.3	83.3	-	50

Table 5. Comparison of antibiotics initiated on the first day of intensive care hospitalization between the two groups

	Non-survivor n(%)	Survivor n(%)	p*
Ceftriaxone	46(41.8)	52(50.9)	0.11
Fluoroquinolone	26(23.6)	20(19.6)	0.47
Piperacillin / tazobactam	20(18.2)	20(19.6)	0.79
Carbapenem	22(20)	15(14.7)	0.31
Teicoplanin	5(4.5)	3(2.9)	0.54
Linezolid	7(6.4)	3(2.9)	0.24

*Pearson Chi-Square test, n=number, There are patients who were started on more than one antibiotic treatment.

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Table 6. Multivariate logistic regression model of predictors of mortality in patients with infection

| | Intensive care unit mortality | |
Risk factor	OR (95% CI)	p*
SAPS II	1.49(1.23-1.61)	0.026
Invasive mechanical ventilation	2.97(1.37-7.22)	<0.01
Vasopressor	3.08(1.54-6.33)	<0.01
Acinetobacter infection	6.27(1.98-19.6)	0.013
Lower respiratory tract infection	8.19(1.53-32.4)	0.038
Urinary tract infection	0.35(0.19-0.82)	0.019

*Multivariable logistic regression, **OR:** odds ratio, **CI:** confidence interval, **SAPSII:** Simplified Acute Physiology Score

Discussion

The results of this study showed that gram-negative bacteria were determined as the most frequent infectious agents isolated in both the survivors and non-survivors. Bacterial infections are one of the most common reason for hospital and ICU admission, the treatment of infections caused by gram-negative organisms is particularly difficult. Although previous studies have revealed an increasing frequency of gram-positive bacteria as infectious agents, gram-negative bacteria are still the most frequent in the ICUs participating and are important since they demonstrate multiple drug resistance (4).

The European Prevalence of Infection in Intensive Care II (EPIC II) study reported that 62% of isolated micro-organisms were gram-negative bacteria, 47% were gram-positive bacteria, and 19% were fungal pathogens (5). In a study from Italy reported that the most frequently isolated micro-organisms were *A. baumanii*, *K. pneumonia* and *P. aeruginosa* in septic shock patients (6). In the current study, the most frequently isolated bacteria were *E. coli* and *K. pneumonia* overall, and *A. baumanii* in the non-survivor group. Infections caused by multi-drug-resistant (MDR) gram-negative bacteria are associated with high rates of morbidity and mortality due to the prolonged stay in hospital because of failure of antibiotic treatment. In previous studies, the sensitivity of *K. pneumonia* to carbapenem has been reported to be 68.8-95.5% and the sensitivity of *E.coli* to carbapenem as 99.7-100% (7, 8). In the current study, while the resistance to carbapenem of *K. pneumonia* was found to be 55.6%, none of the *E.coli* strains were determined to be resistant to carbapenem. The antimicrobial resistance to β-lactam antibiotics, including carbapenems, of micro-organisms such as *P. aeruginosa* and *A. baumanii* is growing. Therefore, treatment options are limited for infections caused by these pathogens. In the 2012 report of the International Nosocomial Infection Control Consortium (INICC) and in studies conducted, *P. aeruginosa* was reported to be resistant to cefepim at 100% and to carbapenem at 47%, and *A. baumanii* to carbapenem at 55.3% (9, 10). A recent study showed high resistance rates of *A. baumanii*. isolates to fluoroquinolones, aminoglycosides, and carbapenems (>95%)(11). In the current study, *P. aeruginosa* resistance to meropenem was found to be 41.4%, which was compatible with the literature. But the resistance of *A. baumanii* to meropenem was 73.6%, which was higher than the findings in the literature. This can be explained by the greater rate of A. baumanii infection in the non-survivor group.

The incorrect or uncontrolled use of broad-spectrum antibiotics leads to difficulties in the differentiation and treatment of resistant strains. The increased carbapenem resistance to of *A. baumanii* may be associated with incorrect empirical antimicrobial selection and long-term, unecessary antibiotic use. The high resistance rate shows the necessity for great attention when deciding to use carbapenem in prophylactic treatment. Another group of drugs used in the treatment of MDR bacteria is aminoglycosides(12). The aminoglycoside resistance rates determined in the current study were 17.1% for *K. pneumonia*, 30.8% for *P. aeruginosa*, and 78.4% for *A. baumanii*. The limited treatment of MDR bacteria and high resistance rates decrease the number of antibiotic options that can be selected in empirical treatment. The antibiotics with the lowest resistance rates were aminoglycoside for *K. pneumonia*, and colistin for *P. aeruginosa* and *A. baumanii*. Previous studies have reported similar resistance rates for the same strains (12).

Gram-positive bacteria are responsible for approximately one-third of ICU infections. In previous studies, the rate of *Staph* has been reported as 13.5% and resistance to methicillin in the range of 71-88% (13). In the current study, the *Staph* rate was similar to data reported in literature and resistance to methicillin was determined as 80%. All the gram-positive bacteria were observed to be sensitive to vancomycin. Nosocomial and community-acquired infections in the ICU are attributed to the increasing frequency of MDR bacteria. Increasing rates of antibiotic resistance have significantly increased the morbidity and mortality rates and costs associated with infections treated in the ICU. Knowledge of the microorganism isolated from the ICU patients and their antibiotic sensitivity helps to reduce morbidity and mortality rates by assisting in the selection of the correct drug in emprical treatment (14). Current antimicrobial management programs formed by antibiotic teams focus on the appropriate use of the existing antimicrobial treatments with the targets of healing the infection caused by MDR gram-negative organism microorganism slowing the progression of antimicrobial resistance, and lowering hospital costs (15).

In Turkey and throughout the world, septic shock still has a high mortality rates which have been reported as 39% (16). Consistent with literature, the mortality rate of patients diagnosed with septic shock in the current study was 41.8%. In the patient group with mortality because of infection, the SAPS II disease severity score was higher, age was older and there was determined to be higher requirement for mechanical ventilation and vasopressors. Lower respiratory tract infections were determined at a higher frequency in non-survivors. Some previous studies have stated that there is not a correlation between infection side and mortality, whereas a more recent study reported there is an association between lower respiratory tract infection and increased mortality rate (17-19). Antimicrobial therapy must be choosen appropriately according ICUs susceptibility profile to decrease mortality and morbidity due to septic shock. Inappropriate or insufficient antibiotic use prolongs the length of stay in hospital, and can lead to the development of MDR infections, and death. Initiating empirical antibiotic treatment based on local sensitivities, daily evaluation of the signs and symptoms of infection, and restricting antibiotic treatment when possible, can prevent the development of resistant micro-organisms and facilitate the treatment of ICU infections.

Conclusion

The most frequently isolated infection agents and resistance characteristics may show differences in each unit. Therefore, in the treatment of resistant microorganisms with high mortality rates selecting antibiotics should be rely on the knowledge of the ICU antibiotic resistance profile and periodic reviews of the antibiotic use habits.

Limitations

• The reason for the high rate of antibiotic resistance is; This may be due to the fact that patients admitted from the emergency room and other in-hospital services were not differentiated.

• Due to the low number of patients in this study, there is a need for further multicentre studies with higher numbers of patients.

AUTHOR CONTRIBUTIONS:

Concept: KG; **Design:** GS; **Supervision:** KG; **Fundings:** DI;
Data Collection and/or Processing: GS; **Analysis and/or Interpretation**: KG;
Literature Search: KG; **Writing Manuscript**: GS; **Critical Review:** KG.

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