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Determining the colonization rate of immunodeficient patients with *Candida* species and species sensitivity to antifungal drugs

Abstract

Background: Candidiasis falls into the most prevalent fungal infections created by opportunist *Candida* species. The number of patients prone to infection with opportunist microorganisms is on the rise in recent years. This study aims to determine the frequency and drug sensitivity of *Candida* species derived from immunodeficient patients hospitalized in Kerman trial hospitals, southeastern Iran.

Methods: This cross-sectional study was conducted on immunodeficient patients hospitalized in Afzalipour and Bahonar hospitals in Kerman during 2012-2013. After obtaining informed consent, data collection forms were completed for all patients by themselves or their parents in the pediatric and adult oncology department. Then, nasal and oral samples were collected from the patients and sent to a laboratory for cultures and sensitivity determination to antifungal medicines. The results of laboratory tests were added to the information form. Data were analyzed using descriptive tests (frequency and relative frequency) and the Chi-squire analytic test.

Results: From 173 patients, 111 (64.2%) cases were male. Many patients (80.2%) had cancer or were under chemotherapy. A history of antifungal treatment was found in 20 (11.6%) patients. A total of 94 (33.9%) cases had positive fungal cultures. Totally, nine *Candida* species and a *Sporobolomyces salmonicolor* were collected from the samples. *Candida albicans* was the most common *Candida* species with a frequency of 45 (16.2%). Age, history of antibiotic use, and the type of immunodeficiency disease were not significantly different among patients with positive cultures. More positive culture results were observed in patients who already consumed antifungal drugs than the others (P = 0.012). Drug resistance proportion was about 11.7%.

Conclusions: Candidiasis has a prevalence of about 33.9% in immunodeficient patients in Kerman City. *C. albicans* is the most common specie in these patients. Drug resistance proportion is about 11.7%..

Keywords: *candidiasis, immune deficiency, drug resistance*

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Introduction

Although fungal infections were less prevalent than bacterial and viral infections in the past, they have caused a significant increase in disease incidence in recent decades. A survey conducted between 1979 and 2000 in the USA indicated that the incidence of fungal infections increased by 207% (1). In another survey, an increase in the death rate was reported due to fungal infections (2).

Predisposing factors, such as extensive and long-term use of antibiotics, corticosteroids, and immunosuppressive drugs, as well as underlying diseases such as malignancy, AIDS, diabetes, etc. have caused an increase in fungal diseases, especially candidiasis, than in the past. In a study, *Candida* species were identified as the fourth cause of death caused by bloodstream infections and comprised 35% of blood infection cases leading to death (14, 2).

Opportunistic pathogenic fungi are among life-threatening infections in immunocompromised patients. Yeasts and above all *Candida* species are the most common fungi isolated from human infections (3). The occurrence of invasive systemic candidiasis is dramatically on the rise despite many advances in health care and treatment methods (15).

Candida is an opportunistic fungus that is present symbiotically in the digestive tract, mucous membranes, and the skin of humans and other animals and can even be found in the environment. This agent will be able to cause disease in any area of the body when the host's resistance is reduced locally or systemically, primarily or secondarily due to predisposing factors. The presence of limitations, such as the low number of antifungal drugs, their toxicity to body cells, or the reduced sensitivity of a series of *Candida* species to these drugs, have been considered important problems in the treatment of this disease (14).

Treatment with azole antifungal agents, particularly fluconazole, is introduced as an effective approach to treating

C. albicans yeast infections, but this treatment method faces serious problems with the emergence of drug resistance (5, 6). Different molecular mechanisms are known in the emergence of *C. albicans* resistance against fluconazole (7). These include reduced drug transport into the cell, changes in the enzymes of the ergosterol biosynthesis pathway, changes in the target enzyme (point mutations, increased expression, and gene alteration), and increasing outward drug release using membrane diffusion pumps. Another important mechanism involved in the formation of azole resistance is a decrease in intracellular drug accumulation, which is associated with the expression and overexpression of CDR genes (*Candida* drug resistance genes) (8-13).

Afsarian et al. (2015) examined the clinical samples of patients with candidiasis to determine species other than *C. albicans*. Out of 304 isolated yeast colonies, 204 and 100 cases were *C. albicans* and other *Candida* species, respectively. The authors recommended evaluating the drug sensitivity of all *Candida* strains to the drugs available in the Iranian market due to the variability of this organism against antifungal drugs (16).

In 2013, a study conducted on people undergoing radiotherapy to the head and neck in Brazil showed that 55.4% of these people were positive for candidiasis. In this study, the most common *Candida* strains were *Albicans*, followed by *Entropicalis*, *Parapsilosis*, and *Glabrata* (24).

Karthaus et al. (2008) studied 585 hemato-oncology and non-oncology patients and reported that *Albicans*, *Glabrata*, and *Tropicalis* were respectively the most common types of *Candida* in positive cultures (26).

Yun-Liang Yang et al. (2008) investigated 964 samples to determine the sensitivity of *gj* amphotericin B and fluconazole. They claimed that *Candida* resistance to amphotericin B was 1.8-2.5%, and 16 out of 17 resistant cases were interestingly species other than *C. albicans* (27).

Obviously, determining the pattern of sensitivity to antifungal drugs of *Candida* species isolated from immunodeficient patients is effective and essential in the prevention and proper treatment of these patients. Therefore, this study evaluated the colonization rate of patients with primary immunodeficiency with *Candida* species and the sensitivity of these species to antifungal drugs.

Methods

This cross-sectional analytical study was conducted on immunodeficient patients in Afzalipour and Shahid Bahonar hospitals in Kerman City during 2012-2013. All patients visiting pediatric and adult oncology wards were included in the study through convenience sampling after obtaining informed consent until reaching a sample size of 277.

Inclusion criteria

People with glucocorticoids, leukemia, and lymphoma were included in the study. First, an information registration checklist, including age, gender, type of immunodeficiency, reason for hospitalization, and history of receiving antifungal and bacterial drugs, was completed for all patients by a trained nurse. Then, samples were taken from the mucous membrane of the mouth and nose using a sterile swab and cultured on the Sabord dextrose agar medium. The samples were packed and insulated at room temperature and then sent weekly to the reference laboratory of Professor Alborazi, Shiraz. To determine filamentous fungi species in the laboratory, slides were prepared directly from the culture medium and observed by an optical microscope. The yeasts were identified using such tests as germ tube formation and sugar fermentation by the API method (Biomerieux, St. Louis, MO).

Drug sensitivity was evaluated based on the CLSI M27-A2 protocol. Antifungal drugs were purchased from special companies (Sigma and Pfizer). To prepare drug stock based on the recommended CLSI standard, the powder of each drug was weighed and dissolved in 1 ml of dimethyl sulfoxide (DMSO). The isolated fungi were cultured on the potato agar medium to confirm their purity. A suspension was prepared from fungal conidia and read at 530 nm (a 0.5 McFarland tube). The prepared suspension was diluted once at 1:20 and then at 1:50 with RPMI 1640 manufactured by Sigma (Germany). First, 100 µl of RPMI was poured into all the wells in the first row of the plate, except the first well, and then 200 µl of the drug, prepared previously by DMSO, was added to the first well. Thus, out of ten wells of a 96-well plate, the first well was filled with only 200 µl of the thyme essential oil solution, and the rest contained 100 µl of RPMI.

In the serial dilution process, 100 µl of the drug was taken from the first well and transferred to the second well. Then, 100 µl of the contents of the ninth well were transferred from the second well to the third and fourth wells and finally to the tenth well. From the tenth well, 100 µl was taken by a sampler and taken out to have the same volume of the RPMI medium and drug in all the wells. Well 11 was a positive control containing 100 µl of RPMI, and well 12 contained only RPMI and drug as a negative control of the test. Then, 100 µl of the fungus together with RPMI was added into each of the 11 wells of the 96-well plate, except for the last well. The plates were incubated at 35 °C for 24-48 h.

The collected data were analyzed statistically using relative frequency and frequency indices to describe the qualitative data, as well as chi-square or Fisher's test with SPSS software version 11/5.

Results

Of 173 participants in this study, 111 people (64.2%) were men. Oral and nasal samples were found in 104 samples, and

69 subjects had only oral samples, with a total of 277 samples, among which 94 samples (33.9%) had positive cultures. Thus, positive fungal cultures were recorded for 86 (49%) out of 173 oral samples and 8 (7.6%) out of 104 nasal samples (Fig. 1). One-third of the studied subjects suffered from ALL, followed by lymphoma (14.5%) as the second most frequent malignancy (Fig. 2).

Positive yeast cultures were observed in 94 (33.9%) out of 277 samples, and a total of nine candidate strains and one case of *Sporobolomyces salmonicolor* were extracted from the samples. The most frequent *Candida* strain was *C. albicans* with a frequency of 45 samples (16.2%). After that, *C. fermentati* and *C. glabrata* strains were in the next ranks with frequencies of 5% and 3.2%, respectively. *C. parapsilosis* with a frequency of one person (0.4%) was the least frequent strain among *Candida* strains isolated from the patients (Fig. 3).

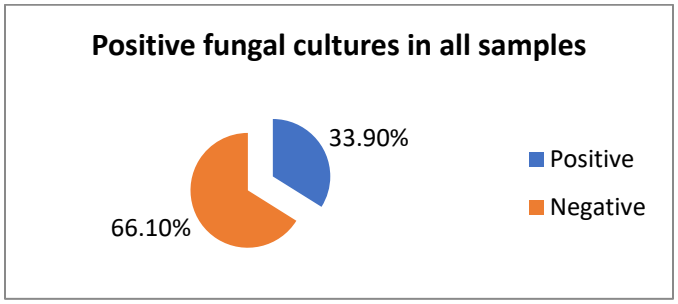

Figure 1. The frequency distribution of fungal culture results in oral and nasal samples

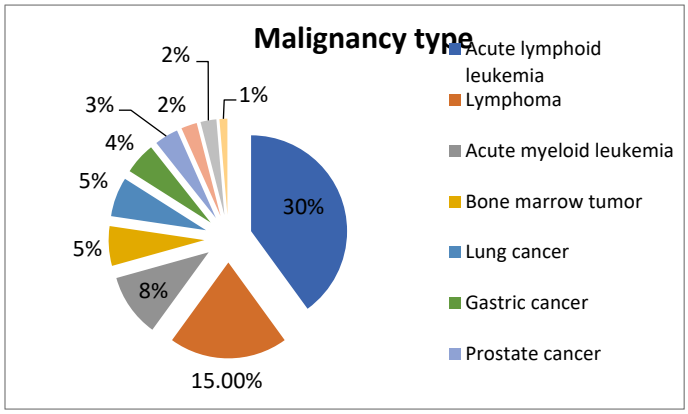

Figure 2: The frequency of the studied subjects based on the type of malignancy

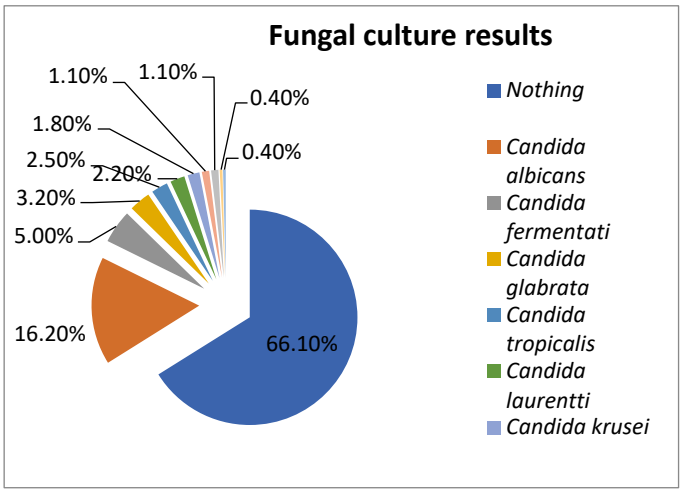

Figure 3: The frequency distribution of the studied samples based on fungal culture results

Examining the resistance of cultured samples revealed drug resistance in 11 people (11.7%). The drug type included itraconazole 3 (27%), amphotrypsin B 2 (18%), caspofingin 2 (18%), fluconazole 1 (9%), voriconazole 1 (9%), ketoconazole 1 (9%), and pesoconazole1 (9%), which were not statistically significant based on the drug type ($p = 0.817$). *C. albicans* was the most resistant among the strains and showed the utmost resistance to itraconazole, but this difference was not significant ($p = 0.817$). No significant difference was observed between the swap sample site (mouth and nose) and drug resistance ($p = 0.216$) (Table 1).

Table 1. The frequency distribution of drug resistance by strains in the studied samples

Antifungal drug	**Resistant strain**					**Total**
	C. albicans	***C. krusei***	***C. lauranti***	**Other *Candida* strains**	***Sproblomyces salmonicolor***	
Ketoconazole	**(2/2%)1**	**(0)0**	**(0)0**	**(0)0**	**(0)0**	**(9/1%)1**
Fluconazole	**(2/2%)1**	**(0)0**	**(0)0**	**(0)0**	**(0)0**	**(9/1%)1**
Voriconazole	**(2/2%)1**	**(0)0**	**(0)0**	**(0)0**	**(0)0**	**(9/1%)1**
Itraconazole	**(4/7%)2**	**(20%)1**	**(0)0**	**(0)0**	**(0)0**	**(27/2%)3**
Amphotericin B	**(2/2%)1**	**(0)0**	**(16/7%)1**	**(0)0**	**(0)0**	**(18/2%)2**
Caspofungin	**(4/5%)2**	**(0)0**	**(0)0**	**(0)0**	**(0)0**	**(18/2%)2**
Posaconazole	**(2/2%)1**	**(0)0**	**(0)0**	**(0)0**	**(0)0**	**(9/1%)1**

A history of receiving antifungal drugs was found in 20 people (11.6%), among whom 15 (75%) people used amphotrypsin B alone, three (15%) people received a combination of amphotrypsin B with voriconazole, and two (10%) people used a combination of amphotrypsin B, voriconazole, and fluconazole. Positive fungal culture results were observed in all people with a history of using antifungal drugs (p = 0.012). In 37.5% of people who used antifungal drugs, nasal colonization was resistant to amphotericin, itraconazole, fluconazole, caspofungin, and ketoconazole, but their oral colonization was resistant to none of the drugs (Table 2).

Table 2. The relationship between fungal culture results and the use of antifungal drugs in the studied subjects

Fungal culture result	Antifungal drug use		Sig.
	Yes	No	
Positive	20(100%)	61(39/9%)	0.012
Negative	(0)0	92(60/1%)	
Total	20(100%)	153(100)	

A history of receiving antibiotics in the last 2 weeks was reported by 159 (91.9%) people. Among the people with a history of taking antibiotics in the last 2 weeks, 75 people (47.1%) had a positive culture result, and six (42.8%) of the individuals who did not take antibiotics had positive culture results, which was not significant in statistical analyses (p = 0.779) (Table 3).

Table 3. The relationship between fungal culture results and the use of antibiotics in the studied subjects

Fungal culture result	Antibiotic use		Sig.
	Yes	No	
Positive	75(47/1%)	6(42/8%)	0.779
Negative	84(52/9%)	8(57/2%)	
Total	159(100%)	14(100%)	

Among the patients, 138 (79.8%) individuals were admitted for chemotherapy, and the rest of the patients were admitted to the hospital due to complications caused by chemotherapy or associated infections. Positive culture results were detected in 70 (50.7%) patients who were hospitalized only because of chemotherapy, and 11 people (31.4%) who were admitted due to complications caused by chemotherapy or associated infections had positive culture results, which was statistically significant (p = 0.012) (Table 4).

Table 4. The relationship between fungal culture results and the reason for hospitalization in the studied subjects

Fungal culture result	Reason for admission		Sig.
	Chemotherapy	Chemotherapy complications/infection	
Positive	70(50/7%)	11(31/4%)	0.012
Negative	68(49/3%)	24(68/6%)	
Total	138(100%)	35(100%)	

Discussion

In this study, 277 oral and nasal samples were examined from 173 immunodeficient patients. Positive fungal cultures were found in half and about 8% of the oral and nasal samples, respectively. Several studies have reported a high prevalence of oral candidiasis (12%-94%) in HIV-infected patients (17-22), and a rate of 60% was reported in a study in Tehran in 2009 (23). Edimilson M. de Freitas et al. (2012) reported a candidiasis prevalence of 58.6% in patients with head and neck cancer undergoing treatment with radiotherapy (24).

Among the total positive fungal cultures of the mouth and nose, the most prevalent strains were *C. albicans*, followed by *C. fermenti* and *C. glabrata*. Edimilson M. de Freitas et al. claimed that *C. albicans*, followed by *C. tropicalis* and *C. parapsilosis*, were the most frequent strains (24). The most common types of *Candida* in positive cultures were C. albicans, followed by C. glabrata and C. tropicalis in a study on cancer patients by Karthaus et al. (26).

In a study in 2009, invasive fungal infections were observed in 17.7% of immunodeficient patients, and *C. albicans* was reported as the most frequent fungus (25).

In a study in Tehran, the strain of *Candida* was determined in all samples of patients with candidiasis. Out of 304 samples, 204 and 100 cases were respectively *C. albicans* and other strains, the most frequent of which were *parapsilosis*, *tropicalis*, and *glabrata* (16).

In the current study, drug resistance was observed in about 12% of the samples with positive fungal cultures. *C. albicans* was the most drug-resistant strain among the strains, and itraconazole drug showed the most resistance to itself.

In a review of the literature, no study was found examining all or most of the common antifungal drugs in terms of resistance. Most of the studies focused on people with AIDS-induced immunodeficiency and less on cancer patients, but different studies sporadically investigated different drugs.

Yun-Liang Yang et al. reported that *Candida* resistance to amphotericin B was 1.8-2.5%, and interestingly, 16 of 17 resistant cases were strains other than *C. albicans* (27). In our

study, a resistance rate of 16.7% was found in a strain (*C. laurenti*) other than *C. albicans*, and amphotericin was included in 18.2% of all cases of resistance to the seven examined drugs.

Different drug resistance rates of *Candida* species to antifungal drugs are reported in studies conducted on AIDS patients based on the technique, geographical location, and type of drug. For example, resistance rates of 25%, 9%, and 30% to fluconazole were reported by George et al. (31), Cassone et al. (29), and Marcelo et al. (30), respectively. In our study, a drug resistance rate of 9.1% to fluconazole was only observed in the *Candida* strain.

Katiraei et al. claimed a significant relationship between oral candidiasis and previous antifungal treatment in immunodeficient patients (23). In another study, only the C*andida glabrata* strain was significantly correlated with previous antifungal treatment (28). In our study, all people with previous antifungal treatment had positive culture results, and this difference was highly significant relative to people who did not receive antifungal treatment.

The relationship between fungal culture results, the previous antibiotic use, and the reason for the person's referral was investigated in two other analyses, in which fungal culture results were not correlated with previous antibiotic use. However, it was significantly higher in people admitted for chemotherapy than in those hospitalized for chemotherapy complications or infection. In 1952, a study was conducted in the USA on the effect of antibiotics on the growth of *Candida*. The results revealed that antibiotics available at that time such as penicillin, chloramphenicol, streptomycin, and tramycin, except for aureomycin hydrochloride, did not stimulate the growth of *Candida in vitro* (32). Nonetheless, other studies did not evaluate most of these associations. The results of our study were also contrary to expectations, hence further and newer studies may be important in this field.

Conclusion

Since immunodeficient patients, especially those undergoing chemotherapy, are in an emergency, it is recommended to identify the type of resistant fungal drugs in each person before the treatment of these patients to use the appropriate drug according to the test results of these patients. The consequences of drug prescriptions to patients resistant to special drugs without sensitivity assessment lead to the emergence of resistant *Candida* species, and on the other hand, the imbalance of the normal *Candida* flora in the body.

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