



Sensitivity Pattern of the *Candida* Species Separated from the Blood and Urine of the Patients with Malignancy in Hospital

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ABSTRACT

Background: Infection with *Candida* species has been increased globally during the past decade. This can be due to the increase in the number of patients with immunodeficiency problems like cancer, HIV AIDs, organ transplantation and hospitalization in ICUs. We aimed to investigate the prevalence rate of the fungal colonization and related species in chemotherapy-subjected children with malignancy.

Methods: Present analytical-applied research was conducted on 128 chemotherapy-subjected children with malignancy. Blood and urine samples were collected from all the patients; afterwards, the urine samples were cultivated on Saborrads Dextrose Agar and the blood samples in ordinary culture bottles (monophasic culture method and blood culturing). Then, the developed fungi were separated from the culture medium and subjected to identification tests.

Results: There was no significant relationship between the age group and infection with fungus ($P=0.998$) but there was a significant relationship between gender and fungus infection ($P=0.049$) in such a way that fungus infection was found more prevalent amongst the females. Overall, 28 individuals (58.33%) were found infected with *C. albicans*; 9 (18.75%) with *C. tropicalis*; 5 (10.42%) with *C. glabrata*; 3 (6.25%) with *C. kefir*; 2 (4.116%) with *C. krusei* and 1 (2.09%) with *C. parapsilosis*.

Conclusion: *C. albicans* is the most common species in this geographical area. The best treatment for these infectious diseases is voriconazole.

Keywords: Fungal infection; Chemotherapy; Children; *Candida*

Introduction

Candida species are yeasts that are present in various levels in different body organs as normal microbial flora (1). The infection with *Candida* species in the world has been increased globally during the past decade for an average percentage of 50 (2) and this can be due to the increase in the number of patients with immunodeficiency problems in patients with cancer, HIV AIDs, organ transplantation and hospitalization in ICUs (3).

Currently, 8% to 10% of the hospitalized nosocomial blood stream infections pertain to *Candida* species (4) recognized as the second cause of death resulting from sepsis in children (5). The expression rate of invasive candidiasis (Candidemia or Candidiasis of deep organ) differs from 0.3 to 5 individuals per every 1000 individuals admitted to the hospitals but, on the contrary, it causes 35% to 80% of the mortalities in critically-ill patients with



immunodeficiency (6). Due to the same reason, the hospitalization duration has been prolonged and a lot of treatment costs are imposed on the treatment-healthcare system (7).

At least, there are 15 various *Candida* species that can cause infections in the humans with the most common of them being *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* (8); amongst these, *C. albicans* is the most common (9). However, infections with non-*Albicans* species have been increased recently due to the increase in the number of patients with immunity system weakness as well as increase in the rate of using azoles (10). Very premature infants with birth weights below 1500g, organ or stem cells' transplantation, neutropenia, hematological malignancies and hospitalization in ICUs and taking of a wide spectrum of antibiotics and undergoing chemotherapy and with parenteral nutrition and primary or acquired immunodeficiency, as candidemia's risk factors, are most exposed to the infection (11,12).

Although, fluconazole is used as the first medication for treating *Candida*-induced infections, its effects have reduced nowadays due to the prevalence of azoles-resistant species (13). Consequently, the recent guidelines recommend echinocandin as the first-line medication for treating *Candida* (13). The immunity system's performance following chemotherapy and the combined binaries leads to different clinical responses in the patients to the antifungal treatments (14). Due to the same reason, the selection of the appropriate antifungal drug depends on the patient's conditions and the type of the infection with *Candida* (15) and the most important and most effective factor in regard of the fungal infections' treatment is the fast diagnosis and correct choice of the treatment (11). The prevention and treatment of the invasive fungal infections are the most important and most challenging problems for the children with cancer (12).

We aimed at investigating the prevalence rate of fungal colonies in chemotherapy-subjected children as well as the distribution of various species causing fungal infection in children undergoing chemotherapy so that the proper treatment pattern can be offered for the children with post-chemotherapy fungal infections through the exact identification of the factors causing such infections.

Materials and Methods

The present analytical-applied research was conducted on 128 chemotherapy-subjected children with malignancy. Blood (3cc) and urine samples were collected from all the patients following which the urine samples were cultured on Saborrads Dextrose Agar and the blood samples were cultured in ordinary culture bottles (monophasic culture method and blood culturing). Then, the developed fungi were separated from the culture environment and subjected to identification tests. The prevalence rate of the various *Candida* species and the sensitivity to various antifungal drugs were tested and the prevalence rates were explored based on gender, age, history of taking antibiotics and presence of neutropenia, mucositis, urinary catheter and peripheral venous catheter.

In order to statistically analyze the data, SPSS software, ver. 19 (IBM Corp., Armonk, NY, USA) was used. To investigate the correlation between two variables, logistic regression statistical model was utilized. The *P*-value was set at below 0.05 for considering data as significant and meaningful.

Ethical considerations

This project has been approved by Urmia University of Medical Sciences with Code of Ethics IR.UMSU.REC.1398.203.

Written consent letters were acquired from all the patients before entering the study and the participants were ensured that the study would not be harmful to them and it

will not also incur them with any expenses. In all of the stages, no work procedure was implemented without the patients' consent and they were allowed to withdraw from the study at any stage even after signing the written consent letter.

Results

Overall, 128 chemotherapy-subjected children with malignancy were randomly selected.

Eighty four children (64.6%) had ALL type of malignancy; 13 children (10.2%) had AML type of malignancy; 5 children (3.9%) had Hodgkin's lymphoma malignancy, 1 child (0.8%) had optic glioma malignancy, 4 children (3.1%) had neuroblastoma malignancy; 3 children

(2.3%) had burkitt lymphoma malignancy; 3 children had rabdomyosarcoma malignancy; 2 children (1.6%) had LCH type of malignancy; 3 children (2.3%) had wilms malignancy; 2 children (1.6%) had PNET type of malignancy; 2 children (1.6%) had lymphoma type of malignancy; 1 child (0.8%) had HLH type of malignancy; 3 children (2.3%) had retinoblastoma type of malignancy and, finally, 2 children (1.6%) had medulloblastoma type of malignancy. Considering the results obtained from Fisher's exact test, the frequency distribution of the malignancy type in the patients with fungal colonization and the patients with negative fungal colonization was identical but it was not statistically significant ($P=0.6$) (Tables 1-3).

Table 1: Age range of the patients with and without fungal infections

Variable		Culture (%) number		
		Positive	Negative	Total
Age group(yr)	0-6	24 (0.1)	39 (0.9%)	63
	7-12	16 (0.2)	27 (0.8%)	43
	>=13	8 (0.4)	14 (0.6%)	22
Gender	Male	24 (0.8)	54 (0.2%)	78
	Female	24 (48)	26 (52%)	50

Table 2: Concomitant frequency distribution of the blood and urine tests' results for the studied children

Test type and result		Urine	
		Positive	Negative
Blood	Positive	4	24
	Negative	24	76

Table 3: Absolute and relative frequency rates of the resistance to antifungal medication studied herein based on the fungus type

Fungus type	Resistance to antifungal medication					
	N(%)					
	Amphotericin B	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Ketoconazole
<i>C. albicans</i>	4 (9.52)	9 (21.43)	13 (30.95)	1 (2.4)	1 (2.4)	14 (33.3)
<i>C. glabrata</i>	1 (16.7)	1 (16.7)	2 (33.2)	1 (16.7)	0	1 (16.7)
<i>C. tropicalis</i>	1 (12.5)	1 (12.5)	4 (50)	0	1 (12.5)	1 (12.5)
<i>C. parapsilosis</i>	0	1 (100)	0	0	0	0
<i>C. krusei</i>	0	0	1 (33.33)	0	1 (33.33)	1 (33.33)
<i>C. kefir</i>	0	1 (33.33)	1 (33.33)	0	0	1 (33.33)

Considering the results obtained from Chi-Square test, there was no significant relationship between the age group and fungal infection ($P=0.998$) but a significant relationship was found between gender and fungal infection ($P=0.049$) in such a way that fungal infection was found more common amongst the females.

The infections with fungus species are showed in Table 4.

Using Kruskal-Wallis test, the effect of the six kinds of antifungal medications was significant only on *C. albicans* ($P<0.01$) and that there was no significant difference for the rest of the fungi in terms of the antifungal drug's effect (Table 5).

Table 4: Frequency and percentage distribution of *Candida* infections based on gender and age of the studied children

Variable		<i>albicans</i>	<i>tropicalis</i>	<i>glabrata</i>	<i>kefir</i>	<i>krusei</i>	<i>parapsilosis</i>	<i>P</i>
Gender	Male	12 (50)	6 (25)	3 (12.5)	2 (8.3)	1 (4.2)	0	0.811
	Female	16 (66.7)	3 (12.5)	2 (8.3)	1 (4.2)	1 (4.2)	1 (4.2)	
Age	0-6	14 (58.3)	5 (20.8)	2 (8.3)	2 (8.3)	1 (4.2)	0	0.986
	7-12	9 (56.3)	2 (12.5)	2 (12.5)	1 (6.3)	1 (6.3)	1 (6.3)	
	>=12	5 (62.5)	2 (25)	1 (12.5)	0	0	0	

Table 5: Frequency distributions of the types of sensitivity in various *Candida* species to the antifungal treatments in this study

Variable		Frequency	Percentage
Amphotericin B	Sensitive	37	77.1
	Intermediate	5	10.4
	Resistant	6	12.5
Ketoconazole	Sensitive	18	37.5
	Intermediate	12	25
	Resistant	18	37.5
Fluconazole	Sensitive	23	47.9
	Intermediate	12	25
	Resistant	13	27.1
Itraconazole	Sensitive	20	41.7
	Intermediate	12	25
	Resistant	16	33.3
Posaconazole	Sensitive	41	85.4
	Intermediate	4	8.3
	Resistant	3	6.3
Voriconazole	Sensitive	45	93.7
	Intermediate	1	2.1
	Resistant	2	4.2

As for *C. albicans*, the antifungal effects of amphotericin B and ketoconazole ($P=0.01$), fluconazole and voriconazole ($P=0.01$), itraconazole and voriconazole ($P<0.01$), itraconazole and posaconazole ($P<0.01$) and in the end, voriconazole and ketoconazole ($P<0.01$) was reported significant. The sensitivity of the various fungus species to voriconazole was in its

highest level followed by posaconazole, amphotericin B, fluconazole, itraconazole and ketoconazole, respectively.

None of the children participating in this study were found with a past history of fungal infection. Fourteen children (10.9%) were found with neutropenia, 46 children (35.9%) with mucositis, 5 children (3.9%) with urinary catheter and all of them with

peripheral venous catheter which are all amongst the risk factors giving rise to the emergence of *Candida* infections. Only mucositis was found having an effect on the result of fungus culturing ($P:0.29$). Moreover, all of the studied children had a history of taking antibiotics.

Considering the results obtained from Fisher's exact test, the distribution of the fungus species is identical in regard of the gender and age for the chemotherapy-subjected children hence no significant difference has been evidenced.

Discussion

Candidemia (blood's infection with various *Candida* species) is one of the five common hospitals' infections amongst the risk factors of which malignancy, prematurity and surgery during postnatal period can be pointed out (16,17). The prevalence rate of the invasive fungal infections ranges from 1% to 38% in the children with malignancy and it is more prevalent in the blood-related malignancies with *Candida* fungi being the most common (18). *C. albicans* was the most common species of invasive *Candida* in children and this is consistent with what has been found herein but the highest mortality rate has been justified for *C. parapsilosis* (19). Recently, the prevalence of non-*albicans* species has also increased (20,21).

The blood infection with non-*albicans* *Candida* species in patients with hematological malignancy and neutropenia for over 7 d after chemotherapy is considered as an independent risk factor for the creation of the systemic *Candida* infections (22). Furthermore, prescription of steroids in high dosages, as well, can cause an increase in the risk of invasive fungal infection (23). However, mucositis was proved herein as the only factor contributing to the development of fungal infections in the patients.

Due to the high mortality rate of the invasive fungal infections, the patients with

high infliction rate should be prescribed with prophylactic antifungal medications (24). In this study, voriconazole was found having the highest effect on the treatment of invasive candidiasis. Due to the same reason, this drug can be possibly used as saving treatment in resistant cases (25). This is while, itraconazole was found with the highest effect on *Candida* species (26). *C. albicans* and *C. parapsilosis* are resistant to fluconazole and voriconazole for less than 6% whereas the resistance rate was higher in *C. tropicalis* and *C. glabrata* and it was also found increasing with the passage of time (27). The amount of drug resistance has been higher in non-*albicans* *Candida* species in contrast to *C. albicans* in such a manner that it has been less than 1% in *C. albicans* and between 2% and 4% in *C. glabrata* (28). One of the risk factors can be the prior use of azoles (29,30). The treatment of non-*albicans* species with azoles might take a longer time and be less successful. The prescription of echinocandins in prophylactic form for these patients may cause decrease in the rate of invasive *Candida* infections' expression (31).

Conclusion

The most common *Candida* species was *C. albicans* and voriconazole is the best and most effective medication for the treating of these infections in the studied patients; however, the prevalence of the various species and their sensitivity to the antifungal drugs differ in various regions.

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Conflict of interest

The authors declare that there is no conflict of interests.

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