Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1448006
J Health Sci Med. 2024;7(3):290-295

Distribution and antifungal susceptibility profiles of *Candida* species isolated from dermatomycosis patients

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Cite this article as: Aydın Kurç M, Kaya AD, Erfan G, Albayrak Ş. Distribution and antifungal susceptibility profiles of *Candida* species isolated from dermatomycosis patients. *J Health Sci Med.* 2024;7(3):290-295.

Received: 08.03.2024 ◆ **Accepted**: 21.04.2024 ◆ **Published**: 27.05.2024

ABSTRACT

Aims: Superficial mycoses are the most common dermatological diseases worldwide, and the causes are becoming increasingly resistant to antifungal agents used in treatment. The aim of our study was to identify the yeast species causing superficial mycoses and determine their susceptibilities to some antifungal agents.

Methods: Skin and nail scraping samples obtained from 726 patients with suspected superficial fungal infection were collected and examined by direct microscopy and culture. Isolates were identified by conventional methods and API ID32 C (Biomeriux, France) commercial kits. The minimum inhibitory concentrations (MIC) of isolates against itraconazole, miconazole, nystatin, and terbinafine antifungals were determined by microdilution method.

Results: A total of 59 yeasts were isolated from the samples. The most frequently isolated species were *Candida glabrata* (n=31, 52.54%), *Candida guillermondii* (n=9, 15.25%), and *Candida albicans* (n=7, 11.86%). In terms of infection sites, the most common involvement was observed in the foot (n=39, 66.1%) and nails (n=16, 27.1%). In terms of their antifungal susceptibilities, the highest resistance was detected against terbinafine (35.6%) and itraconazole (33.9%). Multidrug resistance was observed among strains of the *Candida* species (n=17, 28.8%).

Conclusion: The most striking results of this study can be summarized as high rates of *Candida glabrata* isolation, increase in resistance rates, and a prevalence of 28.8% multidrug resistance. This data once again emphasize the importance of isolation, identification, and antifungal susceptibility testing in the diagnosis and effective treatment of superficial mycoses.

Keywords: Superficial mycoses, *Candida* spp., antifungal susceptibility, multidrug resistance

INTRODUCTION

Superficial fungal infections are dermatological diseases effecting hair, nails, and skin and are commonly seen worldwide with a reported prevalence rate of 20-25%.[1] The infectious agents are mostly dermatophytes of the genus *Microsporum*, *Trichophyton* and *Epidermophyton*, yeasts, and rarely non-dermatophytic filamentous fungi.[2]

Dermatophytosis, pityriasis versicolor, and candidiasis are the three most common superficial fungal infections.[3] Dermatophytosis is classified according to the effected body sites as tinea corporis, tinea capitis, tinea pedis, tinea manum, and tinea unguium.

Candidiasis is an infection caused by *Candida* species, members of the human microbiota and can show systemic involvement, as well as involving skin and mucous membranes. Host immune response play a key role in the development of Candidiasis.[3,4] *Candida albicans (C. albicans)* is the most common species responsible from approximately 80-90% of all skin infections caused by *Candida* genus.[5] However, studies suggest more than 50% increase in the frequency of non-albicans *Candida* (NAC) species, including *Candida glabrata (C. glabrata), Candida parapsilosis (C. parapsilosis), Candida tropicalis (C. tropicalis), Candida krusei (C. krusei), Candida lusitaniae (C. lusitaniae), Candida dubliniensis (C. dubliniensis),* and *Candida guilliermondii (C. guilliermondii)*, recently.[6]

The main groups of systemic antifungals commonly used for the treatment of superficial mycoses are imidazoles (ketoconazole), triazoles (fluconazole and itraconazole), and allylamine (terbinafine). Although various antifungals, both topical and systemic, are available today, there is a need for more effective and less toxic new agents.[7] The variations on spectrum of activity of antifungals, drug bioavailability, drug interactions, or resistance can lead treatment failures. The selection of therapeutic agents need to be related with the causative fungal species, the efficacy,

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safety profile, and pharmacokinetics of antifungals.[8,9] Evaluating the susceptibility profile of the antifungal drugs is crucial for treatment.[8]

The most commonly isolated causative agents of superficial mycosis are dermatophytes, followed by yeast species. The identification of these isolates affects the success of treatments due to their different antifungal susceptibility patterns. Therefore, our study aims to identify yeast isolates obtained from skin and nail samples, which are the causative agents of superficial mycoses, and to determine their antifungal susceptibilities.

METHODS

Ethics

Written approval was obtained for this research from the Ethical Evaluation Commission of the Faculty of Medicine in Namık Kemal University (Date: 29.12.2012, Decision No: 2012/05/01/05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Collection of Samples

In this study, 726 patients who attended to the Dermatological and Venereal Diseases Clinic at Namık Kemal University Hospital, over a period of 18 months (between 11.10.2011 and 08.04.2013) and suspected of superficial fungal infections were included. Skin and nail scraping samples of these patients were collected, and sent to the Microbiology Laboratory. Infected areas were cleaned prior to sampling; a sterile scalpel was used to collect from the corners of skin lesions, while for nail lesions scraping samples were collected until healthy tissues were reached and the samples were transferred into sterile petri dishes. The samples were used for direct microscopic examination and culture inoculations.

Direct Microscopic Examination

Samples were placed on a clean slide, 10-20% KOH (Potassium hydroxide) solution was added, the slide was covered and pressed slightly, and was finally incubated at room temperature for 15-30 minutes for examination. The examination was conducted under the microscope sequentially at a magnification of x10 and x40, and the presence of spores (arthrospores, blastospores, etc.) and hyphae was investigated in all microscopic fields.[10] The microscopic examination was regarded as positive in the presence of any of these structures.

Culturing and Identification of Samples

Multiple inoculations were carried out from the collected samples on Sabouraud Dextrose Agar (SDA) (Merck, Germany) in addition to SDA containing chloramphenicol, cycloheximide, and gentamicin and Potato Dextrose Agar (PDA) (Oxoid, England). All media were incubated for four weeks in an incubator, at 26°C and 37°C. The cultures were checked twice a week and evaluated for fungal growth. Germ tube test was conducted for yeast isolates and their microscopic appearances in Corn Meal-Tween 80 agar (Corn Meal Agar, Beckton Dickinson, USA) were evaluated,[11] followed by identification using API ID32 C (Biomeriux, France) commercial kits.

Antifungal Susceptibility Test

Isolated yeasts were tested for their susceptibilities to the antifungals itraconazole, miconazole, nystatin, and terbinafine. MIC ranges of the antifungal drugs were set between 0.0313-16 µg/mL. Reference microdilution method was applied using RPMI 1640 (Sigma Chemical Co., St. Louis, Mo, USA) containing L-glutamine and without bicarbonate, in order to evaluate susceptibility. After adding 2% dextrose and adjusting the pH to 7.0 using 0.165 M morpholine-propane-sulphonic acid (MOPS, Sigma), this medium was used in Broth Microdilution (BMD) test. *C. albicans* (ATCC 90028), *C. glabrata* (ATCC 90030), *C. parapsilosis* (ATCC 22019), *C. krusei* (ATCC 6258), and *C. tropicalis* (NRRL Y-12968) were used as quality control strains. For the preparation of yeast suspensions, colonies from 24-hour SDA were collected and prepared as homogeneous suspensions in sterile physiological saline and turbidity was adjusted to 0.5 McFarland. After the addition of certain antifungals, media, and yeast suspensions, the micro-plates were incubated at 35°C for 48 hours, and MIC values were evaluated according to the MIC values specified in the M27-S3 and M27-S4 guidelines prepared by "Clinical Laboratory Standards Institute (CLSI)".[12,13] Breakpoints were set by CLSI for azoles as follow; itraconazole (susceptible, MIC≤0.125 µg/ ml; dose dependent, 0.25-0.5 µg/ml; resistant, MIC≥1 µg/mL). Miconazole does not have a specified breakpoint; nonetheless, literature indicates that *Candida* species is susceptible at MIC≤5 µg/mL and resistant at MIC≥5 µg/mL, respectively. According to the literature, terbinafine susceptibility limit values are evaluated as ≤8 µg/mL sensitive and >8 µg/mL resistant.[14-17]

RESULTS

In our study, yeasts were detected in 59 (8.1%) of the skin and nail scraping samples of 726 patients. The average age of patients considered for evaluation was determined as 51.72±14.85 (19-80 years). 39 (66.1%) of the cases were male patients, while 20 (33.9%) were female patients.

When the samples obtained from patients having yeast growth were examined according to the distribution of infected sites, the most common involvement was observed in the foot (n=39, 66.1%) and nails (n=16, 27.1%), followed by the trunk (n=2, 3.4%) and hands (n=2, 3.4%).

In direct microscopic examination using KOH of a total of 59 samples having yeast growth, direct microscopic positivity were detected in 37 (62.7%) of the cases, while 22 cases resulted with direct microscopic negativity (37.3%).

When examining the samples with positive germ tube test and Cornmeal-Tween 80 agar morphology, 31 samples were identified as *C. glabrata* (52.54%), 9 as *C. guillermondii* (15.25%), and 7 as *C. albicans* (11.86%). The distribution of yeasts is given in Table 1.

The results of in vitro antifungal susceptibility tests (MIC range, MIC50 and MIC90) of four antifungals against all yeast isolates are shown in Table 2. According to the antifungal susceptibility test, 11 (18.6%) isolates were found to be dose-dependently susceptible and 20 (33.9%) isolates were found to be susceptible (8 *C. glabrata*, 4 *C. albicans*, and

2 *C. guillermondii*) to itraconazole. Our results indicate that a total of 10 (16.9%) isolates, four of which are *C. glabrata*, two are *C. albicans*, *C. guillermondi, C. krusei, C. lusianiae*, and one *C. tropicalis* isolate were resistant to miconazole. Terbinafine MIC values indicate that 21 (35.6%) strains were resistant (12 *C. glabrata* and 4 *C. albicans*). Moreover, according to our results, multidrug resistance was observed among strains of the *Candida* species (n=17, 28.8%). Multidrug resistance was observed in 8 *C. glabrata*, 3 *C. albicans*, 1 *C. guillermondii*, and 1 *C. krusei* isolates.

Table 1. The distribution of isolated yeasts

Yeast	n	%
Candida glabrata	31	52.54
Candida guillermondii	9	15.25
Candida albicans	7	11.86
Candida tropicalis	4	6.77
Candida dubliniensis	2	3.38
Candida keyfr	1	1.69
Candida krusei	1	1.69
Candida lusitaniae	1	1.69
Candida parapsilosis	1	1.69
Candida zeylanoides	1	1.69
Rhodotorula spp.	1	1.69

DISCUSSION

Superficial mycoses are infections of the keratinized tissues of humans and animals, including the skin, nails, and hair.[18] Epidemiological studies indicate that they are the most common infections worldwide, affecting all age groups and leading to high expenditures for treatment every year.[7] Although dermatophytoses are the most common fungal infection in humans among superficial mycoses, candidiasis and pityriasis versicolor are also quite prevalent.[19]

Superficial mycoses epidemiology can be influenced by many factors such as geography, climate, historical factors, migration, wars, quality of health services, society's educational level in the region, and social factors.[20] When the distribution according to patient age groups was examined in previously conducted studies, it was stated that infection varied between the ages of 2 months and 81 years,[21,22] while the average age was between 38 and 40.[23,24] The average age of patients included for evaluation in our study was determined as 51.72±14.85 (19-80).

Many studies conducted in our country show that the majority of the patients with a preliminary diagnosis of superficial mycosis are male.[25-29] These data are consistent with our study as well.

Traditional and phenotypic methods are widely used for diagnosing pathogenic yeasts in clinical laboratories. However, these methods are limited in terms of identifying the isolates at the species level.[30,31] Microscopic examinations using KOH in our study led to direct microscopic positivity in 37 (62.7%) cases out of a total of 59 samples with yeast fungal growth, while direct microscopic negativity was detected in 22 (37.3%) of the cases.

Table 2. Antifungal susceptibility results of yeasts (MIC)

Antifungals	MIC µg/ml		
	MIC range	MIC_{50}	MIC_{90}
C. glabrata (n=31)			
Itraconazole	0.0313-≥16	0.0313	8
Miconazole	0.0313-≥16	0.0625	16
Terbinafine	0.0313-≥16	0.125	16
Nystatin	0.0313-≥16	0.125	8
C. guillermondii (n=9)			
Itraconazole	0.0313-≥16	0.0313	16
Miconazole	0.0313-4	0.5	4
Terbinafine	0.0313-2	0.125	2
Nystatin	0.0313-8	0.5	4
C. albicans (n=7)			
Itraconazole	1-≥16	0.5	16
Miconazole	2-≥16	0.25	8
Terbinafine	0.0313-≥16	4	16
Nystatin	0.0313-8	2	8
C. tropicalis (n=4)			
Itraconazole	0.0625-≥16	0.0625	0.25
Miconazole	0.0313-8	0.0131	4
Terbinafine	0.0313-4	0.0313	0.125
Nystatin	0.0313-8	0.125	4
C. dubliniensis (n=2)			
Itraconazole	0.0313-0.25	-	-
Miconazole	0.0313-0.5	-	-
Terbinafine	0.0313-2	-	-
Nystatin	0.0313-8	-	-
C. kefyr (n=1)			
Itraconazole	1	-	-
Miconazole	0.0313	-	-
Terbinafine	0.0313	-	-
Nystatin	0.0313	-	-
C. krusei (n=1)			
Itraconazole	≥16	-	-
Miconazole	8	-	-
Terbinafine	≥16	-	-
Nystatin	4	-	-
C. lusitaniae (n=1)			
Itraconazole	≥16	-	-
Miconazole	≥16	-	-
Terbinafine	≥16	-	-
Nystatin	4	-	-
C. parapsilosis (n=1)			
Itraconazole	1	-	-
Miconazole	2	-	-
Terbinafine	≥16	-	-
Nystatin	4	-	-
C. zeylanoides (n=1)			
Itraconazole	4	-	-
Miconazole	2	-	-
Terbinafine	8	-	-
Nystatin	0.0313	-	-
Rhodotorula spp. (n=1)			
Itraconazole	0.125	-	-
Miconazole	0.25	-	-
Terbinafine	0.0625	-	-
Nystatin	0.25	-	-

MIC: Minimum inhibitor concentration

While differences in the localization of the lesions have been observed in previous studies, the foot region followed by nails is the most commonly affected localization in many studies. Out of studies conducted in our country, Bilgili and colleagues[26] found that lesions were most commonly in the foot's sites (45%) followed by nails (41.3%) and groin (6.8%); while Ergin and colleagues[25] determined it to be foot (49.8%) followed by nails (25.3%) and trunk (11.9%), and finally Köktürk and colleagues[32] determined it to be foot (54.1%), nails (21.6%), and groin (14.3%). In line with these results, in our study, body sites attacked by yeasts were most commonly the foot (66.1%) and nails (27.1%).

Khodadadi and colleagues[33] mentioned that candidiasis as the most common superficial fungal infection, with a prevalence of 40.5%. Other studies similarly suggested candidiasis prevalence higher in Brazil (82.9%)[30] and Southeast Serbia (57%).[34] This prevalence was determined as 8.1% in our study.

C. albicans is the most commonly identified species as a causative agent among all *Candida* species. However recent studies show that there is an increase in the frequency of *Candida* non-albicans species, particularly *C. glabrata* and *C. parapsilosis*, in superficial fungal infections.[35] The prevalence of *C. glabrata* has increased significantly in the United States over the past decade, being isolated as the causative agent of candidemia in 20-24% of cases.[36] Previous studies have reported *C. albicans* as the most common cause of candidiasis, while *C. glabrata* and other species such as C. *tropicalis* and *C. krusei* as important pathogens.[37,38] The most commonly isolated species in our study are *C. glabrata, C. guillermondii*, and *C. albicans*.

Resistance to commonly used antifungal agents in the treatment of *Candida* infections limits treatment options recently. The most effective approach in the treatment of *Candida* infections is the identification of the isolated yeasts to the species level, followed by susceptibility testing to contribute to the selection of appropriate treatment methods. This, helps prevent the spread of resistant strains and reduces unnecessary drug use.[39] Our results indicate that 35.6% of the isolates were resistant to terbinafine. It was determined that 38.7% of *C. glabrata* strains were resistant to terbinafine, and their MIC values were also found to be quite high. Another study reports that 80% of *C. glabrata* strains were resistant to terbinafine.[38] Although terbinafine exhibits good activity against dermatophytes, it has lower activity against *Candida* species compared to azoles.[40,41] Additionally, these high resistance rates are thought to be caused by the weak inhibitory activity of terbinafine against all *Candida* species except for *C. parapsilosis*.[42,43]

Itraconazole, a member of the azole group, is effective against most *Candida* species, but shows higher MIC values for *C. glabrata* and *C. krusei*.[44] Our study results show that the resistance rates for miconazole and itraconazole of the azole group were 16.9% and 33.9%, respectively. Additionally, 18.6% of the isolates were determined to be dose-dependently susceptible to itraconazole. In a study conducted by Bilal and colleagues,[38] miconazole resistance was found to be 30.4% and itraconazole resistance was 16.1% for *C. albicans*, while miconazole resistance was detected as 8.33% for *C. glabrata* strains (41.67% of which were dose-dependent susceptibility), with no observed resistance against itraconazole. The occurrence of resistance to miconazole is attributed to inappropriate use as a topical therapeutic agent in the treatment of candidiasis.[45] Furthermore, the high resistance to azoles is attributed to their inappropriate use in both agricultural and clinical settings. Additionally, mutations in genes encoding the drug target are common in *Candida* and non-dermatophyte molds, including *Aspergillus* species.[46]

As s polyene derivative, nystatin has become a topical medication that can be used without causing toxic side effects when applied orally, as it is not absorbed from the gastrointestinal tract.[39] When examining studies conducted on nystatin; Agbulu and colleagues[47] claimed to have found the MIC level for *C. albicans* to be 3.13 µg/mL in their research. In another study, the MIC ranges for nystatin were determined as follows: 0.078-10 µg/mL for *C. albicans*, 0.156-1.25 µg/mL for *C. parapsilosis*, 0.156-2.5 µg/mL for *C. tropicalis* and *C. glabrata,* and 0.156-0.625 µg/mL for *C. krusei*.[48] In our study, the MIC ranges were determined to be 0.0313≥16 µg/mL for *C. glabrata*, 0.0313-8 µg/mL for *C. guillermondii*, and 0.0313-8 µg/mL for *C. albicans*.

The Centers for Disease Control and Prevention (CDC) highlights the rise of multidrug-resistant *Candida* and *Aspergillus* species in their latest updates.[49] Acquired resistance to both azoles and echinocandins, either alone or in combination, has been observed, similar to that in *C. glabrata*.[50] A 28.8% prevalence of multidrug resistance was detected in our study. This may be related with the presence of high numbers of *C. glabrata* isolates in our study.

CONCLUSION

Our study aimed to determine the species-level distribution of yeasts and their susceptibility to various antifungal agents in superficial mycoses, which are the important causes of dermatological diseases that are widely prevalent worldwide and pose challenges in treatment. As the distribution of causative agents and their susceptibilities to antifungal agents and the prevalence of superficial fungal infections varies, our study results with limited number of isolates reflects only the data of a medical center in the Thrace region and can not be generalized, which may be accepted as the limitation of the current study. The most striking findings can be summarized as high rates of *C. glabrata* isolation, and increase in resistance rates, and a prevalence of 28.8% multidrug resistance. In this study results once again emphasize the importance of isolation, identification, and antifungal susceptibility testing in the diagnosis of superficial mycoses, which will lead success in treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Namık Kemal University Faculty of Medicine Ethical Evaluation Commission (Date: 29.12.2012, Decision No: 2012/05/01/05).

Informed Consent

Due to the nature of the study, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
This research was funded by Namık Kemal University Scientific Research Projects Coordination Unit, Grant Number NKUBAP.00.20.AR.12.05.

Author Contributions
All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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