

Original Research Article

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Identification and Anti-Fungal Resistance Profile of Different *Candida* Species Isolated from Patients in ICUs

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ABSTRACT

Keywords

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Candidiasis is one of the most predominant fungal infections that cause a major mortality of the patient. The epidemiology of candida infections have been witnessed a change round the world. We aimed to determine the distribution of candida species isolates from various clinical samples of patients in ICUs and evaluate its antifungal susceptibility to demonstrate the local resistance profile and guiding empirical treatment for clinicians. This study included 714 *Candida* isolates. *Candida* species were identified by MALDI-TOF mass spectrometry. Antifungal susceptibility tests were performed by Vitek 2 system. The percentage of NAC isolates (63.59%) was higher compared with *C. albicans* (36.41%). The highest resistance rate in candida species was against amphotericin B (11.56%). However there was no resistance to caspofungin and micafungin reported. Regarding to voriconazole and fluconazole anti fungal, the resistance rate of *C. albicans* were 13.46% and 8.46% respectively while of NAC species were 6.53%, 5.1% respectively. All *C. krusei* isolates were resistance to fluconazole. The study revealed increased the incidence of NAC over time. Although no remarkable resistance for antifungal agents in our hospital, we establish a critical need to antifungal stewardship program to prevent reaching the era of predominant Multi- drug resistance strain of *Candida*.

Introduction

In the past few decades, the incidence of mycotic infection has trend to increase progressively throughout the world (Pfaller 2007). *Candida* infection is diverse, including asymptomatic colonization, cutaneous candidiasis, or pharyngeal candidiasis and invasive candidiasis including candidemia (Anwar *et al.*, 2012). Nosocomial candidiasis is among the most predominant fungal

infection that causes a major hazard on the health of patients from centers of tertiary care and spread to the community hospitals (Singhi and Deep, 2009). In the United States, 5%-10% of patients admitted in hospitals had acquired nosocomial infection. *Candida* caused about 80% of fungal infections. Several studies observed that *Candida albicans* (*C. albicans*) is the sixth commonest cause of nosocomial infections (Pappas *et al.*, 2009).

Recently, *C. albicans* has been the most common species implicated, when the incidence of non-*albicans Candida* (NAC) has risen dramatically (Bajwa and Kulshrestha, 2013). With previous study, the epidemiology of *Candida* infections have been witnessed a change in many countries round the world, characterized by a progressive shift from a predominance of *C. albicans* to NAC species (Oberoi *et al.*, 2012).

The frequency of *Candida* species other than *C. albicans* varies according to various geographical regions and over time (Pfaller 2007). For example, *Candida glabrata* is the second common species after *C. albicans* in North America (Pfaller and Diekema, 2012). However, in Asia, Australia and Europe, *C. tropicalis* and *C. parapsilosis* are more common (Chen *et al.*, 2006 and Wang *et al.*, 2010). *C. tropicalis* is main cause of candidaemia in India (Xiao *et al.*, 2014). Additionally, uncommon species such as *C. guilliermondii* and *C. rugosa* are emerging (Chander *et al.*, 2013).

A number of virulence factors are the explanation for the alteration of different *Candida* spp. from commensal to vigorous infectious agent, like biofilm formation, adherence to host tissues and medical devices and secretion of extracellular hydrolytic enzymes (Sardi *et al.*, 2013). Even though many studies that published data about the risk factors that cause increasing the risk of *Candida* infection in intensive care unit (ICU). Of those risk factors, severe immunosuppression or illness, increased use of invasive procedures and devices, abdominal surgery, frequent use of broad spectrum antibiotics and empirical use of antimycotic drugs are reported to be associated with such an increase (Goemaere *et al.*, 2018 and Trick *et al.*, 2002).

The aim of our study was to determine the distribution of different *Candida* species

isolates from numerous clinical specimens and evaluate its antifungal susceptibility to demonstrate the local resistance profile of ICUs patients in Zagazig University Hospitals and to guide empirical treatment for clinicians.

Materials and Methods

This is a retrospective study of all *Candida* isolates data retrieved from the computerized databases of the microbiology unit of Clinical Pathology Department, Zagazig University Hospitals and included 714 *Candida* species isolated from patients who admitted to ICUs between the period of November 2016 and December 2018. All the investigations were performed following the relevant guidelines and regulations of Zagazig University.

All Patients included in the study were suffered from symptoms and signs of infection; other bacterial causes were excluded by different culture technique. Patients were diagnosed on the basis of clinical presentation; they were subjected to full history taking with focusing on the risk factors association such as hospital stay duration, underlying medical conditions, invasive medical procedures such as presence of urinary catheter, central line insertion, respiratory ventilation and the usage of antibiotics, chemotherapy, corticosteroids or immunosuppressive drugs.

Samples collection

Non-duplicate isolates were recovered during the study period. *Candida* species were revealed from numerous clinical samples such as blood, respiratory samples as bronchoalveolar lavage, deep tracheal aspirate, pleural fluid and sputum, urine and others miscellaneous sites as oropharyngeal and vaginal swabs. Blood cultures were done using Bact /ALERT culture bottles and incubated for 7 days in the

automated Bact / ALERT 3D Microbial Detection System (bioMérieux, Inc, Durham, USA). The positive blood culture bottles and other isolated samples were initially grown on blood agar and sabouraud dextrose agar for twenty four to forty eight hours at 37°C.

Identification

Candida colonies appeared as flat, smooth and pale off white coloured and identified by gram stain. Germ tube formation had been tested for the isolated colony to differentiate *C. albicans* against NAC. *Candida* species were Identified using matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (bioMérieux, Marcy l’Etoile, France) according to the manufacturer instructions. Small amount of the freshly *Candida* colonies were picked and smeared on the wells of disposable target slides, 1 µL formic acid was added and air dried then 1 µL of VITEK MS CHCA matrix solution (cyano-4-hydroxycinnamic acid) was added to the sample and left to dry at room temperature for 1- 2 min. Then target slide was loaded into the VITEK MS, the mass spectra acquired for each sample were compared to the known mass spectra in the database and given a confidence score.

Antifungal susceptibility testing

The susceptibility to antifungal agents was carried out using Vitek 2 system (bioMérieux, Inc, Durham, USA) for yeast (card no ACT/YS07) containing serial twofold dilutions of six antifungal drugs; fluconazole, flucytosine, voriconazole, caspofungin, micafungin and amphotericin B were provided by the manufacturer and the antifungal susceptibilities were interpreted according to the Clinical and Laboratory Standards Institute guidelines (CLSI) after adjustment of McFarland standard of 2 with colony inoculums. The results were

interpreted as sensitive (S), intermediate (I) and resistant (R).

Minimal inhibition concentrations (MICs) cut- off values for flucytosine ≤ 1 µg/ml was considered to be susceptible (S) and ≥ 64 µg/ml was considered to be resistant (R), MIC was categorized for fluconazole as ≤ 1 µg/ml (S) and ≥ 64 µg/ml (R), for voriconazole was ≤ 0.12 µg/ml (S) and ≥ 8 µg/ml (R), for amphotericin B was ≤ 0.25 µg/ml (S) and ≥ 16 µg/ml (R), for micafungin was ≤ 0.06 µg/ml (S) and ≥ 4 µg/ml (R) and for caspofungin was ≤ 0.25 µg/ml to be (S) while ≥ 4 µg/ml was considered to be (R). The ranges of MICs at which 50% and 90 % of the isolates population of *Candida* species had been inhibited (MIC₅₀ and MIC₉₀, respectively) were calculated. The acceptable percent essential agreement for MICs was set at $\geq 90\%$ for each antifungal agent against all organisms tested.

Statistical analysis

The data was statistically analyzed using SPSS statistical package software computer program version 17 (SPSS Inc., Chicago, IL). Categorical variables are presented as number and percentage. The relationship between usage of antifungal and the distribution of *Candida* species were determined using the Chi-squared test for non-parametric correlation. P value < 0.05 was considered significant.

Results and Discussion

The demographic clinical characteristics by the most common *Candida* species were shown in table 1: *Candida* species was seen in 714 isolates from different specimens. NAC (63.59%) was isolated from patients admitted in ICU compared to *C. albicans* (36.41%) during the studied period (P<0.0001). This result showed an increase of the incidence of

NAC from epidemiological data presented in our hospitals covering the periods from January 2014 to November 2016 found that the incidence of NAC species was (59.4%). The duration of hospital stay (>1 week) was significantly increased inpatients with NAC compared to these with *C. albicans* (p<0.001).

The prevalence rate of *Candida* species isolated from various clinical specimens: As shown in table 2, isolation of different types of *Candida* species from different clinical specimens showed the majority in urine samples (61%), followed by respiratory tract specimens (16%), blood samples (7.9%) and finally (15.1%) isolates from different

miscellaneous samples. The prevalence of *Candida* species was as follows: *C. albicans*, (36.4 %), *C. tropicalis* (57.7 %), *C. glabrata* (2.1 %), *C. krusei* (1.26), *C. parapsilosis* (1.1 %), *C. lusitaniae* (0.6 %), *C. kefyr* (0.42 %) and 0.14% for *C. dubliniensis*, *C. guilliermondii* and *C. rugosa*.

The rate of resistance of *Candida* isolates to anti-fungal agents was shown in table 3: The highest resistance rate in all *Candida* species was against amphotericin B (11.56%). However there was no resistance to caspofungin and micafungin (echinocandins class of antifungal) was reported. Low resistance was showed to flucytosine (2.4%) among *Candida* species.

Table.1 Demographic clinical characteristics by the most common *Candida* species

<i>Candida</i> SPP.	<i>C. albicans</i>	<i>C. Non Albicans</i>	P value
Number of isolated	260 (36.41%)	454 (63.59%)	< 0.0001
Gender:			
Male	203 (78.1%)	315 (69.4%)	0.03
Female	57 (21.9%)	139 (30.6%)	0.21
Underlying condition:			
Diabetes Mellitus	78 (30%)	142 (31.3%)	0.84
Heart/ Pulmonary diseases	114 (43.8%)	191 (42.1%)	0.77
Malignancy	39 (15%)	74 (16.3%)	0.85
Renal Diseases	57 (21.9%)	88 (19.4%)	0.71
Predisposing factors:			
GIT diseases/ operation	32 (12.3%)	69 (15.2%)	0.69
Receipt of Corticosteroids	63 (24.3%)	126 (27.7%)	0.61
Central venous catheter	45 (17.3%)	137 (30.2%)	0.09
Indwelling of urinary catheter	170 (65.4%)	284 (62.5%)	0.53
Receipt of mechanical ventilation	39 (15%)	55 (12.1%)	0.68
Blood product transfusion	89 (34.2%)	107 (23.6%)	0.102
Candiduria	146 (56.1%)	289 (63.7%)	0.12
Antifungal prophylaxis	51 (19.6%)	112 (24.7%)	0.47
Outcome:			
Mortality (30 days)	18 (6.9%)	46 (10.1%)	0.69
ICU stays (> 1 wk)	158 (60.77%)	(372 (81.93%))	<0.0001

Significant if P value <0.05 Data are presented as No. (%)

Table.2 The prevalence rate of *Candida* spp. isolated from various clinical specimens.

Cl. specimen <i>Candida</i> spp	Urine (n=435)	Respiratory (n=115)	Blood (n=57)	Miscellaneous (n=108)	Total (n= 714)
<i>C. albicans</i>	146(33.56%)	40 (34.78%)	28 (49.1%)	46 (42.6%)	260 (36.4%)
C. Non albicans:	289 (66.44%)	75 (65.22%)	29 (50.9%)	62 (57.4%)	454 (63.6%)
C. tropicalis	269(61.84%)	67 (58.3%)	29(50.9%)	48 (44.44%)	412 (57.7%)
<i>C. glabrata</i>	6 (1.4%)	3 (2.6%)	–	6 (5.55%)	15 (2.1%)
<i>C. krusei</i>	3 (0.7%)	3 (2.6%)	–	3 (2.78%)	9 (1.26%)
<i>C. parapsilosis</i>	5 (1.11%)	1 (0.86%)	–	2 (1.85%)	8 (1.1%)
<i>C. leusitaniae</i>	1 (0.23%)	1 (0.86%)	–	2 (1.85%)	4 (0.6%)
<i>C. kefyri</i>	3 (0.7%)	–	–	–	3 (0.42%)
<i>C. dubliniensis</i>	1 (0.23%)	–	–	–	1 (0.14%)
<i>C. guilliermondii</i>	–	–	–	1 (0.93%)	1 (0.14%)
<i>C. rugosa</i>	1 (0.23%)	–	–	–	1 (0.14%)

Data are presented as No. (%)

Table.3 The resistance rate of *Candida* species to antifungal agents

<i>Candida</i> spp.	No. of isolates	Antifungal agent					
		Amphotericin B	Voriconazole	Fuconazole	Flucytosine	Caspofungin	Micafungin
<i>C. albicans</i>	260	43 (16.53%)	35(13.46%)	22 (8.46%)	2 (0.77%)	–	–
C. non albicas	449	39 (8.68%)	31(6.9%)	31 (6.9%)	15 (3.34%)	–	–
<i>C. tropicalis</i>	412	32 (7.77%)	27 (6.53%)	21(5.1%)	13 (3.15%)	–	–
<i>C. glabrata</i>	15	2 (13.33%)	2 (13.33%)	1(11.11%)	1(6.67%)	–	–
<i>C. parapsilosis</i>	8	2 (25%)	–	–	–	–	–
<i>C. krusei</i>	9	2 (22.22%)	1(11.11%)	9 (100%)	1(11.11%))	–	–
<i>C. leusitaniae</i>	4	–	1(25%)	–	–	–	–
<i>C. rugosa</i>	1	1 (100%)	–	–	–	–	–
Total % of resistance	709	82 (11.56%)	66 (8.46%)	53 (7.47%)	17 (2.4%)	–	–

Data are presented as No. (%)

Regarding to triazoles antifungal, the resistance rate of *C. albicans* to voriconazole was 13.46% and 8.46% to fluconazole. In addition, the resistance rate to voriconazole and fluconazole among NAC species had been reported as 6.53%, 5.1% respectively. All *C. krusei* isolates were resistance to fluconazole (100%).

Candida has emerged as principal cause for fungal infections worldwide, which is responsible of high morbidity and mortality in patients who admitted in hospitals with serious underlying diseases (Colombo *et al.*, 2007). However in recent years there is an increasing prevalence of infections caused by NAC species of *Candida* compared to *C. albicans* which shows decreased incidence (Wang *et al.*, 2016). Limited epidemiological studies of *Candida* infection have been done in Egypt and the surrounding countries, in contrast to the extensive numbers of studies done in Europe and North America (Pfaller *et al.*, 2008 and Lockhart *et al.*, 2012). In this context, we studied the frequency of different *Candida* species and their antifungal susceptibility profile in ICUs of Zagazig University Hospitals.

In the present study, we observed that NAC was responsible for (63.59%) of infection caused by *Candida* species in patients admitted in ICUs, making it the most common infectious *Candida* agent. This was consistent with the emergence of predominance of non albicans candidiasis worldwide. Many researchers (Abu-Elteen, 2001; Tortorano *et al.*, 2004 and Bonfietti *et al.*, 2012) have revealed that the distribution of both *C. albicans* and non-albicans was more frequently recovered in ICUs patients compared to other hospital wards.

The remarkable increase in the use of invasive devices as central venous catheterization and urinary catheter, advanced age, severe illness

as diabetes mellitus and immunosuppression was additional contributors to infection. In addition to improper abuse of antibiotics and start with broad spectrum antibiotics as the first line treatment had been the most important cause of increasing *Candida* species colonization which causes suppression of the commensal bacterial flora (Sachin *et al.*, 2014). Moreover, admission in ICU itself has come to be an independent risk factor for the enhancement of *Candida* infection (Zaragoza and Pemán, 2008).

We reported preponderance of *Candida* isolated from the urine samples (61%), followed by respiratory tract specimens (16%), miscellaneous specimens (15.1%) and finally 7.9% isolates from blood samples. Different *Candida* species were isolated most commonly from urine samples. These results are similar to the findings of many studies who revealed that more than 50% of *Candida* isolates from the urine samples belong to NAC species (Zaragoza and Pemán, 2008, Kauffman 2005 and Alvarez-Lerma *et al.*, 2003). Sachin *et al.*, (2014) explained that the NAC spp is well adapted to the urinary tract and also it is difficult to eradicate than *C. albicans*. However, Amer *et al.*, (2015) reported that *Candida* had been isolated from different samples as follows; 27.54% from semen, 20.29% from vagina, 18.84%, from urine, 17.39% from oral cavity, 11.59% from stool and 4.35% from C.S.F.

We found that the prevalence of *Candida* species was as follows: *C. albicans* (36.4 %), *C. tropicalis* (57.7 %), *C. glabrata* (2.1 %), *C. krusei* (1.26), *C. parapsilosis* (1.1 %), *C. lusitaniae* (0.6 %), *C. kefyr* (0.42 %) and 0.14% for *C. dubliniensis*, *C. guilliermondii* and *C. rugosa*.

In contrast, the previous study took place in Egypt during 2015. Results showed that the distribution rate of *C. albicans* was the most

common species representing 68.45% followed by 16.07% *C. tropicalis*, 11.31% *C. glabrata* and 4.17% of *C. krusei* represented in patient with candidiasis (Amer *et al.*, 2015). Also, Esmat *et al.*, (2015) revealed that the highest prevalence of *Candida* isolated from ICU's patients was for *C. albicans* (40.3%) followed by *C. tropicalis* (22.2%); *C. glabrata* (18%), *C. krusei* (12.5%) and *C. parapsilosis* (4.2%) were also isolated. The distribution of *Candida* species was different in the study of Taha *et al.*, (2018) that took place in 2018 and showed decrease in the distribution rate of *C. albicans* to (36.4%); but it is still the predominant isolates followed by 25% for *C. tropicalis*, then 15.9% for *C. parapsilosis* and 11.4% for *C. krusei*. These findings seem compatible with the changes occurred in the *Candida* infections epidemiology in many countries around the world, which are characterized by a progressive shift from a predominance of *C. albicans* to NAC species.

Furthermore, *C. albicans* still is the most common agent in many researches although its incidence was significant decreasing from 68 to 50 % in Europe and from 64% to 45% in Asia (Pfaller *et al.*, 2010 and Pfaller *et al.*, 2013). Moreover, our results were in agreement with a prospective studies of Chakrabarti *et al.*, (2009), who found that the *C. tropicalis* was the most common (42.1%) isolated agent and Kaur *et al.*, (2016) who reported that NAC species is predominant (63.3%) compared by *C. albicans* (36.7%) and a lower rate of *C. glabrata* (10%) and *C. parapsilosis* (6.7%) are isolated while *C. krusei* (3.3%) and *C. kefyr* (2.2%) are relatively rare seen.

The pathogenesis of *Candida* infection depends on the expression of several virulence factors such as phenotypic switching, adhesions and hydrolytic enzymes. Virulence factors expression may alter

according to the infecting species, geographical region, host immune response and type, site and stage of infection. *C. tropicalis* has its ability to express variation of those virulence factors indicating its ability to contribute to the pathogenesis and produce invasive infections (Yesudhasan and Mohanram, 2015).

In this study, the highest resistance rate in all *Candida* species was against amphotericin B (11.56%). However there was no resistance to caspofungin and micafungin (echinocandins class of antifungal) was reported. Low resistance was showed to flucytosine (2.4%) among *Candida* species which similar to the results of Taha *et al.*, (2018) who found thatantibiogram of all *Candida* species revealed that the pathogens were more sensitive to Flucytosine.

Although triazoles antifungal group was the most frequently used in the treatment of yeast infection, we reported that the resistance rate of *C. albicans* to voriconazole was 13.46% and (8.46%) to fluconazole. In addition, the resistance rate to voriconazole and fluconazole among NAC species had been reported as (6.53%, 5.1% respectively).

We observed that, *C. krusei* showed extremely high resistant against fluconazole (100%) and this was similar to Wissing *et al.*, (2013) results, who reported a high percent of resistance for *C. krusei* (100%) to fluconazole because of its intrinsic resistance toward azoles and poor susceptibility to all other antifungals, including amphotericin B.

Our results were supported by of Comert *et al.*, (2007) who reported that *C. albicans* was more susceptible to fluconazole followed by *C. parapsilosis* and *C. glabrata*. However, Ece (2014) revealed that the resistance rate to fluconazole (27.31%) was higher than amphotericin B (19.5%) and flucytosine

(20%). In contrast, Kaur *et al.*, (2016) showed high resistance rate towards fluconazole (37.8%) compared to amphotericin B (7.8%).

We did not find any resistance cases of *Candida* species against echinocandins class of antifungal (caspofungin and micafungin). This result was in agreement with the Dagi *et al.*, (2008) findings. However, resistance of *Candida* species against echinocandins had been reported in some publications (Wisplinghoff *et al.*, 2014 and Chen *et al.*, 2011).

In conclusion, the study revealed increased incidence of NAC overtime. Our results highlighted the importance of determining the antifungal susceptibility of different *Candida* species; there was no remarkable resistance for antifungal agents in our hospital. In addition, this study establishes a critical need to antifungal stewardship program to prevent reaching the era of predominant multi-drug resistant strain of candida.

Ethics approval: The study was performed under a protocol approved by the Institutional Review Board of Faculty of Medicine.

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