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Original Article

Five-year period evaluation of isolated agents and their resistance profiles in intensive care unit patients with malignancy

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Abstract

Introduction: Patients treated in the intensive care unit (ICU) are usually patients who deteriorated health condition and could have longer hospital stay compared to other patients. Hospital infections are more common in ICU patients. The aim of this study was to evaluate the bacteria and treatment resistance profiles isolated from clinical specimens sent for hospital infections in ICU patients between January 1, 2014 and December 31, 2018.

Methodology: Bacteria isolated from various clinical samples sent for hospital infections in hospitalized patients in the Anesthesia and Reanimation Intensive Care Unit were retrospectively analyzed.

Results: Culture positivity was detected in 547 of the sent clinical samples. Eighty Gram-positive bacteria, 389 Gram-negative bacteria and 78 fungi infection were identified in a total of 547 positive cultures. In Gram-positive bacteria, 4 MRSA, 6 VRE and 30 MRCoNS were identified as resistant strains. In Gram-negative bacteria, *Acinetobacter* spp. was the most culture positive strain with the number of 223. Carbapenem resistance was found in 258 of the Gram-negative bacteria and ESBL positivity was found in 44 of the Gram-negative bacteria strains.

Conclusions: Gram-negative bacteria were the most frequently isolated strain in samples. Recently, colistin resistance has been increasing in *Acinetobacter* spp. and the increase in carbapenemase enzyme in *Escherichia coli*, *Pseudomonas* and *Klebsiella* species has increased resistance to carbapenems. Knowing the microorganisms that grow in ICUs and their antibiotic resistance patterns may help to prevent contamination of resistant microorganisms by both appropriate empirical antibiotic treatment and more isolation as well as general hygiene standard precautions.

Key words: Gram-negative bacteria; Gram-positive bacteria; fungus; ICU.

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Introduction

Patients treated in the intensive care unit (ICU) are usually patients who deteriorated health condition and could have longer hospital stay compared to other patients [1]. Such patients might also have frequently administered invasive interventions and might be under broad-spectrum antibiotherapy [1]. Nosocomial infections are more common in the ICU patients [2]. These patients were hospitalized many times before the ICU and often had a history of broad-spectrum antibiotic use.Infections with extensively drug-resistant, multidrug-resistant and pandrug-resistant microorganisms are common [3]. It would be useful to know the bacteria isolated in the ICU and their antibiotic resistance profiles and to review the use of antibiotics in the light of these data.

The aim of this study was to evaluate all microorganisms and treatment resistance profiles isolated from clinical specimens sent for hospital infections in the ICU with hematologic malignancies, solid organ tumors or other underlying diseases in a tertiary care hospital between January 1, 2014 and December 31, 2018. In additionto determine the epidemiological characteristics, risk factors, changes in the distribution and frequency of isolated bacteria. In additionto review the antimicrobial resistance status of bacteria. For this reason, we think that this study will be

useful in determining the antibiotics policies of the country.

Methodology

This is a retrospective study. Approval was obtained from the Ethics Committee of University of Health Sciences Ankara Dr.Abdurrahman Yurtaslan Oncology Training and Research Hospital (Approval date: 03/20/2019 and decision no: 2019-03/235).

Patients who were hospitalized in the ICU between January 1, 2014 and December 31, 2018 and had blood samples/other cultures taken for high fever were included in the study.

At least two bottles of blood cultures were taken at 30 minutes intervals for each patient when the fever was ≥ 38.2°C. Blood cultures were obtained from different peripheral veins, one other also from the catheter, and another from the patients with central venous catheter (CVC). Automated BacT/ALERT 3D (bioMerieux, Marcy-l'Etoile, France) system was used to detect growth in blood cultures. Antibiotic susceptibility tests were performed by using VITEK 2 (bioMerieux, Marcy-l'Etoile, France) AST (Antimicrobial susceptibility testing) cards. Patients were divided into bloodstream infections in accordance with the definitions of Centers for Disease Control and Prevention (CDC).

Clinical specimens were seeded on eosine methylene blue agar, blood agar and Sabouraud dextrose agar. Respiratory tract samples consisted of bronchoalveolar lavage, sputum and/or tracheal aspirate. All samples were evaluated for the presence of leukocytes and bacteria by Gram staining. For Gram-positive bacteria, positive culture properties on the plaque, Gram staining, catalase, coagulase tests and VITEK 2 ID (bioMerieux, Marcy-l'Etoile, France) cards were used. In the identification of Gram-negative isolates, culture positivity/negativity characteristics, Gram stain, oxidase test and VITEK 2 ID cards were used. VITEK 2 AST (bioMerieux, Marcy-l'Etoile, France) cards were used to detect antibiotic susceptibility of growing microorganisms. Disc diffusion test was performed by using Becton Dickinson (Becton, Dickinson and Company, Towson, MD, USA) and Oxoid antimicrobial discs (Oxoid Limited, Hampshire, UK) according to Kirby-Bauer disc diffusion suspectiblity test protocol, inoculation of the Muller Hinton agar plate. VITEK 2 AST were used to detect expanded spectrum beta lactamase in Gram–negative bacteremia.

After detecting the causative agents together with the current diagnoses, the other results of the patients were obtained from the patient records in the electronic environment. Patients were divided into three groups as those with hematological malignancies, those with solid organ tumors and those with other underlying diseases.

The demographic data, underlying disease, focus of infections, culture positive strains and antibiogram results were recorded on a previously prepared form.

Patients aged 18 years or older, patients who were hospitalized in the anesthesia intensive care unit and patients who were diagnosed with infection by clinically, laboratory tests and/or microbiologically were included in the study. Patients under the age of eighteen and patients who were pregnant were excluded from the study.

Statistical analysis

SPSS (IBM SPSS Statistics 24) was used to compare the statistical data. The data were entered into the statistical package program and analyzed using the same package program. Frequency tables and descriptive statistics were used to interpret the findings.

Descriptive data were presented as categorical frequency distribution and percentage (%) and measured as mean ± standard deviation (SD) and median (maximum, smallest values).

Cross Tab with Chi-Square test was used to examine the relationship between two qualitative variables. $P<0.05$ was considered as statistically significant.

Results

The number of patients in the ICU was 1388 and the number of patients whose culture was found to be positive was 351. In 547 total clinical samples, culture positivity was detected as a result of nosocomial infection.

The mean age of the patients was 66 and the age range was between 18 and 100 years old. 53.5% of the patients were female and 46.5% were male.

Culture positivity was detected in 96 (17.5%) patients with hematological malignancies in the ICU, 207 (38%) patients with solid organ tumors, and 244 (44.5%) patients with other underlying diseases (Table 1).

Deep tracheal aspirate culture (157) was the most culture positivity seen test and it was followed by urine culture (108), peripheral blood culture (95), and bronchoalveolar lavage culture (82), respectively. Eighty Gram-positive bacteria, 389 Gram-negative bacteria and 78 fungi infection were identified in a total of 547 positive cultures (Table 1).

Table 1. Distribution of growth factors by disease groups.

	Patients with hematologic malignancies	Patients with solid organ tumors	Patients with other underlying diseases
Reproduction number, n (%)	96 (17.5%)	207 (38%)	244 (44.5%)
Gram-positive bacteria, n (%)	12 (12.5%)	28 (13.5%)	40 (16.1%)
Gram-negative bacteria, n (%)	76 (79.2%)	143 (69.1%)	170 (69.8%)
Fungus, n (%)	8 (8.3%)	36 (17.4%)	34 (14.6%)

Table 2. Distribution of growth factors by years.

	2014	2015	2016	2017	2018	Total
Gram-positive bacteria, n (%)	**11 (10.2)**	**21 (16.1)**	**20 (5.8)**	**19 (17.6)**	**9 (12)**	**80 (14.5)**
S. aureus and CoNS	4 (3.7)	12 (9.2)	14 (11)	12 (11.1)	1 (1.3)	43 (7.9)
S.pneumoniae and *Streptococcus* spp.	1 (0.9)	3 (2.3)	-	1 (0.9)	-	5 (0.9)
E.faecalis and *E.faecium*	5 (4.7)	5 (3.8)	4 (3.1)	6 (5.6)	8 (10.7)	28 (5.1)
Other Gram-positive bacteria	1 (0.9)	1 (0.8)	2 (1.6)	-	-	4 (0.7)
Gram-negative bacteria, n (%)	**66 (73.8)**	**88 (67.7)**	**89 (70.0)**	**70 (64.9)**	**63 (84.0)**	**389 (71.2)**
E.coli	4 (3.7)	3 (2.3)	8 (6.3)	6 (5.6)	3 (4.0)	24 (4.4)
Acinetobacter spp.	48 (44.9)	54 (41.5)	47 (37.0)	37 (34.3)	37 (49.3)	223 (40.8)
Klebsiella spp.	7 (6.5)	11 (8.5)	13 (10.2)	10 (9.3)	8 (10.7)	49 (9.0)
Pseudomonas spp.	14 (13.1)	11 (8.5)	12 (9.4)	9 (8.3)	6 (8.0)	52 (9.5)
S. marcescens	1 (0.9)	1 (0.8)	1 (0.8)	-	3 (4.0)	6 (1.1)
Proteus spp.	1 (0.9)	2 (1.5)	-	2 (1.9)	2 (2.7)	7 (1.3)
Enterobacter spp.	2 (1.9)	1 (0.8)	2 (1.6)	1 (0.9)	4 (5.3)	10 (1.8)
Other Gram-negative bacteria	2 (1.9)	5 (3.8)	6 (4.7)	5 (4.6)	-	18 (3.3)
Fungus, n (%)	**17 (15.9)**	**21 (16.2)**	**18 (14.2)**	**19 (17.6)**	**3 (4.0)**	**78 (14.3)**
Candida albicans	9 (8.4)	11 (8.5)	7 (5.5)	9 (8.3)	2 (2.7)	**38 (6.9)**
Candida tropicalis	2 (1.9)	4 (3.1)	0 (0.0)	4 (3.7)	0 (0.0)	**10 (1.8)**
Candida krusei	1 (0.9)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	**3 (0.5)**
Candida parapsilosis	0 (0.0)	2 (1.5)	1 (0.8)	2 (1.9)	1 (1.3)	**6 (1.1)**
Candida lusitaniea	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.2)**
Candida glabrata	4 (3.7)	1 (0.8)	1 (0.8)	2 (1.9)	0 (0.0)	8 (1.5)
Candida spp.	0 (0.0)	1 (0.8)	9 (7.1)	2 (1.9)	0 (0.0)	12 (2.2)
Total, n	**107**	**130**	**127**	**108**	**75**	**547**

Table 3. Resistance distribution of growth factors by years.

	2014	2015	2016	2017	2018	Total
MRSA	2	-	2	-	-	4
VRE	1	1	1	1	2	6
MRCoNS	-	11	9	9	1	30
Carbapenem resistance	55	61	58	43	41	258
Colistin resistance	1	6	9	11	4	31
ESBL	1	12	7	11	3	44
Total	60	91	86	74	51	363

Table 4. Distribution of multidrug-resistant and pandrug- resistant bacteria according to disease groups.

	Patients with hematologic malignancies	Patients with solid organ tumors	Patients with other underlying diseases
Multidrug-resistant*, n (%)	5 (14.3%)	14 (40.0%)	16 (45.7%)
Acinetobacter spp.	4	10	8
Klebsiella pneumoniae	1	4	7
Pseudomonas spp.	-	-	1
Pandrug-resistant§, n (%)	2 (66.7%)	1 (33.3%)	-
K. pneumoniae	2	1	-

* Multidrug-resistant microorganism as a result of carbapenem or colistin resistance; § Microorganism resistant to all antibiotics including carbapenem and colistin; Antibiotic distribution of multidrug-resistant microorganisms; In patients with hematologic malignancy: 4 *Acinetobacter* spp. were resistant to carbapenem and colistin, and 1 *K. pneumoniae* was resistant to all antibiotics except colistin; In patients with solid organ tumors: 10 *Acinetobacter* spp. were resistant to carbapenem and colistin, and 4 *K. pneumoniae* were resistant to all antibiotics except colistin; In patients with other underlying diseases: 8 *Acinetobacter* spp. carbapenem and colistin, 7 *K. pneumoniae* carbapenem, 1 *Pseudomonas* spp. were resistant to all antibiotics except colistin.

Gram-positive bacterial growth was found to be highest in patients with underlying disease, Gram-negative bacterial growth in hematological malignancies and fungal growth in patients with solid organ tumors, respectively (Table 1). Gram-negative bacteria were most frequently isolated in the cultures of patients in the ICU in between 2014 and 2018. This was followed by Gram-positive bacteria and fungus, respectively (Table 2).

Among the Gram-negative bacteria, *Acinetobacter* spp. was the most culture positive strain with the number of 223 (40.8%). It was followed by *Pseudomonas* spp. (n = 52) (9.5%) and *Klebsiella* spp. (n = 49) (9.0%). Thirty-one *Acinetobacter* spp. have been detected as colistin resistant. Carbapenem resistance was found in 258 of the Gram-negative bacteria and ESBL positivity was found in 44 of the Gram-negative bacteria strains. Resistance distribution of bacterial strains by years was shown in Table 3.

Four methicillin-resistant *Staphylococcus aureus* (MRSA), 6 vancomycin-resistant enterococci (VRE) and 30 methicillin-resistant coagulase-negative staphylococci (MRCoNS) were detected as resistant strains in Gram-positive bacteria (Table 3).

The highest multidrug resistance was found in the clinical materials of patients with other underlying diseases (45.7%). This resistance was most common in *Acinetobacter* spp., *Klebsiella pneumoniae* and *Pseudomonas* spp., respectively. Pandrug- resistant microorganisms was found mostly in the clinical material of patients with hematological malignancies (66.7%) (Table 4).

The highest fungal growth was found in patients with solid organ tumors (17.4%). This was followed by patients with other underlying diseases (14.6%) and patients with hematological malignancies (8.3%), respectively (Table 1). *Candida albicans* was the most detected by years.*C. albicans* was the most detected from all patients. This was followed by *C. tropicalis* and *C. glabrata* (Table 5).

No statistically significant difference was found between the disease groups in terms of any microorganism growth. There was no statistically significant difference between the disease groups in terms of multidrug resistance development.

Discussion

Identification of infections in the ICU is necessary in terms of treatment approach and determination of epidemiological characteristics [4]. Determining causative microorganisms and antibiotic susceptibilities is important in reducing morbidity and mortality as well as guiding empirical treatment [5].

In an international 1265 ICU study, 60% of patients are infected in during the study and infection is a strong and independent predictor of mortality (Odds ratio,1.51; P<0.001) [6]. In general, and especially, the risks of infection with a resistant pathogen are increased

Table 5. Distribution of fungus according to disease groups.

	Patients with hematologic malignancies	Patients with solid organ tumors	Patients with other underlying diseases	
Fungus	**n (%)**	**n (%)**	**n (%)**	**Total, n**
Candida albicans	4 (10.5)	21 (55.3)	13 (34.2)	**38**
Candida tropicalis	0 (0.0)	3 (30.0)	7 (70.0)	**10**
Candida krusei	3 (100.0)	0 (0.0)	0 (0.0)	**3**
Candida parapsilosis	0 (0.0)	4 (66.7)	2 (33.3)	**6**
Candida lusitaniea	0 (0.0)	0 (0.0)	1 (100.0)	**1**
Candida glabrata	0 (0.0)	4 (50.0)	4 (50.0)	**8**
Candida spp.	1 (8.3)	4 (33.3)	7 (58.3)	**12**

with the length of stay in the ICU [7]. Compared with patients in the general hospital population, patients in the ICU have more chronic co-morbidities and more severe acute physiological disorders, so their immune system is relatively suppressed [7].

In this study, 547 of the clinical samples sent due to nosocomial infections in hospitalized patients in the ICU over a five-year period were detected. Of these culture positive patients, 96 (17.5%) had hematological malignancies, 207 (38%) had solid organ tumors and 244 (44.5%) had other underlying diseases.

MRSA, VRE, *Acinetobacter baumannii* and ESBL and/or carbapenemases positive Gram–negative bacteria and carbapenem-resistant *Pseudomonas aeruginosa* are increasingly isolated from patients in ICU [8]. Infections caused by these resistant pathogens are difficult to treat and these infections are associated with increased morbidity, mortality and cost [9].

In this study, 4 MRSA, 6 VRE and 30 MRCoNS were isolated from clinical samples of all three disease groups.

Comparison of reports from the National Health Care Network System and Centers for Disease Control and Prevention from 1999 to 2006 showed that the prevalence of multidrug-resistant pathogens in ICUs has been increasing in the United States [8].

The emergence of broad-spectrum resistance among gram-negative bacteria is particularly worrying as therapeutic options are scarce and sometimes no effective antimicrobial agents are available [10]. In our study, Gram-negative bacteria were the most isolated strain in clinical samples of all three patient groups.

Recently, colistin resistance has been increasing in *Acinetobacter* species and the increase in carbapenemase enzyme in *Escherichia coli*, *Pseudomonas* and *Klebsiella* species has increased resistance to carbapenems [8]. In our study, colistin resistance was 12.4% and carbapenem resistance was 75.8% in *Acinetobacter* species.

Some features increase the risk of infection with multidrug-resistant pathogens in ICUs, contributing to selective pressure and/or increased colonization pressure [11]. Infections caused by multidrug-resistant pathogens are associated with increased mortality, length of hospital stay, and hospital costs [12].

Patients with infections due to multidrug-resistant organisms are often at risk of chronic or acute disease and die from serious and complex underlying diseases [13]. Specifically, risk factors for resistant infections reported from ICUs are; aging, functional independence and/or decreased cognition, high severity of underlying concomitant conditions (eg diabetes, renal failure, malignancies, immunosuppression) and acute disease indices, including inter-institutional transfer, before admission to ICU prolonged hospital stay (especially in nursing homes), common situations in health settings (eg. hemodialysis units), frequent contact with healthcare professionals who simultaneously care for multiple patients who may serve as intermediaries for pathogen transfer between patients (shared equipment and contaminated environments) [13]. Presence of implanted devices such as central venous catheters, urinary catheters, and endotracheal tubes, bypassing natural host defense mechanisms and entry portals to pathogens, recent operations or other invasive procedures, receiving antimicrobial treatment before applying to the ICU create a selective environment leading to the emergence of multidrug-resistant bacteria [14].

In this study, Gram-negative bacteria were the most common agents in all three disease groups. The group with the highest Gram-negative bacterial growth was hematological malignancy group(79.2%). The reason for this was thought to be the long term immunosuppression due to both underlying disease and chemotherapy with the prior long term antibiotic use in this patient group.

ESBL-producing *E. coli*-related infections have become widespread in hospitals around the world [15]. A total of 44 ESBL-producing strains were also identified in our study.

The relationship between prior antibiotic usage and infections of drug-resistant organisms has been shown in several studies and in several methodologies [16]. In case-control studies, exposure to antibiotics has been consistently associated with the emergence of resistance to the same or a different class of antimicrobial agents [16]. In a study, antibiotic exposure was the most powerful single predictor for infections with drug-resistant Gram-negative pathogens [16].

Patients in the ICU are the highest risk group for *Candida* infections [17]. In addition to the risks associated with age, trauma, or burns, other factors include central venous catheters, total parenteral nutrition, broad-spectrum antibiotics, high APACHE score, acute renal failure, especially when requiring hemodialysis, surgery, especially abdominal surgery, gastrointestinal system perforations and are high risk factors [18]. In our study,fungus growth was detected in patients with solid organ tumors (17.4%).*C. albicans* was the most detected from patients with solid organ tumor. This was followed by *C. glabrata* and *C. tropicalis*. The reason for this was thought to be due to

the deterioration of organ integrity due to solid tumors, translocations and/or prior broad spectrum antibiotics used in these patients.

Conclusion

As a result, culture positive microorganisms in ICUs and their antibiotic resistance patterns may provide convenience in selecting appropriate empirical antibiotic therapy and antifungal therapy for patients. It may also help to protect patients from contamination with resistant microorganisms by following the standard measures of much more isolation and general hygiene.

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Author's contributions

DM was the designer, coordinator, data collector and corresponding author. SM was the author, data collector and planner of study. The other authors were data collectors and authors.

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