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Distribution of Pathogens and Antibiotic Sensitivity Profile in Oncologic Patients: A Cross-Sectional Study

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ABSTRACT

Background: Infection is one of the most serious complications and leading cause of morbidity and mortality in patients with hematological-oncological disorders. We aimed to assess distribution of pathogens and their antibiotic resistance pattern in patients admitted to hematology-oncology department of Namazi Hospital, Shiraz from April 2016 to March 2017.
Methods: The current cross-sectional study found out 234 patients with positive culture from different sites. Patients with all kind of malignancies were included in the study. Isolation of the pathogens and antibiotic resistance pattern was conducted using disc diffusion Method.
Results: Among 234 subjects with positive culture, gram negative and gram positive bacteria, and fungi comprised 45.3%, 32.4%, and 22.2% of the cases, respectively. The most common pathogens were E. coli (20.9 %) and Non-albicans Candida (20.9 %). Data analysis found E. coli, Acinetobacter, Enterococci, and catheter-related coagulase-negative Staphylococci highly resistant to fluoroquinolones, imipenem, vancomycin and ceftazidime, respectively.
Conclusion: New strategies in prescribing antibiotics are demanded due to altered pathogenic sensitivity to the conventional antibiotics. Meanwhile, measures such as standard precautions and transmission-based precautions (i.e., contact, droplet, and airborne precautions) should be taken more seriously to decrease the emergence of bacterial and fungal infections.

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Introduction

Infection is one of the most serious complications and leading cause of morbidity and mortality in patients with hematological-oncological disorders.[1-3] There has been an increasing trend in the risk of severe infections due to immunosuppression resulted from intensive antineoplastic chemotherapy and therapeutic procedures.[2] Infection also imposes poorer outcome and complicates the process of recovery in oncologic patients.[4] Different studies in this field have reported a variety of crude mortality rates related to infection that ranges from 12 to 42%.[5-12]

In order to reduce the mortality rate and improve the patients' quality of life, physicians should identify and treat the infectious disease as soon as possible by administering suitable anti-microbial therapy.[13] Providing the best anti-microbial coverage requires a precise knowledge of local distribution of pathogens which infect different sites of the hematological-oncological patients such as blood, urogenital system, abdomen, respiratory system and etc.[14] It is very important to consider this fact that there are significant differences in common organisms causing infections in different hospitals.[15] There is also significant difference in different periods of time in a single healthcare center. A study conducted in hematology department of Beijing hospital showed

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that gram-negative bacteria were the most common pathogens;[16] while another study carried out in department of hematology, Hefei, revealed that the majority of the infections were caused by gram-positive bacteria and demonstrated that gram-positive bacteria, gram-negative bacteria and fungi accounted for 42.2%, 34.3% and 3.5% of the infections, respectively.[17]

Furthermore, patients with hematological malignancies are prone for development of infections by anti-microbial resistant microorganisms; where the number of multi-drug resistant organisms has increased dramatically.[18-20] Indeed, it has been proved that these pathogens are associated with more complications and poor outcomes and can lead to higher rate of morbidity and mortality.[21,22] In a 4-year prospective study, it has been demonstrated that there were better outcomes in patients with sensitive gram-negative infections compared with multi-drug resistant gram-negative ones.[5] Similar to pathogen distribution, resistance pattern of these agents differs vastly among different healthcare centers and different periods of time[23] and thus it is important to consider the pattern of resistance and sensitivity to various antibiotics.

The current study was aimed to evaluate pathogen distribution and resistance profile of microorganisms in hematology-oncology department of Namazi hospital, shiraz and make attempts to improve conditions of the patients and reduced mortality.

Materials and Methods

This cross-sectional study identified 234 patients with positive culture out of 1073 patients hospitalized in hematology oncology department of Namazi hospital, Shiraz during 2016-2017 (21.8%). Inclusion criteria were set to address: Patients with malignancies who had positive culture, a positive aspergillus PCR in blood samples or any evidence of mucormycosis found in the pathology sample. On the other hand, patients who had received antibiotics in the past two weeks, or did not show coincident chest x-ray infiltration along with positive sputum culture, or had positive culture with candida with less than 1000 colony-forming units were excluded from data analysis.

Clinicopathological data including sex, age, primary disease, comorbidities and chemotherapeutic regimens were obtained from their medical records.

The study specimens were collected from blood, urine, throat, wound discharge, sputum, pleural and abdominal fluid. To test the antimicrobial susceptibility, disc diffusion method was utilized as we placed antibiotic-containing wafers on the bacterial culture surface, leaving the plate to inoculate. Antibiotic susceptibility would be assumed if the antibiotic-containing wafers stopped growing of the bacteria.

Results

234 patients (ranging from 17-71 years of age), including 126 men; mean age of 51.2±17.4 and 45.98±15.84 years for men and women, respectively were identified who had positive cultures. AML was found to be the most common malignancy in the patients (32.5%), followed by ALL (15.4%) and solid tumors (Table 1).

Table 1: Oncological patients with positive culture in terms of the malignancy

	Frequency	Percent
AML[1]	76	32.5
ALL[2]	36	15.4
MM[3]	25	10.7
Ovarian cancer	17	7.3
T-cell lymphoma	15	6.4
Gastric lymphoma	9	3.8
Lung cancer	6	2.6
CLL[4]	6	2.6
MDS[5]	5	2.1
Colon cancer	4	1.7
CML[6]	3	1.3
DLBL[7]	3	1.3
Breast cancer	3	1.3
Lymphoma	3	1.3
Osteosarcoma	3	1.3
Salivary gland carcinoma	3	1.3
Soft tissue sarcoma	2	0.9
Neck mass	2	0.9
ITP[8]	2	0.9
Aplastic anemia	2	0.9
Adrenal mass	1	0.4
NHL[9]	1	0.4
Burkitt lymphoma	1	0.4
Plasma cell neoplasm	1	0.4
Prostate adenoca	1	0.4
R/O lymphoma	1	0.4
Rectal cancer	1	0.4
Adenocarcinoma	1	0.4
Thalassemia	1	0.4
Total	234	100.0

The majority of the samples were taken from the blood (47%), followed by urine (32.9%), sputum (5.6%), blood catheter (4.3%), wound discharge and abdominal fluid (3% each one) and throat or pleural fluid (2.1% each one), respectively.

Distribution of Pathogenic Microorganisms

Among 234 subjects with proven pathogens, 106 gram-negative bacteria, 76 gram-positive bacteria and 52 fungi were isolated (Table 2). The most common pathogens detected were E. coli (20.9 %) and Non-albicans Candida (20.9 %).

The most common organism recovered from blood culture was methicillin-resistant staphylococcus aureus followed by E.coli in 20 and 19 isolates, respectively. Furthermore, E.coli and Candida non-albicans were responsible for the majority of infections in the urogenital system (Table 3).

Methicillin-resistant coagulase-negative staphylococci were involved in 6 out of 10 cases of catheter-related bloodstream infections. Meanwhile, there was a significant relationship between different pathogens and the site of infection (P<0.001).

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Table 2: Distribution and frequency of pathogens isolated from different sites of patients with oncological diseases.

Organism	Frequency	Percent
C.N.A[1]	49	20.9
E. coli[2]	49	20.9
Enterococci	25	10.7
MRCoNS[3]	25	10.7
Kebsiella.spp	16	6.8
Stenotrophomonas maltophilia	14	6.0
NFB[4]	10	4.3
Acintobacter	8	3.4
S. aureus[5]	8	3.4
Strep.spp	7	3.0
MRSA[6]	5	2.1
Staph.DNase-	4	1.7
Enterobacter.spp	3	1.3
C.A[7]	3	1.3
G negative rod	3	1.3
Diphtheroid	2	.9
Proteus.spp	1	.4
Pseudomonas	1	.4
Salmonella.D	1	.4
Total	234	100.0

1- Candida non albicans species, 2- Escherichia coli, 3- Methicillin-resistant coagulase-negative staphylococci, 4- Nonfermentative bacilli, 5- Staphylococcus aureus, 6- Methicillin-resistant Staphylococcus aureus, 7- Candida albicans

Antibiotic Sensitivity Profile of Isolated Pathogens

Data analysis showed that fluoroquinolones that are used in the prophylaxis and treatment of E.coli infections were found to be relatively inactive against them. Furthermore, among antibiotics used in susceptibility test for Acinetobacter baumannii, colistin was the only effective antibiotic against Acinetobacter. Enterococci species were found to be highly resistant against studied antibiotic classes; the resistance against each antibiotic used in the research was greater than 91%, alerting us to make changes in prophylaxis and treatment strategies. Furthermore, high rate of resistance to ceftazidime, clindamycin and cloxacillin were observed in catheter-related coagulase-negative Staphylococcal blood infections; however, this organism was highly sensitive to vancomycin (Table 4).

Chemotherapy Regimens in Patients Enrolled Into the Study

The majority of patients were receiving chemotherapy during their course of hospitalization. The most frequent administered protocol in our patients was high-dose cytarabine (HiDAC) regimen, (53 patients). Hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and prednisolone) regimen was the second most commonly used protocol which was administered to 28 individuals, generally in the treatment of Acute Lymphoblastic Leukemia (ALL). 67 out of 234 patients were those whose induction chemotherapy was initiated in another healthcare centers and were then referred to Namazi hospital. Table 5 shows the frequency of patients receiving each protocol.

The most common site of infection in patients receiving HiDAC was blood stream followed by urogenital system. Complete data referring to the site of infection and

Table 3: Pathogenic distribution in different sites of patients with malignancy

		Culture								Total
		Blood	Urine	Throat	Wound discharge	Sputum	Pleural	Abdomen	Catheter	
Organism	Acinetobacter	4	0	1	1	2	0	0	0	8
	C.A[1]	0	1	0	1	1	0	0	0	3
	C.N.A[2]	16	24	1	0	7	0	1	0	49
	Diphtheroid	2	0	0	0	0	0	0	0	2
	E. coli[3]	18	25	0	1	0	3	1	1	49
	Enterobacter.	0	1	0	0	2	0	0	0	3
	Enterococci	8	12	0	1	0	1	2	1	25
	G negative rod	1	2	0	0	0	0	0	0	3
	Kebsiella.spp	7	6	2	0	1	0	0	0	16
	MRCoNS[4]	14	2	0	1	0	0	2	6	25
	MRSA[5]	3	0	1	0	0	0	1	0	5
	NFB[6]	9	0	0	0	0	0	0	1	10
	Proteus.spp	1	0	0	0	0	0	0	0	1
	Pseudomonas	1	0	0	0	0	0	0	0	1
	S. aureus[7]	6	0	0	2	0	0	0	0	8
	Salmonella.D	1	0	0	0	0	0	0	0	1
	Staph.DNase-	2	0	0	0	0	1	0	1	4
	stenotrophomonas maltophilia	14	0	0	0	0	0	0	0	14
	Strep.spp	3	4	0	0	0	0	0	0	7
Total		110	77	5	7	13	5	7	10	234

1. Candida albicans, 2. Candida non albicans species, 3. Escherichia coli, 4. Methicillin-resistant coagulase-negative Staphylococci, 5. Methicillin-resistant Staphylococcus aureus, 6. Non-fermentative bacilli, 7. Staphylococcus aureus

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Table 4: sensitivity profile of organisms isolated from different sites of infection

Organisms \ Antibiotics	Gentamicin		Ceftazidime		Ceftizoxime		Vancomycin		Cloxacillin		Ciprofloxacin		Ceftriaxone		Clindamycin		Imipenem		Amikacin		Erythromycin		Cotrimoxazole		Tetracycline		Colistin	
	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R
Acinetobacter	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	25	75	25	75	25	75	100	0
E. coli[1]	75.6	24.4	58.5	41.5	65.8	34.2	60	40	51.4	48.6	25	75	25	75	50	50	75.7	24.3	75.7	24.3	19.1	80.9	19.1	80.9	19.1	80.9	68.4	31.6
enterobacter.spp	100	0	66.7	33.3	66.7	33.3	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0	100	0
Enterococci	8.7	91.3	4.3	95.7	0	100	4.5	95.5	0	100	0	100	0	100	4.8	95.2	0	100	0	100	5	95	5	95	5	95	0	100
Kebsiella.spp	86.7	13.3	64.3	35.7	71.4	28.6	69.2	30.8	61.5	38.5	57.1	42.9	57.1	42.9	69.2	30.8	69.2	30.8	69.2	30.8	35.7	64.3	35.7	64.3	35.7	64.3	69.2	30.8
MRCoNS[2]	37.5	62.5	62.5	37.5	58.8	41.2	90.5	9.5	42.1	57.9	35	65	35	65	19	81	70.6	29.4	70.6	29.4	13.6	86.4	13.6	86.4	13.6	86.4	56.3	43.7
MRSA[3]	60	40	60	40	60	40	100	0	40	60	60	40	60	40	60	40	100	0	100	0	100	0	100	0	100	0	100	0
NFB[4]	16.7	83.3	42.9	57.1	28.6	71.4	50	50	50	50	57.1	42.9	57.1	42.9	50	50	50	50	50	50	40	60	40	60	60	40	60	40
S. aureus[5]	100	0	100	0	25	75	85.7	14.3	83.3	16.7	83.3	16.7	83.3	16.7	28.6	71.4	25	75	25	75	28.6	71.4	28.6	71.4	28.6	71.4	66.7	33.3
Stenotrophomonas maltophilia	66.7	33.3	18.2	81.8	45.5	54.5	77.8	22.2	77.8	22.2	88.9	11.1	88.9	11.1	77.8	22.2	66.7	33.3	66.7	33.3	81.8	18.2	81.8	18.2	81.8	18.2	90	10

Table 5: Different chemotherapeutic protocols administrated to patients enrolled into the study

Chemotherapy protocol	Frequency	Percent
HiDAC	53	22.6
hyper CVAD	28	12.0
Bortezomib	19	8.1
7+3 regimen	14	6.0
Carboplatin	12	5.1
FLAG	12	5.1
GDP	9	3.8
MTX	9	3.8
R-CHOP	2	.9
cyclosporine	2	.9
Leukemia (CLL)	2	.9
MAID	2	.9
TPF	1	.4
FOLFOX	1	.4
CODOX-IVAG	1	.4
None	67	28.6
Total	234	100.0

chemotherapeutic agents is displayed in Table 6. The relationship between the chemotherapeutic agent and the site of infection was statistically significant (P<0.001). There was also a significant correlation between the kind of chemotherapy and various organisms that afflicted the patients (P<0.001).

Comorbidities were just observed in 51 out of 234 patients with positive culture. Diabetic mellitus was the most common comorbidity among our patients. No other prominent comorbidity was seen (Table 7).

Discussion

Nowadays, due to widespread use of antibiotics, misprescription and unnecessary drug prescription, resistance has been emerged among different microorganisms to the extent that the antimicrobial resistance has been far beyond the efforts made by authorities, making our applicable drug list smaller and smaller day by day; to give an instance, the spectrum of activity of some popular drugs such as penicillins and cotrimoxazole has been decreased.[24] On the other hand, pathogenic distribution is changing over time, challenging our decisions for prophylaxis against the most common pathogens. As observed in recently comprehensive researches, there are newly emerging or reemerging pathogens capturing the place of the former more common bacteria.[25-27] Thereupon, it is our task to get started and gather data to design new effective chemoprophylaxis and, also effective drug regimens for treatment of infectious complications in patients with malignancies.

A series of investigations have shown that gram negative bacteria are the most common bacteria in the hospital environments.[28-30] Our finding followed the same pattern for pathogenic microorganisms. Among 234 positive cultures, frequency of G-negative bacteria, G-positive bacteria, and fungi were 45.3%, 32.4%, and 22.2%, respectively. Escherichia coli positive cultures constituted 21% of all positive cultures. Unfortunately,

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Table 6: Various infected sites of the patients with malignancies according to each protocol

		Culture								Total
		Blood	Urine	Throat	Wound discharge	Sputum	Pleural	Abdomen	Catheter	
Chemotherapy	7+3	6	5	1	2	0	0	0	0	14
	BORTEZOMIB	9	8	0	0	1	0	0	1	19
	CARBOPLATIN	8	3	0	0	0	0	0	1	12
	CODOX-IVAG	1	0	0	0	0	0	0	0	1
	Cyclosporin	1	1	0	0	0	0	0	0	2
	FLAG	8	1	0	0	0	1	1	1	12
	FOLFOX	0	1	0	0	0	0	0	0	1
	GDP	5	1	1	0	0	0	2	0	9
	HiDAC	21	20	1	1	2	1	3	4	53
	hyper CVAD	18	4	1	1	2	0	0	2	28
	Leukemia (CLL)	0	1	0	1	0	0	0	0	2
	MAID	0	0	0	0	2	0	0	0	2
	MTX	4	2	0	0	3	0	0	0	9
	none	29	28	1	2	3	2	1	1	67
	R-CHOP	0	2	0	0	0	0	0	0	2
	TPF	0	0	0	0	0	1	0	0	1
Total		110	77	5	7	13	5	7	10	234

Table 7: Type and frequency of comorbidities among patients with positive culture and malignancy

	Frequency	Percent
DM[1]	30	12.8
CKD[2]	3	1.3
COPD[3]	3	1.3
IHD[4]	3	1.3
HTN[5]	2	0.9
Cushing	1	0.4
thalassemia	1	0.4
HPS[6]	1	0.4
HB[7]	1	0.4
Hypothyroidism	1	0.4
AKI[8]	1	0.4
Parkinson	1	0.4
RF[9]	1	0.4
S.S[10]	1	0.4
SLE[11]	1	0.4
none	183	78.2
Total	234	100.0

1. Diabetic mellitus, 2. Chronic kidney disease, 3. Chronic Obstructive Pulmonary Disease, 4. Ischemic heart disease, 5. Hypertension, 6. Hantavirus pulmonary syndrome, 7. Hepatitis B, 8. Acute kidney injury, 9. Renal failure, 10. Systemic scleroderma, 11. Systemic lupus erythematosus

long-term studies concern us about a cumulative rise in E. coli antimicrobial resistance. In a study conducted in 2015, Brad Spellberg et al. showed that prevalence of fluoroquinolone-resistant E. coli strains are highly rising.[31] In a review study, prevalence of sulfonamide-resistant E. coli strains was showed to be so increased that sulfonamide-resistant genes are highly found in E.coli isolates.[32] Our findings demonstrated that resistance against ciprofloxacin and co-trimoxazole was 75% and 80.9%, respectively. These findings may suggest revising the use of the fluoroquinolones in prophylaxis and treatment of E. coli infections.

Acinetobacter strains were another organism with a rising resistance pattern in the current study. Ruiqiang Xie et al. declared that Acinetobacter baumannii is an antibiotic-resistant organism that colistin could be an effective antibiotic suggested against it.[33] In the similar way, the results of Acinetobacter antimicrobial susceptibility testing in this research were in accordance with the global data, being highly resistant to almost all antibiotics used in the investigation except colistin which was completely active against acinetobacter. In another study in 2018, Muhammad Asif et al. stated that extensively drug resistant strains of Acinetobacter are frequently found in the hospital departments.[34]

Another disastrous finding in the current study was finding highly resistant Enterococci species. Our data analysis showed that Enterococci antibiotic susceptibility was fewer than 9% for all the antibiotic classes used in the study. Unfortunately, resistance to vancomycin was seen to be 100%. Due to more widespread antibiotic resistance and higher prevalence of Enterococci, our results suggest that they are even more challenging than Acinetobacter strains. In 2017, Wassilew N et al. reported an outbreak of vancomycin-resistant Enterococcus species in Switzerland.[35] Recently, Mahony AA et al. demonstrated that a new clone of Enterococcus faecium with no detected antibiotic sensitivity is becoming epidemic.[36]

Surprisingly, fungi prevalence, especially non-albicans Candida species, has been raised so much, alarming the emergence of fungi as a new common hospital pathogen. 94.2% of fungi strains were non-albicans Candida in our study. In a retrospective study, a significant increase in candidemia was demonstrated in a hematology/oncology department.[37] In another research by Matteo Bassetti et al. an increase in rate of candidiasis and also a shift from Candida albicans toward Candida non-albicans (CNA) species was documented.[38] Xiurong Ding has also pointed this great disbalance in favor of CNA and blamed medical device use and corticosteroid therapy as risks factors

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for increasing prevalence of candidiasis.[39] These new patterns of distribution warn us about a future medical issue, alerting us to take new protocols of prophylaxis in hematology-oncology wards.

Catheter-related bacteremia is one of the most leading causes of morbidity and mortality in hospitalized patients and poses a heavy financial burden on healthcare systems;[40-42] unfortunately, the incidence rate and also antimicrobial resistance of catheter-related organisms are increasing.[43] Coagulase-negative methicillin-resistant staphylococcus aureus which is reported to account for a high percentage of bloodstream infections in the United States is among the organisms causing catheter-related bacteremia.[44] A study conducted in Hospital Universitario de Canarias indicated that this organism is among the most important and frequent that cause catheter-related infections.[45] In this study, ten cases of catheter-related blood stream infection were identified which methicillin-resistant coagulase-negative Staphylococcus was isolated from six cases. It is important to notice that timely diagnosis and early application of appropriate and adequate antimicrobial treatment is associated with better outcome.[46,47] In our setting, high rate of resistance to ceftazidime (37.5%), clindamycin (81%) and cloxacillin (57.9%) were seen in coagulase-negative staphylococcal bloodstream infections; given that, these antibiotics are not recommended as drug of choice for empirical therapy.

In hematological malignancies, particularly those with involvement of myeloid lineage such as AML, the majority of patients experience complications related to progressively severe leukopenia or even leukocytosis without functionally normal leukocytes, such as recurrent infections.[48] HiDAC (High dose Cytarabine) protocol is one of the highly recommended regimens to induce complete remission in AML.[49] However, using a high-dose chemotherapy regimen given with an intention to cure leads to severe prolongation of myelosuppression in most patients which impose serious or possibly fatal side effects such as increase in the risk of Infection.[50] In the current study, episodes of infection were seen in 53 patients receiving HiDAC regimen, particularly blood and urinary tract infections. Thus, appropriate antimicrobial prophylaxis should become a part of their routine treatment to prevent anticipating infections. Continuous monitoring of blood and urine and extreme caution during procedures such as catheterization is needed; also it is recommended to make patients aware of hygiene considerations such as clean defecation and urination.

Coexistence of other morbidities such as Diabetes Mellitus (DM) is an additional risk of acquiring infection. DM was the most common comorbidity in our study; concordant to the other studies.[51,52] There are other studies reporting DM as the most common comorbidity in cancer patients suffering from different kind of infections.[53,54]

Conclusion

A series of investigations as well as our study suggest that pathogenic resistance to the conventional antibiotics has been increasing; therefore, changes in conventional prophylaxis and treatment strategies should be considered. Future studies are demanded to discover antibiotic resistance pattern in oncology departments.

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