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Original Article

A 20-year retrospective clinical analysis of *Candida* infections in tertiary centre: Single-center experience

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ABSTRACT

Introduction: Fungal infections have risen exponentially in the last decade. In fact, candidiasis has become the most frequent type of hospital acquired infection especially in patients receiving treatment for chronic and terminal illnesses in a hospital. A retrospective analysis for a period of twenty year was undertaken to analyze the incidence rate of candidiasis, especially of *Candida* species, patients treated in a tertiary care center.
Materials and methods: Clinical data was collected from samples of patients who were receiving tertiary care were presenting with clinically suspected fungal infections. Direct microscopy with 10% potassium hydroxide was done to visualize the presence of fungal elements, and Gram staining was done for any suspected yeast infection. The samples were inoculated on Sabouraud's Dextrose Agar and kept at 22 °C.
Results: A total of 1256 samples with presumed fungal etiology were included in the study. The maximum number of fungal infections were present in elderly (70–79 years age). Females (53.8%) were more affected (45.5%). 21% isolates were identified as yeast but belonged to non-*Candida* fungi. Among *Candida* species, *Candida albicans* was the most dominant species (58.3%) followed by *Candida glabrata* (6.4%). The year-round data of fungal cases showed that the highest incident of *Candida albicans* infection were in January with a mean value of 3.80, while the lowest infections were reported in June, with prevalence of 2.32 of *C. albicans*. The twenty-year data analysis showed that the years 2001 and 2000 showed the highest incidents of *C. albicans*, with a mean prevalence of 7.50 and 6.83, respectively. Specimen vs fungal prevalence data showed that 38% of the *C. albicans* were isolated from body aspirate specimens, followed by 26% from swab specimens.

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Conclusion: The high prevalence of *Candida* spp. in the present study suggests increased susceptibility of patients with critical or chronic illnesses to fungal infections.

Introduction

Over the last few decades, the incidence rate for fungal infections has increased globally [1] especially in healthcare settings [2]. Fungal infections range from nail, or skin infection to mucosal candidiasis and other serious fungal diseases, which are responsible for increased morbidity and mortality [3]. The global burden of fungal disease has been estimated to be over 5.7 billion people (more than 80% of the world's population) [4].

Martin et al., reported an increase of 207% in fungal related sepsis cases in the United States (US), from 1979 through 2000 [5]. This trend is accompanied by the fact that the fungal infections are common in certain high-risk individuals, including patients with critical or terminal diseases, neutropenic individuals or had received organ transplantation. Health care setting have become an important predecessor of fungal infection and various factors contribute to the problem. These include increase in elderly populations in countries that have advanced medical care, increased incidence of cancers and myeloablative treatments for these cancers, increase in intensive care for serious patients, and a rise in the number of organ and hematopoietic stem cell transplantation. According to Hahn-Ast et al., serious fungal infections cause substantially increase in mortality and morbidity in patients receiving immunosuppressive chemotherapy for hematological malignancies [6]. This trend is expected to continue in the coming decades, which indicates a subsequent increase in the incidence of nosocomial and invasive fungal infections.

Among fungi and yeast species, *Candida* species have been identified to be most common cause of nosocomial pathogens. *Candida* species is characterized as pathogenic fungi [7]. The analysis of fungal burden across the globe shows that out of 45 countries, Candidemia is a serious health burden in 39 countries with around 159, 253 total cases. 60% of the cases were reported in the ICU followed by cancer and transplant units (13%). A record prevalence of candidemia was reported in Pakistan (21 cases/100,000 patients) followed by Brazil (14.9 cases/100,000 patients) and Russia (8.29 cases/100,000 patients). The lowest incidence figures were reported in Jamaica, Austria, and Portugal with 5, 2.1 and, 2.2 cases per 100,000 patients [3].

C. albicans is the most widespread pathogen behind majority of candidemia cases worldwide [8]. However, several non-*C. albicans* spp. *including C. parapsilosis, C. glabrata, C. tropicalis, and C. krusei*, have emerged as significant pathogens of fungal bloodstream infections. According to the findings of Moretti et al., a five-year surveillance study in Brazil hospital showed that *C. albicans* caused 44% of the infections, followed by *C. tropicalis* (21.7%), *C. parapsilosis* (14.4%), *C. glabrata* (11.2%), and *C. krusei* (3.5%). They reported that the incidence of *C. glabrata* significantly increased from 4.8 to 23.5% in a period of five years [9]. In a study of non-neutropenic patients in China, Wu et al., found that *C. albicans* accounted for 57.8% of all cases, followed by *C. tropicalis*, *C. parapsilosis*, and *C. glabrata* [8]. Similar reports have been collected from hospitalized patients in Turkey and UK [10,11]. The present study has been designed to evaluate the prevalence of fungal infections in patients who visited a local hospital over the period of twenty years. These data can help us highlight the prevalence and seriousness of fungal infection and their burden on the healthcare system.

Methods

Data collection

A retrospective study was conducted in Fungal culture data from the 2000–2019 period were obtained from the Laboratory Information System of the Mycology Laboratory at Johns Hopkins Aramco Healthcare and extracted from the electronic laboratory information system.

Inclusion and exclusion criteria

Data available on samples from patients who were referred by their primary physicians for fungal screening tests were collected from laboratory information system to be analyzed in the present study. The data retrieved belong to laboratory samples that included nail clippings, sputum, blood, body tissues, pus swabs, and urine, that were aseptically collected and transported in sterile containers or syringe at the time of sample collection. All data on positive samples for fungal growth were selected for further assessment, while others were excluded from analysis. Clinical data was used to obtain the demographic features of the samples that included gender, age, and month/year of incidence.

Isolation and identification

The data were collected after confirming the fungal infection in the positive samples according to the laboratory procedure manual, samples were treated upon isolation and further for identification as per the adopted procedures in the laboratory at the time of sample collection. In this respect, the samples were initially examined by preparing wet mounts and the isolates were processed as described by Ref. [2].

Statistical analysis

The data was analyzed by Statistical Package of Social Sciences (SPSS) version 21.0. Continuous variables were analyzed by *t*-test testing, respectively. Variance of *Candida* species among the non-*Candida* and yeast isolates were calculated by the Fisher's exact test. The difference in fungi incidence trends between the time periods from 2000 to 2009 AND from 2010 to 2019 based on male and female genders, age groups and type of clinical samples was examined using univariate analysis of variance (ANOVA). The data was analyzed at 95% Confidence interval ($p \leq 0.05$ indicates a significant difference).

Results

Isolation and identification of fungal species

A total of 1256 samples with presumed fungal etiology were included in the study. All the samples were analyzed through direct microscopy with 10% potassium hydroxide showed the visual presence of fungal elements such as hyphal filaments, cell wall and single cells. The fungi positive samples were also subjected to Gram staining for the differentiation *of Candida* spp. (filamentous

Table 1
Frequency of *Candida* spp. and other fungi in samples.

Fungal species	Gender		Total N(%)[a]	P-value[b]
	Female N(%)[a]	Male N(%)[a]		
C. albicans	403 (**59.6%**)	329 (**56.7%**)	732 (58.3)	0.682
C. dubliniensis	12 (1.8)	15 (2.6)	27 (2.1)	0.881
C. glabrata	40 (5.9)	40 (6.9)	80 (6.4)	0.999
C. parapsilosis	36 (5.2)	32 (5.5)	68 (5.4)	0.911
C. tropicalis	15 (2.2)	27 (4.6)	42 (3.3)	0.232
C. krusei	8 (1.2)	7 (1.2)	15 (1.2)	0.885
C. kefyr	0	1 (0.2)	01 (0.1)	0.423
C. guilliermondi	2 (0.3)	0	02 (0.2)	0.423
Other *Candida* spp.	6 (0.9)	7 (1.2)	13 (1.0)	0.831
C. lusitaniae	3 (0.4)	1 (0.2)	04 (0.3)	0.592
Other yeast	151 (22.3)	121 (20.9)	272 (21.7)	0.854
Total	676 (53.8)	580 (46.2%)	1256 (100)	

[a] Number of fungi and percentage (N and %).
[b] Analysis of the variance (ANOVA) for incidence trend.

or hyphal form) from yeast (single celled fungi). The samples were grown on Sabouraud's Dextrose Agar and morphological analysis of fungal growth showed the presence of different fungal species and predominant fungi was identified to be *Candida* spp., with a prevalence of 79%. Nine different species of *Candida* were identified, including *C. albicans, C. dubliniensis, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei, C. kefyr, C. guilliermondi,* and *C. lusitaniae*. Non-*Candida* or yeast fungal infections were present in 21% of the samples. With respect to the presence of different fungal species in males and females samples, there were no significant differences between males and females regarding infections with all reported fungi species (Table 1).

Age and gender-wise prevalence of different fungi

The data was analyzed based on prevalence of fungal infection in both genders. Results showed that fungal infections were more prevalent in women (58.3%) as compared to men (46.2%). The demographic data related to age showed that the prevalence of fungal infections was different in different age groups. The data was divided into nine age groups and the prevalence of fungal infections, *Candida*, and non-*Candida*, was noted in each group (Table 2). Results showed that the highest number of *C. albicans* infections were found in age group 70–79 with 113 cases, followed by age group 50–59 and children <10 years, with 106 and 104 cases out of 1256, respectively. Statistical analysis showed that the numbers of recorded infections for all fungi species in all age groups were not statistically different suggesting that neither species statistically prevail in a specific age group compared to other age classes. Of note, the highest numbers of infections were recorded in the age groups 40–49 and 50–59, followed by 70–79 group. Also, the age group <10 years old was amongst the groups that recorded the highest numbers being ranked 5th out of 9 age groups.

Month and year-wise prevalence of different fungi

The clinical data was analyzed based on prevalence of fungal infections over the time of year for 20 years. The data was divided into two main groups: month and year-wise prevalence of different fungi. The results for month-wise prevalence of fungi showed that the incidents of *C. albicans* infection were highest in January with a mean value of 3.80, *C. glabrata* (1.70) and other yeasts (1.40) followed by in April, with prevalence values of 3.79 and 1.21 for *C. albicans* and other yeasts, respectively. The lowest number of fungal infections were observed in June, with mean prevalence values of *C. albicans* (2.32), *C. dubliniensis* (0.16), *C. glabrata* (0.58), *C. tropicalis* and *C. krusei* (0.11) and other yeast (0.11) (Fig. 1).

Table 2
The prevalence of different fungal species in various age groups.

Fungal species	Age group (Years)										
	<10 N(%)[a]	10–19 N(%)[a]	20–29 N(%)[a]	30–39 N(%)[a]	40–49 N(%)[a]	50–59 N(%)[a]	60–69 N(%)[a]	70–79 N(%)[a]	80 and above N(%)[a]	Total N(%)[a]	P-value[b]
C. albicans	104 (66.7)	55 (56.7)	58 (61)	72 (55.4)	96 (53.9)	106 (56.4)	84 (52.8)	113 (66.8)	44 (52.4)	732 (58.3)	0.782
C. dubliniensis	0	3 (3.1)	3 (3.1)	0	4 (2.2)	3 (1.6)	7 (4.4)	4 (2.3)	3 (3.5)	27 (2.1)	0.911
C. glabrata	6 (3.8)	5 (5.1)	2 (2.1)	3 (2.3)	11 (6.1)	10 (5.3)	20 (12.5)	12 (7.1)	11 (13.1)	80 (6.3)	0.526
C. parapsilosis	5 (3.2)	3 (3.1)	2 (2.1)	8 (61.5)	12 (6.7)	15 (7.9)	14 (8.8)	7 (4.1)	2 (2.4)	68 (5.4)	0.688
C. tropicalis	8 (5.1)	0	6 (6.3)	3 (2.3)	3 (1.7)	5 (2.6)	7 (4.4)	6 (3.5)	4 (4.7)	42 (3.3)	0.749
C. krusei	3 (1.9)	3 (3.1)	1 (1.05)	0	0	6 (3.2)	0	1 (0.6)	1 (1.2)	15 (1.2)	0.298
C. kefyr	0	0	0	0	0	0	1 (0.6)	0	0	1 (0.08)	0.495
C. guilliermondi	0	0	0	0	0	1 (0.5)	0	1 (0.6)	0	2 (0.16)	0.569
Other *Candida species*	2 (1.3)	1 (1.03)	2 (2.1)	2 (1.5)	2 (1.1)	1 (0.5)	0	1 (0.6)	2 (2.4)	13 (1.03)	0.940
C. lusitaniae	0	0	1 (1.05)	1 (0.77)	2 (1.1)	0	0	0	0	4 (0.32)	0.624
Other yeast	28 (17.9)	27 (27.8)	20 (21.0)	41 (31.5)	48 (26.9)	41 (21.8)	26 (16.3)	24 (14.2)	17 (2.0)	272 (21.6)	0.983
Total	156	97	95	130	178	188	159	169	84	1256	

[a] Number of fungi and percentage (N and %).
[b] Analysis of the variance (ANOVA) for incidence trend.

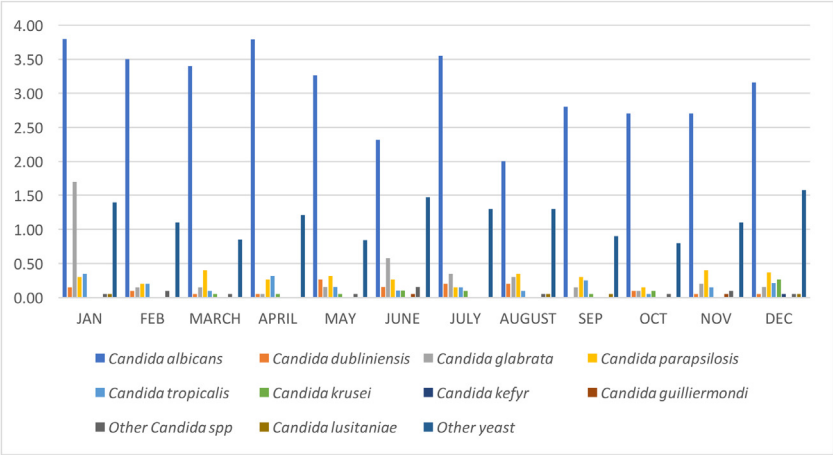

Fig. 1. The month-wise prevalence of different fungal infection.

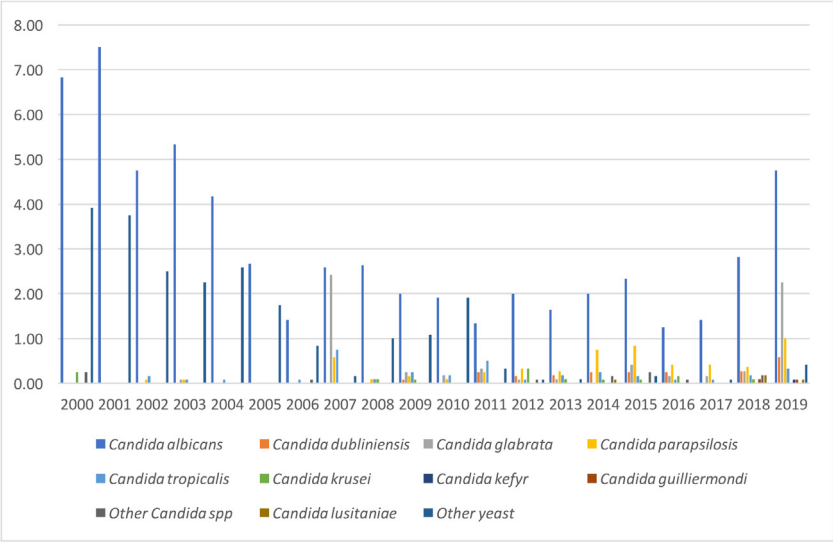

Fig. 2. The year-wise prevalence of different fungal infection.

The year-wise prevalence data of different fungal infections showed that the highest number of infections were observed in the year 2001 and 2000. The species prevalence during these two years showed that *C. albicans* had a mean prevalence of 7.50 and 6.83 in 2001 and 2000, respectively. The prevalence trend of different fungi in twenty years is shown in Fig. 2.

Clinical specimen-wise prevalence of different fungi

The prevalence of fungal infection was analyzed based on specimen type. The specimens were divided into five types: swabs, body aspirates, body fluids/tissues scrapings, sputum and wound. The results showed that the swab specimens and aspirates samples had the highest prevalence of *C. albicans*, with 192 and 283 positive samples, followed by *C. glabrata* in 14 and 41 specimens, *C. dublinieissis* in 7 and 14 specimens, respectively (Table 3). In body fluids/scraping specimens, *C. albicans* was present in 78 samples and *C. parapsilosis* in 48 samples. Sputum and wound samples showed 144 and 38 cases of *C. albicans,* respectively. Non-*Candida* infections were found in 66, 54, 62 samples of swab, body aspirates and body fluids/tissues scrapings specimens: respectively. Statistically, there was a significant difference between isolated samples regarding presence of *C. tropicalis* and *C. krusei* being present more often in body Fluids/discharges/tissues ($p = 0.002$ and 0.011, respectively), where *C. tropicalis* was found in 21 samples out of 42 samples and *C. krusei* was found in 10 samples out of 15 samples.

Discussions

A total of 1256 samples of patients that were receiving tertiary care in hospitals and had presumed fungal infections were included in the study. The morphological and biochemical identification of isolates showed that 79% of fungi belonged to *Candida* spp., including *C. albicans, C. dubliniensis, C. glabrata, C. parapsilosis, C. tropicalis, C. krusei, C. kefyr, C. guilliermondi,* and *C. lusitaniae;* and 21% isolates were identified as other yeast and were categorized as non-*Candida* fungi. Similar results have been found by Yang et al., who reported the presence of *C. albicans*, *C. tropicalis*, *C. glabrata* and *C. parapsilosis* in critically ill patients [2]. Recent epidemiological studies suggest that the overall burden of invasive candidiasis continues to be high, especially in the growing populations of patients who are at risk of opportunistic infections, such as the elderly or immunosuppressed [12].

Among *Candida* species, *C. albicans* was the most dominant species of *Candida* (58.3%) followed by *C. glabrata* (6.4%). Similar findings have been reported in other studies that *Candida* species

Table 3
Clinical specimen-wise prevalence of different fungal species.

Fungal species	Type of clinical samples						
	Body swab N(%)[a]	Body aspirates N(%)[a]	Body fluids/discharges/tissues N(%)[a]	Sputum N(%)[a]	Wound N(%)[a]	Total N(%)[a]	P-value[b]
C. albicans	192 (26)	283 (38)	78 (10)	141 (19)	38 (5)	732 (58.3)	0.248
C. dubliniensis	7 (2.3)	14 (3.3)	3 (1.2)	2 (0.9)	1 (1.1)	27 (2.1)	0.563
C. glabrata	14 (4.6)	41 (9.8)	17 (6.9)	3 (1.4)	5 (5.8)	80 (6.3)	0.252
C. parapsilosis	7 (2.3)	3 (0.7)	48 (19.6)	6 (2.7)	4 (4.7)	68 (5.4)	0.218
C. tropicalis	3 (1.01)	16 (3.8)	21 (8.6)	0	2 (2.35)	42 (3.3)	0.002*
C. krusei	1 (0.3)	2 (0.5)	10 (4.0)	1 (0.45)	1 (1.1)	15 (1.2)	0.011*
C. kefyr	0	0	0	1 (0.45)	0	1 (0.08)	0.486
C. guilliermondi	1 (0.3)	0	0	1 (0.45)	0	2 (0.16)	0.486
Other *Candida species*	3 (1.01)	2 (0.5)	3 (1.2)	5 (2.3)	0	13 (1.03)	0.258
C. lusitaniae	1 (0.3)	1 (0.25)	2 (0.8)	0	0	4 (0.32)	0.598
Other yeast	66 (22.3)	54 (12.9)	62 (25.4)	56 (25.9)	34 (0.4)	272 (21.6)	0.575
Total	295	416	244	216	85	1256	

[a] Number of fungi and percentage (N and %).
[b] Analysis of the variance (ANOVA) for incidence trend.

were the most prevalent fungal pathogens, especially in critically ill people [8,13–15]. Further, Yang et al., reported that *C. albicans* was responsible for 63% of all candidiasis infections in their study [2]. The age-wise prevalence of fungal infections in the present study showed that the maximum number of fungal positive cases were present in elderly (70–79 years age) with 113 cases (15%), followed by age group 50–59 and children <10 years, with 106 (14.4%) and 104 (14%) cases out of 1256, respectively. An epidemiologic study in Latin America by Nucci et al., reported that there is high incidence of *C. albicans, C. tropialis C. parapsilosis*, with the highest prevalence in children (44.2%), followed by adults between under 60 years (36.2%) and elderly above 60 (19.6%) [16].

The results for month-wise prevalence of fungi showed that the incidents of *C. albicans* infection were highest in January with a mean value of 3.80, *C. glabrata* (1.70) and other yeasts (1.40) followed by in April, with prevalence values of 3.79 and 1.21 for *C. albicans* and other yeasts, respectively. The lowest number of fungal infections were observed in June, with mean prevalence values of *C. albicans* (2.32), *C. dubliniensis* (0.16), *C. glabrata* (0.58), *C. tropicalis* and *C. krusei* (0.11) and other yeast (0.11) (Fig. 1). Similar results have been reported by Edi-Osagie and Emmerson who reported that 73% cases of *Candida* infections occurred during winter season from the months September to February [17].

The year-wise prevalence data of different fungal infections showed that the highest number of infections were observed in the year 2001 and 2000. The species prevalence during these two years showed that *C. albicans* had a mean prevalence of 7.50 and 6.83 in 2001 and 2000, respectively (Fig. 2). A ten-year (2003–2012) retrospective study of *Candida* infections in a tertiary care center in Saudi Arabia showed an increase in the *Candidiasis* prevalence in the decade and was highest in the year 2010 with 108 cases out of 625 total cases [18].

The specimen-wise prevalence of different fungal species incident results showed that the swab specimens and aspirates samples had the highest prevalence of *C. albicans*, with 192 and 283 positive samples, followed by *C. glabrata* in 14 and 41 specimens, *C. dublinieissis* in 7 and 14 specimens, respectively (Table 3). Maheshwari et al., analyzed the clinical specimens including oral swabs, blood, sputum/bronchoalveolar lavage samples, and body fluids/discharges for the presence of *Candida* species. They reported that the highest prevalence of *Candida* species was present in oral swabs (66%) followed by sputum and urine specimens, while *C. glabrata* was most common in urine samples. *C. dubliniensis*, *C. krusei*, *C. parapsilosis*, *and C. kefyr* were mainly detected in oral swabs [19].

Conclusion

This twenty-year retrospective study on the prevalence of fungal infections in patients who received treatment in a tertiary care center showed a high prevalence of *Candida* species in the patients. *Candida albicans* has been found to be the most prevalent pathogenic fungi that can cause life-threatening problems, especially in children and the elderly. The present study highlights the need of giving special consideration to fungal infections in patients with chronic illnesses to protect them from serious infections.

Author contributions

M, AAR. contributed significantly to the study design. Conceptualization, M, AAR; data curation, M, AAR, BAS; formal analysis, M, OE, SA, AA, JAA; methodology, BAS, AAR, FMA; project administration, M, AAR; supervision, AAR and JAA; writing—original draft, M; writing—review and editing, M, AAR, SA, OSE, SA, AA and JAA. All authors have read and agreed to the published version of the manuscript.

Data availability statement

All data required to understand this article are presented in the study any raw data further requested will be provided from the corresponding authors.

Ethical approval

The study has been approved by the research ethics committee at JHAH (IRB-18-21).

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None to declare.

Conflicts of interest

The authors declare no conflicts of interest.

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